Acute coronary syndrome in human immunodeficiency virus-infected patients: characteristics and 1 year prognosis

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Aims
Natural history and prognosis of acute coronary syndrome (ACS) in HIV-infected patients remain to be determined. We sought to compare coronary risk factors, angiographic features, acute results of percutaneous coronary intervention, in-hospital outcomes, and pre-specified 1 year prognosis of HIV-infected and HIV-uninfected patients with ACS.

Methods and results
HIV-infected and HIV-uninfected patients with a first episode of ACS were matched for age (± 5 years), sex, and type of ACS. The primary endpoint was the rate of major adverse cardiac and cerebral events (MACCE), comprising cardiac death, recurrent ACS, recurrent coronary revascularization, and stroke. Overall, 103 HIV-infected and 195 HIV-uninfected patients were enrolled (mean age 49.0 ± 9.4 years, 94% men). Coronary risk factors were well balanced, but HIV-infected patients more frequently used illicit drugs (23 vs. 6%, P = 0.001) and had higher triglyceride concentrations (246 ± 189 vs. 170 ± 139 mg/dL, P = 0.002) compared with HIV-uninfected patients. Angiographic features of coronary artery disease were similar (multivessel disease 41 vs. 39%, P = 0.83). At 1 year, the rate of occurrence of first MACCE did not differ between groups [hazard ratio (HR) 1.4, 95% CI 0.6–3.0]. Recurrent ACS was more frequent in HIV-infected patients (HR 6.5, 95% CI 1.7–23.9) with no difference in the rate of clinical restenosis.

Conclusions
These results suggest that the acute management of ACS in HIV-infected patients can routinely be the same as that of HIV-uninfected patients, but that specific secondary prevention measures are needed to alleviate the increased risk of recurrent ACS.

Keywords
Acute coronary syndrome; HIV infection; Percutaneous coronary intervention; Antiretroviral therapy

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**Introduction**

In western countries, coronary artery disease (CAD) is an emerging complication in HIV-infected patients receiving combined antiretroviral therapy (cART). This could be related to their longer lifespan, to metabolic disturbances secondary to cART,1–2 and to HIV per se.3 Cardiovascular disease is now the third most common cause of death in HIV-infected patients in the USA, and the fourth most common in France.4–5 The prevalence of CAD increases with the duration of cART, particularly protease inhibitors (PIs).1–2 and is more common in HIV-infected than in HIV-uninfected populations.6–7 Traditional risk factors for myocardial infarction in the HIV-infected population, including smoking and dyslipidaemia, are usually more frequent than in the HIV-uninfected population.7,6,8–9 In addition, there is an increasing evidence to suggest that chronic HIV infection, low-grade chronic inflammation, immunological status, and cART are involved in the development of premature atherosclerosis and atherothrombosis in HIV-infected individuals.1–3,6,7–9 In studies focusing on acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI) in the HIV-infected population,10–17 discrepancies have been reported in coronary risk factors, angiographic features,11–13,17 and prognosis during the acute and longer-term phases.12,15–17 The aims of our study were to compare coronary risk factors, angiographic features, acute results of PCI, in-hospital outcomes, and the pre-specified long-term prognosis of HIV-infected and HIV-uninfected patients with a first episode of ACS.

**Methods**

**Study design**

From September 2003 to March 2006, we conducted a prospective observational study in 23 French cardiac intensive care units. Acute coronary syndrome was defined according to the European Society of Cardiology/American College of Cardiology definition18 and comprised ST-segment elevation myocardial infarction (STEMI), non-STEMI, and unstable angina pectoris. Consecutive HIV-infected patients with a first episode of ACS were enrolled. Two consecutive HIV-uninfected patients with a first episode of ACS matched for age (±5 years), sex, and type of ACS were enrolled in the same centre a maximum of 6 months after enrolment of the HIV-infected patient.  

Adult patients (≥18 years) were eligible for enrolment if they were admitted within 24 h of the onset of symptoms with a suspected ACS diagnosis. Patients with a history of cardiovascular disease (documented CAD, prior myocardial infarction, heart failure, or pulmonary hypertension), cardiogenic shock at admission, or life-threatening illness that precluded 3-year follow-up were excluded. As age and sex are strong risk factors for cardiovascular disease, matching the HIV-uninfected group for age and sex with the HIV-infected group allowed us to control potential confounders.

Patients’ characteristics, cardiovascular risk factors and therapies, medical histories, and baseline clinical data were collected prospectively. Coronary risk factors at admission included current smoking, hypercholesterolaemia (low-density lipoprotein (LDL) cholesterol ≥160 mg/dL or on lipid-lowering therapy), hypertriglyceridaemia (triglycerides ≥150 mg/dL), hypertension (blood pressure ≥140/90 mmHg or use of antihypertensive drugs), diabetes mellitus (fasting glycaemia ≥126 mg/dL or on antidiabetic treatment), family history of premature CAD, and body mass index. Illicit drug use (cocaine, heroin, other intravenous drugs) and alcohol consumption were recorded. The use of chronic therapy (taken for ≥1 month before admission) with antihypertensive medications, antidiabetic drugs, statins, fibrates, and aspirin was recorded. Admission electrocardiograms were reviewed by one independent cardiologist blinded to the patients’ HIV status and treatments. Patient risk level was evaluated at admission using the GRACE 6-month risk score for death.19

The study complied with the Declaration of Helsinki and was approved by the Committee for the Protection of Human Subjects in Biomedical Research of Saint Antoine University Hospital, Paris, France. Written informed consent to participate in the study was obtained from all patients. This study was registered at ClinicalTrials.gov (identifier NCT00139958).

**HIV and biological parameters**

Information was collected concerning HIV infection, including clinically related events (opportunistic infections), prior exposure to antiretroviral therapy, time since HIV diagnosis, CD4 and CD8 cell counts (assessed by flow cytometry), plasma HIV-1 RNA levels (measured using an ultrasensitive assay; log of 50 copies/mL) within the 6 months before the index ACS, and co-infection with hepatitis B and/or C virus.

At admission, patients were divided into four groups according to past and at-admission exposure to antiretroviral treatment: naive, not naive but not treated, treated, and cART [defined as at three or more antiretroviral molecules, or a combination of two boosted PIs, or a combination of one boosted PI and one non-nucleoside reverse transcriptase inhibitor (NNRTI)]. We also provided information on past exposure to antiretroviral treatments and duration on cART, PIs, NNRTIs, and nucleoside reverse transcriptase inhibitors (NRTIs).

A physical examination was done to evaluate clinically related signs of lipodystrophy [defined as lipoatrophy (face or limb fat-wasting), lipo hypertrophy (abdominal fat accumulation), or a combination thereof]. In HIV-uninfected patients, HIV serology (western blot analysis) was performed to verify their HIV-negative status (prior approval was obtained in all patients).

Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, and triglyceride concentrations after 12 h of fasting were determined at each centre during the first 3 days. Complete blood count, fasting glycaemia, C-reactive protein, troponin I concentrations, and creatinine clearance (Cockcroft–Gault formula) were evaluated at admission locally using standard methods.

**Angiographic and coronary revascularization**

Baseline, post-procedural, and follow-up coronary angiograms were recorded digitally and assessed offline by two experienced operators blinded to the patients’ HIV status, treatments, and types of stent implanted. Vessel disease was defined as the number of vessels with ≥50% stenosis. TIMI flow grade was evaluated before and after PCI. The complexity of the lesions was classified according to the modified grading system of the American College of Cardiology/American Heart Association.20 Procedural success was defined as a residual stenosis <30% and a TIMI 3 flow grade at completion of PCI. Stent thrombosis was defined as the presence of ACS with angiographic evidence of thrombosis or stent occlusion. Acute stent thrombosis was defined as that occurring from Days 0 through 7 and late stent thrombosis as that occurring after Day 7. Target lesion revascularization (TLR) was defined as any repeat revascularization by PCI (urgent or non-urgent) or coronary bypass surgery of the initial culprit lesion during
follow-up. Target vessel revascularization (TVR), but non-TLR, was defined as any repeat procedure for a lesion other than the initial lesion within the target vessel. The rate of urgent PCI defined as an unplanned coronary revascularization was described in both groups. All ACS treatments (anticoagulants, antiplatelets, thrombolytics, anti-ischaemic drugs, statins, and fibrates) during hospitalization and at discharge were recorded. Left ventricular ejection fraction was evaluated using echocardiography and/or ventriculography during the index hospitalization and during the entire follow-up when available.

**Study endpoints**

Patients were scheduled for follow-up at hospital discharge, 30 days, and every 6 months during the following 3 years. We report here 1-year follow-up data. Major adverse cardiac and cerebral events (MACCE), including cardiac death, recurrent ACS, recurrent coronary revascularization (urgent or non-urgent), and stroke, were the primary endpoint of the study. All follow-up events were adjudicated by an independent events committee, comprising three experienced cardiologists who were unaware of the patients’ HIV status. All clinical events during hospitalization and follow-up were recorded. All cases of death (cardiovascular, cardiac, other vascular, and non-cardiovascular), re-infarction, stroke, congestive heart failure, pulmonary oedema, cardiogenic shock, cardiac arrest, renal failure, and severe or major bleeds were adjudicated centrally using standardized definitions. Whether patients received smoking cessation counselling and stopped smoking during follow-up were recorded at each visit. Information on the use of stress testing (including exercise electrocardiogram and/or single-photon emission-computed tomography and/or dobutamine stress echocardiography) was collected during the entire follow-up.

Demographic, clinical, biological, and procedural data and in-hospital and post-discharge events were collected in a specific case report form.

**Statistical analysis**

Using a two-sided test, with a type 1 error of 5%, the study had an 80% power to detect a hazard ratio (HR) of 1.8 for MACCE over the 3-year follow-up, assuming a 25% rate in HIV-uninfected patients, by including 100 HIV-infected patients and 200 HIV-uninfected patients. To take into account matching between both study groups, conditional logistic regression models were used on their baseline demographics, clinical characteristics, and angiographic and procedural characteristics. For continuous variables, which do not follow a normal distribution, the Wilcoxon matched-pair signed-rank test was used to compare the two groups.

Time to event was defined as the time between entry into the coronary care unit and the occurrence of any MACCE, or drop-out, or 12 months after entry into the study, whichever occurred first. Time to event was analysed using Kaplan–Meier estimates. Hazard ratios for the occurrence of events were estimated using a stratified univariate Cox model, which takes into account the matching. The odds ratio (OR) for urgent and non-urgent PCI vs. no PCI was estimated using polychotomous regression. All analyses were performed using SAS® statistical software version 9.1 (SAS Institute Inc., Cary, NC, USA).

**Table 1 Baseline demographic and clinical characteristics**

<table>
<thead>
<tr>
<th></th>
<th>HIV-infected group (n = 103)</th>
<th>HIV-uninfected group (n = 195)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>48 ± 9.1</td>
<td>50 ± 9.5</td>
<td>–</td>
</tr>
<tr>
<td>Men</td>
<td>96 (93)</td>
<td>184 (94)</td>
<td>–</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22 ± 3.1</td>
<td>27 ± 4.7</td>
<td>&lt;0.0001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Current smoker</td>
<td>61 (59)</td>
<td>125 (64)</td>
<td>0.44&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Illicit drug use</td>
<td>23 (23)</td>
<td>12 (6)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cocaine use</td>
<td>5 (5)</td>
<td>4 (2)</td>
<td>0.19&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>41 (45)</td>
<td>84 (46)</td>
<td>0.62&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypertriglyceridaemia</td>
<td>63 (66)</td>
<td>79 (44)</td>
<td>&lt;0.01&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Family history of premature coronary artery disease</td>
<td>21 (20)</td>
<td>52 (27)</td>
<td>0.26&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (18)</td>
<td>47 (24)</td>
<td>0.31&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (9)</td>
<td>23 (12)</td>
<td>0.62&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>GRACE risk score</td>
<td>82 ± 18</td>
<td>85 ± 19</td>
<td>0.18&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>ST-segment elevation myocardial infarction</td>
<td>50 (49)</td>
<td>109 (56)</td>
<td>–</td>
</tr>
<tr>
<td>Troponin I, ng/mL</td>
<td>27 (9.4–76)</td>
<td>43 (17–84)</td>
<td>0.49&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Non-ST-segment elevation myocardial infarction</td>
<td>21 (20)</td>
<td>41 (21)</td>
<td>–</td>
</tr>
<tr>
<td>Troponin I, ng/mL</td>
<td>8.4 (1.3–18)</td>
<td>8.4 (2.3–22)</td>
<td>0.56&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>32 (31)</td>
<td>45 (23)</td>
<td>–</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>54 ± 12</td>
<td>54 ± 10</td>
<td>0.52&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values expressed as n (%), mean ± standard deviation, or median (interquartile range).

<sup>a</sup>Wilcoxon matched-pair signed-rank test.

<sup>b</sup>Univariate conditional logistic regression.
Results

Baseline characteristics

A total of 113 HIV-infected patients and 207 HIV-uninfected patients hospitalized with a first episode of ACS were enrolled. Ten HIV-infected patients (two with prior myocardial infarction, two with prior stroke, one with initial cardiogenic shock, and five with impossible long-term follow-up due to life-threatening illness: end-stage hepatic disease in three and end-stage neurological disease for two) and 12 HIV-uninfected patients (two with prior stroke, one with prior myocardial infarction, one with pericarditis, two with no HIV status available, and six who did not match the HIV-infected case) were excluded because either they did not fulfill the inclusion criteria or could not be matched. Patient demographics and coronary risk factors are given in Table 1. The mean age of the cohort was 49 ± 9.4 years; 94% were men, with a high rate of current smokers (63%) and hypercholesterolaemia (46%). Cardiovascular risk factors were well balanced. However, HIV-infected patients showed a higher rate of known hypertriglyceridaemia and illicit drug use compared with HIV-uninfected patients. Among illicit drug users, the frequency of cocaine use was not significantly different between HIV-infected and HIV-uninfected patients (P = 0.19). The consumption of two or more glasses of wine per day did not differ (13 vs. 17%, P = 0.39). The number and distribution of coronary risk factors were not significantly different between the two groups, with 57% of the entire cohort with more than one risk factor. Chronic use of statins (11 vs. 13%, P = 0.38), fibrates (5 vs. 4%, P = 0.65), and aspirin (4 vs. 4%, P = 0.94) before admission was rare, and did not differ between HIV-infected and HIV-uninfected groups. Electrocardiographic findings at admission did not differ, with the same rate of anterior and inferior STEMI s in HIV-infected and uninfected patients (anterior, 44 vs. 29%; inferior, 44 vs. 68%, respectively, P = 0.70).

Biological parameters

Fasting serum lipid parameters and other biochemical variables are presented in Table 2. Of note, although HDL-cholesterol concentrations were not different between groups and were within the normal range, the mean levels were low. The number of patients with renal insufficiency (creatinine clearance <60 mL/min) was higher in the HIV-infected group [n = 12 (12%) vs. 8 (4%), P = 0.01]. The HIV-infected group had a long history of HIV infection and duration of treatment, with a lengthy exposure to NRTIs and PIs (Table 3). At admission, 93% was receiving cART; 88% receiving NRTIs, 70% PIs, and 36% NNRTIs. Twenty-one HIV-infected patients were co-infected with hepatitis C virus (21%) and 9 (9%) with hepatitis B virus. Fifty (49%) HIV-infected patients had a history of opportunistic infection and 49 (48%) had clinical lipodystrophy syndrome (79% lipoatrophic, 4% lipohypertrophic, 17% both).

Angiographic and revascularization features

Almost all patients underwent coronary angiography, with the exception of two HIV-infected patients. The extent and severity of angiographic CAD did not differ between groups (Table 4). Multivessel disease was present in 41 (41%) HIV-infected and in 76 (39%); P = 0.96) HIV-uninfected patients. One patient in each group had a strictly normal coronary angiogram; two HIV-infected and three HIV-uninfected patients had no significant atheromatous coronary lesions (stenosis <50%). Twenty-five (16%) patients received thrombolysis, pre-hospital in 70% (n = 17) of the cases. The rate of TIMI 3 flow grade for STEMI before PCI was higher in HIV-infected vs. HIV-uninfected patients (49 vs. 24%, P = 0.04), with no difference in rates of pre-hospital thrombolysis between groups (8% in HIV-infected vs. 12% in HIV-uninfected, P = 0.40) and in post-PCI TIMI flow. The rate of coronary artery bypass surgery was 4% in HIV-infected patients and 3% in HIV-uninfected patients (P = 0.77).

In-hospital events

In-hospital course and use of discharge medications did not differ between groups. In the entire cohort, the rate of cardiac events during the index hospitalization was low, with two myocardial

<table>
<thead>
<tr>
<th>Table 2 Baseline biological parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV-infected</strong></td>
</tr>
<tr>
<td>group (n = 103)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
</tr>
<tr>
<td>Total cholesterol/HDL cholesterol ratio</td>
</tr>
<tr>
<td>Non-high-density lipoprotein cholesterol, mg/dL</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
</tr>
<tr>
<td>White blood cell count, 10⁶</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
</tr>
</tbody>
</table>

Values expressed as mean ± standard deviation unless otherwise specified.

aWilcoxon matched-pair signed-rank test.
re-infarctions (HIV-infected group), seven patients with acute congestive heart failure (two HIV-infected, five HIV-uninfected), and three with cardiogenic shock (one HIV-infected, two HIV-uninfected). The use of evidence-based discharge medications was high, with similar rates of prescription of beta-blockers (84 vs. 88%, \( P = 0.35 \)), renin–angiotensin system blockers (56 vs. 61%, \( P = 0.66 \)), and statins (89 vs. 92%, \( P = 0.51 \)) in HIV-infected vs. HIV-uninfected patients, respectively. The use of dual antiplatelet drugs was lower in HIV-infected patients, but the difference was not statistically significant (72 vs. 81%, \( P = 0.07 \)), and was due primarily to a lower rate of PCI (76 vs. 88%, \( P = 0.03 \)) in this group. One acute stent thrombosis occurred at Day 5 in an HIV-infected patient and another at Day 1 in an HIV-uninfected patient.

### One-year clinical outcome

The median follow-up of the entire cohort was 12 months (interquartile range, 12–12). Only three patients were lost to follow-up. The rate of decreased left ventricular ejection fraction (≤35%) was not different between the HIV-infected and HIV-uninfected groups during the index hospitalization and at 1-year follow-up (5 vs. 8%, \( P = 0.35 \) and 7 vs. 8%, \( P = 0.99 \), respectively). Rates of MACCE are reported in Table 5. Ten HIV-infected patients and 18 HIV-uninfected patients had a MACCE, with no statistically significant difference between the groups (HR 1.4, 95% CI 0.6–3.0). Nine HIV-infected and five HIV-uninfected patients had a recurrent ACS (HR 6.5, 95% CI 1.7–23.9). Six patients had unstable angina and three had STEMI in the HIV-infected group; four had an unstable angina and one had STEMI in the HIV-uninfected group. Clinical restenosis (TLR) was found in seven HIV-infected patients and in 11 HIV-uninfected patients (HR 1.4, 95% CI 0.5–3.8), in line with the rate of TVR (HR 1.6, 95% CI 0.6–4.3). Figure 1 shows the Kaplan–Meier curves of MACCE-event probability for the two groups, and Figure 2 for recurrent ACS-event probability. The OR for urgent PCI was higher in the HIV-infected group compared with the HIV-uninfected group (OR 3.29, 95% CI 0.94–11.53, \( P = 0.06 \)) and was non-significantly lower for non-urgent PCI (OR 0.47, 95% CI 0.17–1.29, \( P = 0.14 \)). The use of stress testing after the index ACS at 1-year follow-up was less frequent in the HIV-infected group compared with the HIV-uninfected group (63
No cases of late stent thrombosis were reported during the first year of follow-up. When considering traditional risk factors, after 1 year, the rate of tobacco cessation was lower in HIV-infected patients compared with HIV-uninfected patients (51 vs. 80%, \( P = 0.002 \)). At 1 year, four HIV-infected and no HIV-uninfected patients had an episode of congestive heart failure that required urgent hospitalization.

### Table 5  Major adverse cardiac and cerebral events at 12-month follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>HIV-infected group (n = 103)</th>
<th>HIV-uninfected group (n = 195)</th>
<th>Hazard ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse cardiac and cerebral events</td>
<td>10 (10)(^b)</td>
<td>18 (9)(^b)</td>
<td>1.4 (0.6–3.0)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Recurrent acute coronary syndrome</td>
<td>9 (9)(^b)</td>
<td>5 (3)(^b)</td>
<td>6.5 (1.7–23.9)</td>
</tr>
<tr>
<td>Recurrent coronary revascularization</td>
<td>9 (9)(^b)</td>
<td>15 (8)(^b)</td>
<td>1.4 (0.6–3.2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>7 (9)(^b)</td>
<td>11 (7)(^b)</td>
<td>1.4 (0.5–3.8)</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>8 (10)(^b)</td>
<td>12 (7)(^b)</td>
<td>1.6 (0.6–4.3)</td>
</tr>
</tbody>
</table>

Values expressed as \( n \) (%).
\(^a\)Estimated from a stratified univariate Cox model.
\(^b\)Kaplan–Meier estimations.

![Figure 1](image.png)  Kaplan–Meier estimations of MACCE-event probability according to HIV status. Asterisk denotes a stratified Cox analysis taking into account for matching.

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**Discussion**

In this prospective multicentre study of HIV-infected patients with a first episode of ACS, compared with HIV-uninfected patients matched for age, sex, and type of ACS at admission, traditional coronary risk factors and angiographic parameters did not differ between the two populations, with the exception of hypertriglyceridaemia and use of illicit drugs, which were more frequent among HIV-infected patients. After 12 months, whereas the
Overall rate of MACCE did not differ between the two populations, recurrent ACS and urgent PCI were more frequent in HIV-infected patients, without an increased rate of clinical restenosis.

Previous studies of HIV-infected patients with ACS found that these individuals were younger, more often male, and smokers compared with HIV-uninfected patients. Our data concur with these findings: the mean age of first occurrence of ACS in HIV-infected patients was <50 years, the subjects were predominantly men, and current smoking was the most prevalent coronary risk factor. However, only two of the previous studies included an HIV-uninfected group and only one study matched the HIV-uninfected group for age. In contrast with Hsue et al., we report the same high prevalence of current smokers in both groups exposed or not to HIV infection, because the HIV-uninfected group was matched for age. We also report a much higher proportion of HIV-infected patients using illicit drugs compared with HIV-uninfected patients (23 vs. 6%, \( P < 0.001 \)). In previous studies, the rate of illicit drug use may have been underestimated due to the use of information from databases or from self-report.

HIV infection and antiretroviral therapy can cause lipid disturbances. At admission, fasting triglyceride concentrations were higher in HIV-infected patients vs. HIV-uninfected patients, while other lipid parameters were not statistically significantly different, with a low HDL-cholesterol concentration within the normal range in both groups. This finding contrasts with data from the two studies that included a HIV-uninfected group, in which HIV-infected patients had lower HDL-cholesterol concentrations than HIV-uninfected patients (mean < 35 mg/dL in the HIV-infected group). Again, this difference may be explained by the inclusion of an age-matched HIV-uninfected group in our study, and by the difference in the immune status of our HIV-infected patients compared with those in the previous studies (median CD4 cell count 462 per mm\(^3\) in the present study vs. <340 per mm\(^3\) in the others). This could also be explained by the lower number of HIV-infected patients receiving CART at the time of onset of their ACS in those studies: 53% in Hsue et al.’s study compared with 93% in the present study. Uncontrolled HIV disease has an impact on HDL-cholesterol metabolism along with acute or chronic dysimmunity, which could accelerate atherothrombosis and may explain the higher rate of restenosis reported in other studies.

In the present study, the angiographic findings did not differ between the two groups. In particular, there was no difference in terms of extension and severity of CAD. In accordance with previous studies, the most frequent type of ACS was STEMI, and single-vessel disease was predominant, as expected in young patients with an ACS. When considering the two studies that included an HIV-uninfected comparison group and the present study, similar results concerning the extent and severity of CAD and the immediate outcome were found between HIV-infected and HIV-uninfected patients. We showed that PCI can be performed safely during the acute phase of ACS in HIV-infected patients, without a higher risk of acute or late stent thrombosis and no increased risk of TVR or TLR. This result may be explained by the high rate of PCI and stenting in our study; 93% of the entire cohort who underwent PCI had stenting (34%...
with drug-eluting stents), which is higher than in previous studies.\textsuperscript{11–12,15} Matetzky et al.\textsuperscript{12} first reported a statistically significantly higher rate of TVR in HIV-infected vs. HIV-uninfected patients (43 vs. 11%, respectively, \( P = 0.02 \)). In this study, HIV-infected patients were at high risk of recurrent ischaemic events because patients with previous ACS, coronary artery bypass graft surgery, or PCI were included. The rate of previous PCI was higher in the HIV-infected group compared with the HIV-uninfected group (42 vs. 17%, \( P = 0.04 \)). In contrast, in the present study, only patients with de novo ACS were included, and those with previous ACS, coronary artery bypass surgery, or PCI were excluded. A relatively high rate of repeat coronary revascularization was also reported by Escaut et al.,\textsuperscript{11} who observed a 21% rate of TLR at 36 months among 14 HIV-infected patients who underwent PCI. Similarly, Segev et al.\textsuperscript{17} reported a 42% rate of clinical restenosis in 12 HIV-infected patients undergoing PCI after 16-month follow-up, but with no control group. In Hsue et al.’s study,\textsuperscript{15} no significant difference was observed in terms of clinical restenosis between the subgroup of HIV-infected and HIV-uninfected patients with stents [11/22 (50%) vs. 2/11 (18%), \( P = 0.078 \)].

Regarding the mid-term prognosis of ACS, we found similar results to Matetzky et al.\textsuperscript{12} (15-month follow-up), with a higher rate of recurrent ACS (HR 4.6, 95% CI 1.4–15.0) in HIV-infected vs. HIV-uninfected patients, with no increase in the rate of MACCE or clinical restenosis.

In the present study, why recurrent ACS and urgent PCI should be more frequent in HIV-infected patients when the baseline angiographic characteristics and the initial management of ACS were similar to age-matched HIV-uninfected patients is unclear. Cardiovascular risk in HIV-infected patients is not fully explained by traditional risk factors. HIV infection by itself, and antiretroviral therapy associated with chronic inflammation, could increase the risk of plaque rupture and atherothrombosis.\textsuperscript{3,25} Meanwhile, routine secondary prevention does not take into account this challenge. However, secondary prevention in HIV-infected patients should focus primarily on tobacco cessation and achieving LDL goals, as these objectives were less frequently achieved in HIV-infected patients compared with HIV-uninfected patients at 1-year follow-up in the present study. This may account for the increased recurrence of ACS and related urgent PCI observed in our study, but it does not result in an increased risk of MACCE and clinical restenosis. This could be in part explained by the lack of difference in terms of recurrent coronary revascularization during follow-up in both groups. The definition of recurrent coronary revascularization used in our study included both urgent and non-urgent PCIs. We found that recurrent PCI was driven predominantly by recurrent ACS (90%) in the HIV-infected group (in relation to the higher rate of urgent PCI), and in contrast by silent ischaemia (70%) in the HIV-uninfected group (related to the higher rate of non-urgent PCI). The higher rate of recurrent revascularization guided by silent ischaemia in the HIV-uninfected group could be in part explained by the higher use of stress testing found in HIV-uninfected patients compared with HIV-infected patients. This discrepancy could be due to a lesser need for a non-invasive procedure in HIV-infected patients, due to the unknown prognosis of the HIV disease itself, and therefore less aggressive management by the cardiologist.

Our results should be interpreted in the light of several considerations. First, the lack of difference in the rates of MACCE could be explained by the fact that this was a mid-term evaluation (1-year follow-up); however, clinical restenosis, stent thrombosis, and recurrent ACS most commonly occur during the first year after the index ACS. In addition, screening of silent myocardial ischaemia was lower in the HIV-infected group, which could have led to a lower rate of non-urgent coronary revascularization and hence to the strikingly similar rate of MACCE, although this group had a higher rate of recurrent ACS and urgent PCI. Second, the use of cardiac medications was not controlled during the study; however, the results obtained for the occurrence of clinical events during follow-up did not take into account the use of cardiac therapies. Finally, the biological parameters were not centralized and were determined locally; however, both HIV-infected patients and their two matched HIV-uninfected patients were enrolled in the same centre. Nevertheless, this is the largest study performed to date, with multicentre enrolment and a pre-specified HIV-uninfected group matched for age, sex, and type of ACS, and with scheduled follow-up, limiting selection bias between the two groups.

**Conclusions**

This prospective, multicentre study shows that HIV-infected patients do not differ from age-matched HIV-uninfected patients in terms of traditional coronary risk factors and angiographic characteristics after a first episode of ACS, except for a higher rate of illicit drug use and hypertriglyceridaemia in HIV-infected patients. Percutaneous coronary intervention can be performed safely and with excellent mid-term results. However, recurrent ACS and urgent PCI were more frequent in HIV-infected patients, with no difference in the rates of MACCE and clinical restenosis at 1-year follow-up. This suggests that the coronary risk of HIV-infected patients is not fully addressed by conventional secondary prevention measures and that more aggressive preventive measures and/or specifically targeted treatments may be required to alleviate this risk.

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Appendix
Cardiologic centres and investigators

Infectious disease contributors

References


