Cardiovascular disease, and particularly coronary heart disease, is an emerging area of concern in the HIV population. Since the advent of efficient antiretroviral therapies and the consequent longer patient life span, an increased risk for myocardial infarction has been observed in HIV-infected patients compared with the general population in Western countries. The pathophysiology of this accelerated atherosclerotic process is complex and multifactorial. Traditional cardiovascular risk factors—overrepresented in the HIV population—associated with uncontrolled viral replication and exposure to antiretroviral drugs (per se or through lipid and glucose disturbances) could promote acute ischemic events. Thus, despite successful antiviral therapy, numerous studies suggest a role of chronic inflammation, together with immune activation, that could lead to vascular dysfunction and atherothrombosis. It is time for physicians to prevent coronary heart disease in this high-risk population through the use of tools employed in the general population. Moreover, the lower median age at which acute coronary syndromes occur in HIV-infected patients should shift prevention to include patients <45 years of age. Available cardiovascular risk scores in the general population usually fail to screen young patients at risk for myocardial infarction. Moreover, the novel vascular risk factors identified in HIV-related atherosclerosis, such as chronic inflammation, immune activation, and some antiretroviral agents, are not taken into account in the available risk scores, leading to underestimation of cardiovascular risk in the HIV population. Cardiovascular prevention in HIV-infected patients is a challenge for both cardiologists and physicians involved in HIV care. We require new tools to assess this higher risk and studies to determine whether intensive primary prevention is warranted. (J Am Coll Cardiol 2013;61:511–23) © 2013 by the American College of Cardiology Foundation

An association between HIV infection, antiretroviral therapy (ART), and coronary heart disease (CHD) has been reported in several studies in recent years (1–4). HIV infection has become a chronic disease in countries in which effective combination ART (cART) has been available since the mid-1990s. Over the same period, an increasing number of reports have been published on the occurrence of acute coronary syndromes (ACS) in this population, in those age <50 years. This article discusses the current understanding of the interaction between HIV infection, immune activation, antiretroviral drugs, conventional risk factors, and CHD. Several key areas of importance to cardiologists in the management of patients with HIV infection and CHD are addressed:

- Is CHD more prevalent, and does it occur prematurely, in the HIV population compared to the general population?
- Does cART affect the risk for CHD?
- Is the pathophysiology of CHD in the HIV-infected population similar to that in the general population?
- What are the clinical and angiographic presentations of CHD in the HIV-infected population?
- Is the prognosis of CHD different in HIV-infected patients?
- Can CHD be prevented in patients infected with HIV?

Epidemiology

As a consequence of cART, the spectrum of diseases related to HIV has shifted in Western countries from opportunistic AIDS-related diseases toward long-term age-related complications, including cardiometabolic alterations and cancers.
Recent reports have shown that cardiovascular deaths accounted for 6.5% of total deaths in a large observational cohort of HIV-infected patients from Europe and North America, for 8% of deaths among HIV-infected people in France, and for 15% of deaths in a North American HIV outpatient study (5–7).

Prevalence and incidence of CHD. Data from 2 observational studies show that, compared to the general population, HIV-infected patients have a higher rate of CHD (defined as myocardial infarction [MI]) (2,8). In the French Hospital Database on HIV (FHDH), compared to the general population and irrespective of age class, the standardized mortality ratio was 1.5 in HIV-infected men and women (1.4 for men and 2.7 for women) (2), and in a North American cohort, the risk ratio was 1.7 (8). In several cohorts from published studies, the mean age at which MI occurred in HIV-infected patients was around 48 years, far less than that reported in the general population. However, the median age of the HIV population is also far less than that of the general population, leading to a younger age at diagnosis of MI. This prematurity, if any, could be due to an acceleration of atherosclerosis by HIV and/or an earlier exposure to conventional cardiovascular risk factors.

Impact of cART on CHD. Although it is now clearly established that cART is linked to metabolic disorders, the long-term impact of these conditions remains the subject of discussion. cART is currently defined as any combination of 3 antiretroviral drugs, usually 2 nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI), or a non-nucleoside reverse transcriptase inhibitor (NNRTI) and an integrase inhibitor. The first signs of an increased risk for CHD possibly related to PIs appeared in 1998, with the publication of reports of MI occurring in young HIV-infected patients treated with PIs and associated with raised concentrations of cholesterol (9–12). Thereafter, some (3,13–20), but not all (21–23), studies have shown a link between the risk for CHD and exposure to PIs (Table 1). Although a number of these studies had methodologic limitations, the 2 most important and recent observational cohorts (3,20) with a sufficient duration of exposure to PIs showed that the duration of exposure was associated with an increased risk for MI. This was the case for cumulative exposure to any PI (except for saquinavir) (odds ratio: 1.15 per year; 95% confidence interval [CI]: 1.06 to 1.26) in the FHDH study (3) and for indinavir or lopinavir/ritonavir (relative risk [RR] [95% CI] per additional year: 1.12 [1.07 to 1.18] and 1.13 [1.05 to 1.21], respectively) but neither for saquinavir nor nelfinavir in the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study (20). No conclusive data are available on atazanavir or darunavir. After adjustment for lipid concentrations, the impact of these PIs (indinavir, lopinavir, ritonavir) remained significant. This finding may support the direct impact of PIs, independent of lipid-induced abnormalities, on the risk for MI. Moreover, the rate of MI associated with PI exposure changed little, regardless of whether the effects of PIs were boosted with ritonavir (3,20). However, the PI risk–benefits ratio remains positive, as the increase in life expectancy conferred by cART far outweighs the associated risk for MI. Law et al. (24) calculated that the 3-year risk for MI increased from 0.30% (95% CI: 0.20% to 0.38%) in antiretroviral-naïve patients to 1.07% (95% CI: 0.43% to 1.77%) in patients receiving antiretroviral agents from all 3 classes. In this publication, the estimated 3-year risk for AIDS or death was between 6.2% and 11.1% among ART-treated patients staying on treatment, rising to between 22.5% and 29.4% when they ceased taking ART. Neither the FHDH nor the D:A:D study found any significant association between the development of MI and cumulative exposure to an NNRTI (efavirenz or nevirapine).

Regarding NRTIs, the D:A:D study (20) found an association between cumulative and recent exposure to abacavir and an increased risk for MI (RR [95% CI]: 1.07 [1.00 to 1.14] and 1.70 [1.17 to 2.47], respectively), whereas the FHDH study (3) did not find any causal relationship because the observed association with short-term or recent exposure to abacavir was unstable in sensitivity analyses. Recent exposure to didanosine was associated with an increased risk for MI in the D:A:D study (RR: 1.41; 95% CI: 1.09 to 1.82), but not in the FHDH study. Three meta-analyses (25–27) and a retrospective study from the Veterans’ cohort (28) showed no significant association between abacavir use and MI. In contrast, a retrospective study nested in the Canadian public health insurance database showed an increased risk for MI in the HIV population compared with the general population, and that exposure to abacavir was associated with an increased risk for MI (29). These differences can be explained by the presence of confounding factors, such as smoking, kidney function, cocaine and/or intravenous drug use, and potential selection biases. Therefore, at present it is not possible to draw any conclusions regarding a causal relationship between treatment with abacavir and the risk for developing MI (30).

Cardiovascular Risk Factors

Patients infected with HIV are at higher calculated risk for CHD compared with the general population of the same age (31,32). Typically, compared with age-related controls, HIV-infected patients exhibit higher rates of conventional risk factors such as smoking (32), dyslipidemia (31,33),...
hypertension (34,35), and insulin resistance or diabetes mellitus (16,33–34,36). Conventional cardiovascular risk equations do not take into account emerging cardiovascular risk factors such as inflammation (37,38), immune activation (39–41), coagulation disorders (42,43), kidney disease (44), HIV itself (45), and cART that have been associated with the increased risk of MI or atherosclerosis in HIV-infected patients. Cocaine use, may increase the risk for ACS, is relatively common among HIV-infected patients, particularly in North America, and consumption is increasing in Europe (46). Renal function and albuminuria have also been strongly associated with the risk for MI in HIV-infected patients (44). All of these cardiovascular risk factors are interconnected and synergistic, leading to difficulties in analyzing the specific role of each, particularly the impact of HIV itself and of cART. Recently, the D:A:D study group developed a risk-assessment tool tailored to HIV-infected patients and incorporating exposure to PIs and NRTIs (47).

Importantly, cardiovascular risk should also be evaluated in HIV-infected children because vertically infected individuals have been exposed long-term to both HIV and cART. A risk for cardiomyopathy has been described in HIV-infected children exposed to HIV and/or cART from HIV-infected mothers, and in uninfected children of HIV-infected mothers exposed to ART (48–50). The presence of dyslipidemia, chronic inflammation, and subclinical atherosclerosis has been reported in HIV-infected children (51,52). Indeed, a recent study using magnetic resonance angiography suggested possible early coronary atherosclerosis in HIV-infected children (53). Moreover, the risk for premature atherosclerosis in adulthood among HIV-infected children requires further investigation to develop accurate strategies of prevention.

Pathophysiology

The pathophysiology of CHD in HIV-infected patients is complex, combining both conventional vascular risk factors and emerging risk factors. The effects of HIV infection in cART-naïve patients and in cART-treated patients should be considered separately. Many factors associated with the risk for CAD in HIV-infected patients have been determined in several studies by association or indirectly and therefore lead to hypothetic and speculative explanation for the moment.

HIV infection and risk for CHD in treatment-naïve patients. Recently, Baker and Lundgren (4) reviewed the potential impact of HIV infection on the cardiovascular system in untreated HIV-infected patients. They suggested that HIV infection could promote atherosclerosis through mechanisms related to immune activation, chronic inflammation, coagulation disorders, and/or lipid disturbances (Fig. 1). The SMART (Strategies for Management of Antiretroviral Therapy) study (45) was designed to assess an HIV treatment strategy of continuous compared with episodic ART guided by CD4+ count. That study indirectly highlighted the role of HIV replication and dysimmunity after the cessation of ART in the increased risk for MI. In fact, in the patients on episodic ART, the risk for major cardiovascular events was greater than in the group on continuous therapy (hazard ratio [HR] for major cardiovascular, renal, or hepatic disease: 1.7 [95% CI: 1.1 to 2.5; p = 0.009]; HR for fatal or nonfatal cardiovascular disease: 1.6 [95% CI: 1.0 to 2.5; p = 0.05]).

Enhanced endothelial injury (Fig. 1) due to adhesion molecules (54), HIV Tat protein, and related angiogenic effects (55) has been shown. Direct HIV infection could also stimulate proliferation of human vascular smooth muscle cells and therefore promote atherosclerosis (56). HIV infection could lead to coagulation disorders (a “prothrombic state”) associated with increased concentrations of D dimer, fibrinogen, factor VII, von Willebrand and tissue factors, and abnormal platelet reactivity (43,55). Finally, HIV alone, independent of cART, is associated with known atherogenic dyslipidemia associated with increased concentrations of triglycerides (impaired lipase activity) and decreased concentrations of high-density lipoprotein cholesterol correlated with a higher concentration of cytokines (57).

Antiretroviral agents and risk for CHD. In cART-treated HIV-infected patients, immune activation and low-grade chronic inflammation may promote atherosclerosis (Fig. 1). Whether the inflammatory balance and/or immune activation participates in atherosclerosis acceleration remains debated and speculated (39,58). However, the roles played by chronic immune activation and inflammation in HIV pathogenesis have become increasingly apparent and are associated with pathologies linked with aging and so-called “inflammaging,” such as bone demineralization, CHD, cancer, and immune senescence (59). Chronic inflammation has been associated with an increased risk for death (37,60,61). Immune activation can promote atherosclerosis and increased arterial stiffness in the absence of residual viral replication (62–66). Whether the control of immune activation could decrease accelerated atherosclerosis in HIV-infected patients remains to be determined. Finally, increased intestinal bacterial translocation associated with immune activation and its impact on atherosclerosis warrants further investigation (67).

Whether cART, and in particular PIs, increases the risk for CHD has been extensively debated over the past decade (68,69) (see previous discussion). The impact of cART on lipid and glucose metabolism via adipocyte dysfunction leading to a lipodystrophy syndrome (Fig. 1) has been demonstrated both in vitro and in vivo in HIV-infected patients (33,36,70). The potential metabolic effects and proatherogenic effects of each class of antiretroviral agents are depicted in Table 2 (data should be interpreted with caution because the metabolic impact of these different drugs has not been compared directly). These effects vary from one drug to another, and are associated with other risk factors such as environmental and genetic factors (71).
<table>
<thead>
<tr>
<th>First Author</th>
<th>Year (Ref. #)</th>
<th>Design</th>
<th>Events Studied</th>
<th>Period</th>
<th>n py</th>
<th>Coronary Events</th>
<th>ART-Exposed Patients; py</th>
<th>Duration of Follow-Up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friis-Moller et al.</td>
<td>2007 (1)</td>
<td>Specifically designed cohort; validation of cases</td>
<td>MI</td>
<td>1999–2005</td>
<td>23,437</td>
<td>345</td>
<td>150,758 py</td>
<td>83 months (median)</td>
<td>RR: 1.16 (95% CI: 1.09–1.23) per year of cART exposure; RR: 1.16 (95% CI: 1.10–1.23) per year of PI exposure; RR: 1.05 (95% CI: 0.98–1.13) per year of NNRTI exposure</td>
</tr>
<tr>
<td>Lang et al.</td>
<td>2010 (3)</td>
<td>Case-control study nested in database</td>
<td>MI</td>
<td>2000–2006</td>
<td>74,958</td>
<td>289 vs. 884 controls</td>
<td>94%</td>
<td>79 vs. 84 months</td>
<td>MI incidence: 1.24/1,000 PY; OR cumulative exposure to PI (except saquinavir): 1.53 (95% CI: 1.21–1.94) per year; RR recent exposure to abacavir not significantly increased when taking into account cocaine and IV drug use (OR: 1.27; 95% CI: 0.60–2.49)</td>
</tr>
<tr>
<td>Jütte et al.</td>
<td>1999 (13)</td>
<td>Database on medical records; no validation of cases</td>
<td>MI</td>
<td>1990–1998</td>
<td>1,324</td>
<td>8</td>
<td>469</td>
<td>10 months (median)</td>
<td>Incidence: 2.1/1,000 PY in non-PI-treated patients vs. 10.6/1,000 PY in PI-treated patients</td>
</tr>
<tr>
<td>Rickerts et al.</td>
<td>2000 (14)</td>
<td>Database on medical records; validation of cases</td>
<td>MI</td>
<td>1983–1998</td>
<td>4,993</td>
<td>29</td>
<td>NR</td>
<td>49 months (mean)</td>
<td>OR: 2.61 (95% CI: 1.19–5.66) cART vs. no cART</td>
</tr>
<tr>
<td>Holmberg et al.</td>
<td>2002 (15)</td>
<td>Database on medical records; validation of cases</td>
<td>MI</td>
<td>1993–2002</td>
<td>5,672</td>
<td>21</td>
<td>3,247</td>
<td>Higher risk for PI vs. non-PI; HR: 6.5 (95% CI: 0.9–47.8)</td>
<td></td>
</tr>
<tr>
<td>Friis-Moller et al.</td>
<td>2003 (16)</td>
<td>Specifically designed cohort; validation of cases</td>
<td>MI</td>
<td>1999–2002</td>
<td>23,468</td>
<td>126</td>
<td>17,484 py</td>
<td>22 months (median)</td>
<td>RR: 1.26 (95% CI 1.12–1.41) per year of cART exposure</td>
</tr>
<tr>
<td>Mary-Krause et al.</td>
<td>2003 (17)</td>
<td>Database on medical records; validation of cases</td>
<td>MI</td>
<td>1996–1999</td>
<td>34,976 men</td>
<td>60 (49 treated with PI)</td>
<td>21,906 39,023 py</td>
<td>34 months (median)</td>
<td>Higher risk for ≥30 vs. &lt;18 months of PI exposure; SMR: 3.6 (95% CI: 1.8–6.2)</td>
</tr>
<tr>
<td>D'Arminio Monforte et al.</td>
<td>2004 (18)</td>
<td>Specifically designed cohort; validation of cases</td>
<td>CCVE</td>
<td>1999–2002</td>
<td>36,145</td>
<td>CCVE: 207 Mt: 126</td>
<td>NR</td>
<td>RR: 1.26 (95% CI: 1.14–1.38) per year of cART exposure</td>
<td></td>
</tr>
<tr>
<td>Obel et al.</td>
<td>2007 (19)</td>
<td>Database on medical records; no validation of cases</td>
<td>Ischemic CVD</td>
<td>1995–2004</td>
<td>In non-cART period: 9,271 py vs. 1,272,956 py; in CVD period: 13,593 py vs. 1,389,722 py</td>
<td>Before cART initiation: 14 vs. 1,946; after cART initiation: 57 vs. 2.617</td>
<td>13,593 py vs. 1,389,722 py</td>
<td>After cART initiation, the increased risk became substantially higher: RR: 2.12 (95% CI: 1.62–2.76); RR did not further increase in the initial 8 yrs of cART</td>
<td></td>
</tr>
<tr>
<td>Worm et al.</td>
<td>2010 (20)</td>
<td>Specifically designed cohort; validation of cases</td>
<td>MI</td>
<td>1999–2008</td>
<td>33,308</td>
<td>580</td>
<td>NR</td>
<td>NR</td>
<td>MI incidence: 3.2/1,000 PY (95% CI: 3.0–3.5); RR cumulative exposure to IDV and LPV/RTV: 1.12 (95% CI: 1.07–1.18) and 1.13 (95% CI: 1.05–1.21), respectively; RR recent exposure to abacavir and didanosine: 1.70 (95% CI: 1.17–2.47) and 1.41 (95% CI: 1.09–1.82), respectively</td>
</tr>
</tbody>
</table>

Continued on next page
effects of PIs on high-density lipoprotein cholesterol concentrations, together with the proper effect of HIV itself on this lipoprotein, seem to play a crucial role in the increased risk for CHD in the HIV population, which is much higher than that related to the rise in triglyceride concentrations typically found in this context (72,73). PI-induced endothelial injury has been associated with dyslipidemia, oxidative stress, and senescence (74). In contrast, the AIDS Clinical Trials Group 5152 study showed that cART improved endothelial dysfunction in treatment-naive HIV-infected patients after 24 weeks of therapy (75). Therefore, the short-term and long-term adverse events with PIs may have a different impact on the risk for CHD. Recently, similar molecular pathophysiological mechanisms have been observed in cells from patients with the Hutchinson-Gilford syndrome (progeria) and treated with PIs in vitro (74,76). In fact, progeria is associated with premature aging and early CHD caused by the accumulation of progerin (truncated prelamin A). Aging of vascular smooth muscle cells is associated with the accumulation of prelamin A, leading to premature senescence (76). Importantly, some PIs boosted with ritonavir induce in vitro senescence of human fibroblast and endothelial cells as the result of prelamin A accumulation. Therefore, the authors speculate that premature aging and early CHD in HIV-infected patients could be partly caused by the acquired prelamin A accumulation.

Clinical Presentation

The spectrum of CHD in HIV-infected patients is similar to that in non–HIV-infected patients, with various clinical presentations including silent ischemia, stable angina, and ACS (unstable angina, non–ST-elevation MI and predominant ST-elevation MI). In HIV-infected patients, the presence of CHD is usually revealed by the occurrence of ACS. In published studies on ACS in HIV-infected patients (Table 3) (21,77–82), the typical patient is a young man (<50 years of age in >90% of cases) with a long known duration (>8 years) of HIV disease (however, this criterion is not accurate, as the duration of HIV seropositivity does not represent the duration of HIV infection, and therefore the nadir CD4 cell count could be used) who is taking cART (53% to 96%), generally including a PI (>59%); is a smoker (>45%); and is dyslipidemic (17% to 58%). In these studies, the most frequent presentation is ST-segment elevation MI (29% to 64%), followed by non–ST-segment elevation MI (20% to 48%) and unstable angina (18% to 46%). Men are affected predominantly, as in the general population, representing between 81% and 97% of the cohorts (21,77–82).

Studies on frequency, causes, and determinants of sudden death in HIV-infected patients are lacking. One mechanism of sudden death could be PI-induced ventricular fibrillation. In fact, whether HIV PIs induce QT prolongation is being discussed, but if this is the case, the impact does not appear to be clinically relevant (83,84).
Angiographic Features

The coronary angiographic features of CHD in HIV-infected patients have been reported in a number of studies that varied in terms of their design (cohort, case control, cross-sectional) and number of patients enrolled (16 to 103) (Table 4) (21, 77–82, 85–87). The extension of CHD is usually low; between 35% and 56% of patients had 1-vessel disease; 18% to 28%, 2-vessel disease; and 13% to 76%, 3-vessel disease. The percentage of patients with nonsignificant coronary stenosis (50%) when reported, is low (3% to 14%). Whether the angiographic features of CHD differ in the HIV-infected population compared with the uninfected population is not obvious (80–82, 86–87). Only Hsue et al. (81) observed that non–HIV-infected patients had more extensive disease compared with HIV-infected patients (number of diseased vessel 1.9 ± 1.2 vs. 1.3 ± 1; p = 0.007). However, the control group was not matched for age with the HIV-infected group. In the other studies (80, 82, 86, 87) with the specific angiographic comparison predefined and with age-matched control patients, no differences were found (Table 4). The primary method of revascularization reported in these publications on ACS is percutaneous coronary intervention (PCI) (25% to 76%), followed by coronary artery bypass grafting (CABG) (4% to 18%) and medical therapy alone (10% to 20%).

Prognosis With ACS and Coronary Revascularization

The prognosis of HIV-infected patients during the acute phase of ACS has been evaluated in a few studies (78–80, 82). The in-hospital mortality rate varied from 0% to 8%, and no differences in terms of heart failure and...
Table 2  Main Classes of Antiretrovirals and Their Impact on Lipid and Glucose Metabolism and CHD

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Adverse Metabolic Effects</th>
<th>Impact on CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>Dyslipidemia*; insulin resistance; variable with different drugs</td>
<td>Duration of exposure independently increased risk for MI</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Dyslipidemia + + +; insulin resistance + +</td>
<td>This drug is never used alone, but as a pharmacological booster in association with other PIs</td>
</tr>
<tr>
<td>洛托那韦+ 吉非替</td>
<td>Dyslipidemia + + +; insulin resistance +</td>
<td>Cumulative exposure independently increased risk for MI</td>
</tr>
<tr>
<td>Atazanavir + 吉非替</td>
<td>Dyslipidemia +; insulin resistance +</td>
<td>No data available (not enough patients exposed)</td>
</tr>
<tr>
<td>Darunavir + 吉非替</td>
<td>Dyslipidemia +; insulin resistance +</td>
<td>No data available (not enough patients exposed)</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Dyslipidemia; insulin resistance + + +</td>
<td>Controversial results</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Dyslipidemia +; insulin resistance +</td>
<td>No association with risk for MI</td>
</tr>
<tr>
<td>Amrenavir + 吉非替</td>
<td>Dyslipidemia +; insulin resistance +</td>
<td>No data available (not enough patients exposed)</td>
</tr>
<tr>
<td>Tiprenavir + 吉非替</td>
<td>Dyslipidemia + + +; insulin resistance +</td>
<td>No data available (not enough patients exposed)</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Dyslipidemia +; insulin resistance +</td>
<td>No association with risk for MI</td>
</tr>
<tr>
<td>NRTI</td>
<td>Insulin resistance + ( stavudine &gt; didavudine ); dyslipidemia with didanosine and stavudine</td>
<td>Two NRTIs (abacavir and didanosine) have been associated with increased risk for MI but controversial results</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Dyslipidemia variable with different drugs; efavirenz to a lesser extent than PIs; nevirapine mild dyslipidemia but with increased high-density lipoprotein cholesterol</td>
<td>No association with increased risk for MI</td>
</tr>
<tr>
<td>Other classes; maraviroc; raltegravir</td>
<td>No effects reported</td>
<td>No data available (not enough patients exposed)</td>
</tr>
</tbody>
</table>

*Dyslipidemia defined as increased total cholesterol, low-density lipoprotein cholesterol, triglycerides and decreased high-density lipoprotein cholesterol. Weak effect: + Weak effect. + + Important effect. NRTI = nucleoside reverse transcriptase inhibitors; other abbreviations as in Table 1.

Table 3  Spectrum of Cardiovascular Risk Factors in Several Studies Including HIV-Infected Patients With ACS

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>HIV Status Period Study Design</th>
<th>n</th>
<th>Age, yrs</th>
<th>Type of ACS</th>
<th>Nicotine Use</th>
<th>Cocaine Use</th>
<th>Premature Familial CHD</th>
<th>Hypertension</th>
<th>Diabetes Mellitus</th>
<th>Dyslipidemia</th>
<th>cART/PI; CD4 Cell Count, Cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>David et al. (21)</td>
<td>HIV + 1999–2000 Retrospective</td>
<td>16</td>
<td>43 (42–66)</td>
<td>STEMI 50; SA 50</td>
<td>81</td>
<td>63</td>
<td>31</td>
<td>63</td>
<td>13</td>
<td>50</td>
<td>69%/100%; Median: 234; nadir: 101</td>
</tr>
<tr>
<td>Escaut et al. (77)</td>
<td>HIV + 2003</td>
<td>17</td>
<td>46 ± 6</td>
<td>STEMI 64; UA 18; SA 18</td>
<td>71</td>
<td>0</td>
<td>12</td>
<td>35</td>
<td>24</td>
<td>40</td>
<td>94%/65%; Mean 272;</td>
</tr>
<tr>
<td>Varrile et al. (78)</td>
<td>HIV + 1998–2001 Prospective</td>
<td>29</td>
<td>46 ± 10</td>
<td>STEMI 52; NSTEMI 48</td>
<td>55</td>
<td>10</td>
<td>14</td>
<td>14</td>
<td>10</td>
<td>21</td>
<td>76%/66%; &gt;500: 62%</td>
</tr>
<tr>
<td>Ambrose et al. (79)</td>
<td>HIV + 1996–2000 Retrospective</td>
<td>51</td>
<td>48 ± 9</td>
<td>STEMI 36; UA 33; NSTEMI 31</td>
<td>55</td>
<td>8</td>
<td>45</td>
<td>29</td>
<td>12</td>
<td>48</td>
<td>NA/59%; Mean: 470</td>
</tr>
<tr>
<td>Matetzky et al. (80)</td>
<td>HIV + vs. HIV− 1998–2000</td>
<td>24 vs. 48</td>
<td>47 ± 9 vs. 48 ± 7</td>
<td>STEMI 58; NSTEMI 42; in the entire cohort</td>
<td>58 vs. 48* 0</td>
<td>50 vs. 44*</td>
<td>29 vs. 44*</td>
<td>12 vs. 19*</td>
<td>58 vs. 56*</td>
<td>92%/71%; Mean 318</td>
<td></td>
</tr>
<tr>
<td>Hsue et al. (81)</td>
<td>HIV + vs. HIV− 1993–2003 Database</td>
<td>68 vs. 68</td>
<td>50 ± 8 vs. 61 ± 11</td>
<td>UA 46; STEMI 29; NSTEMI 25; in the entire cohort</td>
<td>46 vs. 28†</td>
<td>NA</td>
<td>24 vs. 16*</td>
<td>36 vs. 41*</td>
<td>9 vs. 28*</td>
<td>17 vs. 28†</td>
<td>53%/92%; Median: 341; nadir: 113</td>
</tr>
<tr>
<td>Boccara et al. (82)</td>
<td>HIV + vs. HIV− 2003–2006 Prospective</td>
<td>103 vs. 195</td>
<td>48 ± 9 vs. 50 ± 9</td>
<td>STEMI 49; UA 31; NSTEMI 20; in the entire cohort</td>
<td>59 vs. 64* 5 vs. 2*</td>
<td>20 vs. 27*</td>
<td>18 vs. 24*</td>
<td>9 vs. 12*</td>
<td>45 vs. 46*</td>
<td>96%/83%; Median: 462; nadir: 123</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05, †p < 0.05
ACS = acute coronary syndromes; NA = not available; NSTEMI = non-ST-segment elevation myocardial infarction; SA = stable angina; STEMI = ST elevation myocardial infarction; UA = unstable angina; other abbreviations as in Table 1.
### Table 4  Angiographic and Revascularization Features of CHD in HIV-Infected Patients

<table>
<thead>
<tr>
<th>First Author Year (Ref. #)</th>
<th>Population</th>
<th>Age, yrs</th>
<th>Follow-Up, Months</th>
<th>Extent of CHD, %</th>
<th>No. of Diseased Vessels</th>
<th>Culprit Vessel, %</th>
<th>Revascularization, %</th>
<th>Clinical Restenosis Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>David 2002 (21)</strong></td>
<td>16 HIV+</td>
<td>43 (42–66)</td>
<td>No follow-up</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>68% PCI; 13% CABG; 19% Med</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Escaut 2003 (77)</strong></td>
<td>17 HIV+</td>
<td>46 ± 6</td>
<td>34 (12–64)</td>
<td>50% 1 VD</td>
<td>2.56</td>
<td>LAD 82%; LCA 41%; RCA 35%; LMD 6%</td>
<td>100% PCI</td>
<td>18% HIV+</td>
</tr>
<tr>
<td><strong>Varriale 2004 (78)</strong></td>
<td>29 HIV+</td>
<td>46/H11006</td>
<td>10 ND</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>35% PCI; 10% CABG</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Ambrose 2003 (79)</strong></td>
<td>51 HIV+</td>
<td>48/H11006</td>
<td>9 ND</td>
<td>47% 1 VD; 22% 2 VD; 20% 3 VD; 11% NSS</td>
<td>NR</td>
<td>NR</td>
<td>49% PCI; 18% CABG; 12% Med</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Matetzkiy 2003 (80)</strong></td>
<td>24 HIV-, 48 HIV+</td>
<td>47 ± 9</td>
<td>14.7 ± 8</td>
<td>76% ≥2 VD; 14% NSS</td>
<td>NR</td>
<td>NR</td>
<td>71% ATL; 13% CABG</td>
<td>43% HIV+</td>
</tr>
<tr>
<td><strong>Hsue 2004 (81)</strong></td>
<td>68 HIV-, 68 HIV+</td>
<td>50 ± 8</td>
<td>NR</td>
<td>NR</td>
<td>HIV+ 1.3 ± 1.0; HIV− 1.9 ± 1.2*</td>
<td>NR</td>
<td>52% PCI; 11% CABG</td>
<td>52% HIV+ vs. 14% HIV−*: with stenting (76%); 50% HIV+ vs. 18% HIV−‡</td>
</tr>
<tr>
<td><strong>Boccara 2011 (82)</strong></td>
<td>103 HIV+, 195 HIV−</td>
<td>49 ± 9</td>
<td>12</td>
<td>56% 1 VD; 28% 2 VD; 13% 3 VD; 3% NSS</td>
<td>1.5 ± 0.8</td>
<td>LAD 51%; LCA 14%; RCA 23%; 12% unknown</td>
<td>76% PCI; 4% CABG; 20% Med</td>
<td>9% HIV+ vs. 7% HIV−; HR: 1.4 (95% CI: 0.5–3.8)</td>
</tr>
<tr>
<td><strong>Mehta 2003 (85)†</strong></td>
<td>129 HIV+</td>
<td>42 ± 10</td>
<td>ND</td>
<td>35% 1 VD; 18% 2 VD; 47% 3 VD</td>
<td>NR</td>
<td>LAD 62%; LCA 45%; RCA 50%; LMD 6%</td>
<td>25% PCI + CABG</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Boccara 2006 (86)</strong></td>
<td>50 HIV+, 50 HIV−</td>
<td>43 ± 6</td>
<td>20</td>
<td>60% ≥2D</td>
<td>HIV+ 1.74 ± 0.75; HIV− 1.62 ± 0.72‡</td>
<td>NR</td>
<td>100% PCI</td>
<td>14% HIV+ vs. 16% HIV−‡</td>
</tr>
<tr>
<td><strong>Ren 2009 (87)</strong></td>
<td>97 HIV+, 97 HIV−</td>
<td>53 ± 9</td>
<td>36</td>
<td>2 vs. 2</td>
<td>LAD 42%</td>
<td>100% PCI</td>
<td>18% HIV+ vs. 13% HIV−; 11% HIV− DES vs. 2% HIV− DES</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05; †From several case reports. ‡p > 0.05.

CABG = coronary artery bypass grafting; DES = drug-eluting stent; LAD = left anterior descending; LCA = left circumflex artery; LMD = left main disease; Med = medical therapy alone; ND = not documented; NR = not reported; NSS = not significant stenosis; PCI = percutaneous coronary intervention; RCA = right coronary artery; VD = vessel disease; other abbreviations as in Table 1.
Concerning CABG, only a few studies (90–93) have included HIV-infected patients (Table 5). These studies showed that the immediate and postoperative periods after CABG are uneventful and do not differ from those in non–HIV-infected patients. At long-term follow-up, there was no difference in rate of cardiovascular death. CABG had no immunosuppressive effects and did not worsen the prognosis of patients with HIV disease. Regarding heart transplantation in HIV-infected patients with severe left ventricular dysfunction, few data are available (94,95), but HIV itself is not a contraindication, but the authors recommend case-by-case discussions between HIV physicians and cardiologists.

**Prevention and Treatment**

Cardiovascular risk stratification in HIV-infected patients needs to be evaluated before starting and during treatment with cART. Reducing risk factors should become routine in the care of HIV-infected patients, who now live longer. Intervention studies aimed at reducing cardiovascular risk in HIV-infected patients are now warranted (e.g., smoking cessation, increased physical activity, use of lipid-lowering drugs and aspirin).

Guidelines on cardiovascular risk reduction in HIV-infected patients have been published and generally follow those for the general population (96–98). It is important to highlight the treatment of atherogenic dyslipidemia frequently found in HIV-infected patients taking cART. Serum concentrations of lipids, particularly triglycerides, should be evaluated in the fasting patient before cART is started, at 3 to 6 months after initiation, and then yearly in the absence of abnormalities. National Cholesterol Education Program III guidelines should be applied to HIV-infected patients, as suggested by other guidelines for the management of dyslipidemia in HIV-infected patients (96–99). Lipid-lowering therapy should be prescribed with caution in HIV-infected patients because of the potentially severe interaction between statins and fibrates, as well as PIs (Table 6). Several statins are metabolized via the cytochrome P450 (CYP) 3A4 pathway. PIs and ritonavir mainly inhibit CYP and could increase the toxicity of some statins (Table 6). NNRTIs (e.g., efavirenz) are inducers of CYP and could reduce statin efficacy. In the HIV-infected patient taking a PI, if a statin is prescribed (e.g., for primary or

### Table 5: Clinical Studies Published on CABG Surgery in HIV-Infected Patients

<table>
<thead>
<tr>
<th>Study/First Author (Ref. #), Period, Mean Age</th>
<th>Patients Undergoing CABG</th>
<th>Hospital Death</th>
<th>Pre- vs. Post-Operative Immune Status</th>
<th>Long-Term Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trachiotis (90), 1994–2000, 41 yrs</td>
<td>27 HIV+</td>
<td>0</td>
<td>No change</td>
<td>81% Event-free at 36 months; no late death</td>
</tr>
<tr>
<td>Filsousfi (91), 1998–2004, 47 yrs</td>
<td>7 HIV+</td>
<td>0</td>
<td>No change</td>
<td>No late death at 47 months</td>
</tr>
<tr>
<td>Jimenez-Exposito (92), 1997–2004, 35 yrs</td>
<td>7 HIV+, 21 HIV–</td>
<td>0</td>
<td>No change</td>
<td>100% Event-free at 30 months; no difference vs. HIV–</td>
</tr>
<tr>
<td>Boccara (93), 1997–2005, 47 yrs</td>
<td>27 HIV+, 54 HIV–</td>
<td>0</td>
<td>15% decrease in CD4 cell count, without clinical complications</td>
<td>54% Event-free at 41 months</td>
</tr>
</tbody>
</table>

Modified from Boccara et al. (93).

CABG = coronary artery bypass grafting.
secondary prevention in the high-risk patient), the preferable choice is pravastatin, fluvastatin, low-dose atorvastatin, or low-dose rosuvastatin, as these statins have a low risk for interaction with PIs (99–101). Pitavastatin—a new statin not metabolized by the CYP 3A4 isozyme and primarily excreted unchanged in the bile with little renal elimination—has not been evaluated in this context but could present a therapeutic option; this statin has not, however, shown any clinical benefit in randomized trials (102). Whether a PI should be switched to an NNRTI or to a new drug such as integrase or chemokine (C-C motif) receptor 5 (CCR5) inhibitors when dyslipidemia is present, to avoid adjunctive therapy with a statin, is debatable. In fact, physicians treating HIV-infected patients have several therapeutic options in this context: to continue PI therapy and add a statin or to switch the PI to an NNRTI or a novel drug such as an integrase inhibitor. No trials comparing the 2 strategies in terms of cardiovascular prevention have been performed. The impact on lipids of switching from first-generation NRTIs to second-generation NRTIs is low (as they are less proatherogenic), and the associated beneficial impact on CHD is unknown. Fibrates should be prescribed when the triglyceride concentration is above 500 mg/dL (96–98). In this case, the measurements of non–high-density lipoprotein cholesterol, apolipoprotein B, or both may be useful because low-density lipoprotein cholesterol measurement may underestimate the true CHD risk, especially in lipodystrophic patients. Ezetimibe may be useful and well tolerated in achieving the low-density lipoprotein goal in association with a statin (103), as HIV-infected patients are susceptible to muscular pain before statin prescription. However, no clinical benefit of ezetimibe has been shown in the general population except for patients with chronic kidney disease in primary prevention (104). The risk–benefits ratio of treating HIV-infected patients with dyslipidemia is unknown. Male patients age >45 years and female patients >55 years with hypertension and/or diabetes and/or familial premature CHD are candidates for lipid-lowering therapy. In secondary prevention, whether PI therapy should be discontinued after an ACS and cART switched, if virologically possible, to a drug class with a better “atherogenic profile,” needs further investigation. Finally, statins as potent lipid-lowering drugs and major agents in primary and secondary cardiovascular prevention, along with their properties to reverse PI-related senescence of cells and accumulation of prelamin A in vitro (74) and inflammation in vivo (105), need to be tested in a large study of primary prevention in HIV-infected patients.

Regarding hypertension, blockers of the renin angiotensin system should be the first therapy because of their protective effects on the vasculature, on glucose metabolism and kidney function (44,70).

The prescription of antiplatelet drugs such as aspirin, clopidogrel, prasugrel, and ticagrelor should follow the guidelines for the general population (106). In primary prevention, aspirin should be given if the level of CHD risk is high and in the absence of contraindications (107). Recently, questions have been raised about platelet function and activity in HIV-infected patients (42,108). A potential interaction between the most commonly prescribed PI (ritonavir) and prasugrel has been found recently (by decreasing its activity) in vitro (109). Ticagrelor is metabolized by CYP 3A4/5 and should not be prescribed in HIV-infected patients undergoing PI therapy, particularly ritonavir (a potent inhibitor of this CYP isozyme) (110). Studies on antiplatelet “resistance” in HIV-infected patients need to be performed urgently. However, the rate of stent thrombosis after PCI does not appear to be higher in the HIV population than in the non–HIV-infected patients (82,87).

### Table 6 Interactions Between Lipid-Lowering Drugs and ART

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cytochrome P450*</th>
<th>Interactions With Other Antiretrovirals</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>No or weak P450 interactions</td>
<td>Increased AUC with LPV-RPV and ATV-RPV; decreased with NNRTI (efavirenz)</td>
<td>Recommended at 5–10 mg daily</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>3A4</td>
<td>Increased AUC with RTV-SQV; decreased with NNRTI (efavirenz)</td>
<td>Recommended at 10 mg daily</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>No P450 interactions</td>
<td>AUC decreased with RTV-SQV and increased with DRV; decreased with NNRTI (efavirenz)</td>
<td>Recommended at 20–40 mg daily</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>2C9</td>
<td>NNRTI (etravirine) could increase plasma level</td>
<td>Recommended at 40 mg daily</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>3A4</td>
<td>32-fold increase in AUC with RTV-SQV; decreased with NNRTI (efavirenz)</td>
<td>Possible high toxicity with PI; not recommended</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>3A4</td>
<td>Not tested</td>
<td>Possible high toxicity with PI; not recommended</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>No P450 interactions</td>
<td>Not tested</td>
<td>No recommendations at present</td>
</tr>
<tr>
<td>Bezafibrate</td>
<td>No P450 interactions</td>
<td>Not tested</td>
<td>Recommended at 400 mg daily</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>No P450 interactions</td>
<td>Not tested</td>
<td>Recommended at 200 mg daily</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Interaction with statins</td>
<td>Not tested</td>
<td>Recommended at 900–1,200 mg daily</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>No P450 interactions</td>
<td>Not tested</td>
<td>Recommended with statin, or alone if statin not tolerated</td>
</tr>
</tbody>
</table>

*Involved in lipid lowering drug metabolism.

ATV = atazanavir; AUC = area under the plasma concentration–time curve; DRV = darunavir; SQV = saquinavir; other abbreviations as in Table 1.
Conclusions

With their longer life expectancy—due to the use of cART—HIV-infected patients are increasingly at risk for CHD. Available data suggest the presence of an accelerated process of coronary atherosclerosis in this population due to multiple factors, including a higher prevalence (compared with non–HIV-infected patients) of conventional risk factors, emerging risk factors (chronic inflammation, immune activation, and senescence related to HIV infection itself), and the role of cART. Evaluating new strategies to prevent CHD in HIV-infected patients is a major concern. Optimizing cART for each individual to reduce the risk for CHD is warranted. Understanding the pathophysiology of the atherosclerotic aging process in this population requires further investigation. Management of CHD should follow the same recommendations as those for the general population, with caution exercised due to the potential for drug–drug interactions, particularly with statins and PIs. Whether aggressive primary and secondary prevention of CHD and of substantial ischemic events should be recommended in the HIV population needs further evidence.

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Key Words: atherosclerosis • chronic inflammation • coronary heart disease • human immunodeficiency virus • immune activation.