REVIEW

Epidemiology of coronary heart disease in HIV-infected versus uninfected individuals in developed countries

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Human immunodeficiency virus

Summary  The widespread use of combination antiretroviral therapy (cART) among people living with HIV in developed countries has lead to significantly improved life expectancy. However, extensive use of the effective cART coincides with increasing reports of coronary heart disease (CHD) among people living with HIV, and CHD has become a major cause of death. CHD results from a complex and multifactorial atherosclerotic process involving the over-representation of traditional cardiovascular risk factors, particularly smoking, uncontrolled viral replication, chronic inflammation, immune activation, and exposure to antiretroviral drugs. Consequently careful selection of antiretroviral drugs, cardiovascular risk reduction, and lifestyle modifications are needed. In individuals living with HIV, cardiovascular risk assessment is becoming an important element of care.

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Cardiovascular diseases (CVDs) are the leading cause of death worldwide [1]. In individuals infected by the human immunodeficiency virus (HIV), CVDs account for an increasingly large proportion of deaths, especially in those treated with effective combination antiretroviral therapy (cART) [2,3]. This article aims to assess the current epidemiological evidence linking HIV infection to coronary heart disease (CHD), and the specific clinical factors that may exist at clinical presentation in HIV-infected individuals compared with uninfected individuals.

Overall risk of coronary heart disease

The natural history of HIV disease has changed in countries where people living with HIV have access to cART. The individuals receiving combination ART regimens experience fewer opportunistic AIDS-related diseases and live longer than those without access to cART. These same individuals however develop long-term age-related complications. Cardiac complications have shifted from myocardial and pericardial diseases linked to immunosuppression to atherosclerotic diseases including myocardial infarction and peripheral and cerebrovascular diseases [4–6]. Several large observational cohorts and cohort collaborations including persons living with HIV have examined their specific causes of mortality. The Antiretroviral Therapy Cohort Collaboration, including patients from Europe and North America, reported that cardiovascular deaths accounted for 6.5% of total deaths [2]. Cardiovascular deaths accounted for 15% of total deaths in the US outpatient HOPS study [3], for 10% in the French ”Mortalité 2010” survey [7], and for 6% in the Swiss HIV Cohort Study [8].

Reports from as early as 2007 describe an increased risk of myocardial infarction in HIV-infected versus uninfected populations [9–12]. Using data from the US health care system-based cohort study, in 2007, Triant et al. put forward an adjusted risk ratio of 1.75 (95% confidence interval [CI] 1.51–2.02) for myocardial infarction in HIV-infected versus uninfected groups [9]. In 2011, using information collected by the Régie de l’Assurance Maladie du Québec (RANQ), Durand et al. estimated the adjusted incidence ratio for myocardial infarction in HIV-infected individuals compared to uninfected individuals was 2.11 (95% CI 1.69–2.63) [10]. Furthermore, in 2013, Freiberg et al. found HIV-positive veterans in the Veterans Aging Cohort Study Virtual Cohort (VACS-VC) had an increased risk of incident myocardial infarction compared with uninfected veterans, with an adjusted hazard ratio (HR) of 1.48 (95% CI 1.27–1.72) [11].

Based on information drawn from the French Hospital Database on HIV (FHDH), in 2010, Lang et al. found the sex- and age-standardized morbidity ratio of people living with HIV compared to the general population was estimated as 1.5 (95% CI 1.3–1.7) overall [12]. As in several cohorts, the Lang et al.’s study showed that people living with HIV experience myocardial infarction earlier, at around age 50 [9,12–15], while in the uninfected population myocardial infarction commonly occurs after 60 years of age. Such findings suggest a potential acceleration of atherosclerosis in HIV-infected populations. However, before stating that there is a premature aging process, it is crucial to note that the age distribution of HIV-infected and uninfected populations differ. Consequently, it is important to take this variability into account when making comparisons. Recently, Petoumenos et al. observed only limited evidence of accelerating risk of CVD with age in the D:A:D cohort compared with the general population [16]. In any case, if people living with HIV may experience accelerated atherosclerosis development it is possibly the result of their higher exposure to cardiovascular risk factors including tobacco and illicit drugs, higher prevalence of co-morbidities, antiretroviral therapy, and/or the result of the HIV infection per se. This will be discussed later in the article.

Traditional cardiovascular risk factors and clinical presentation

In primary prevention, people living with HIV already have a higher calculated risk of CHD compared to the same-age general population [17,18]. They are also at higher rate of cardiovascular risk factors, such as smoking and dyslipidemia [17,18]. Furthermore, HIV-infected individuals seem to be at higher risk of coronary artery disease than the general population. As demonstrated in 2004 by Bergersen et al. [19], twice as many people living with HIV taking highly active
ART had an estimated 10-year CHD Framingham risk > 20% as compared to control participants. From a cohort of 309 individuals living with HIV, in 2004 Neumann et al. [20] found the risk of cardiovascular events is related to the age of HIV-infected individuals. The overall 10-year probability for cardiovascular events was higher in the oldest group (≥50 years; median 20.5%) than in the youngest group (18–30 years; median 1.9%; P < 0.01). These findings suggest that an increased duration of life due to more effective ART has a significant impact on the rate of cardiovascular events in HIV-infected populations.

Hadigan et al. [21] in 2003 estimated the 10-year CHD risk among 91 men and women living with HIV who experienced fat redistribution, and compared it with the risk estimated for 273 age-, sex-, and body mass index-matched subjects enrolled in the Framingham Offspring Study. The 10-year CHD risk estimate was significantly elevated among HIV-infected individuals with fat redistribution, particularly among men. However, when matched with control subjects by waist-to-hip ratio, the 10-year CHD risk estimate did not differ significantly between groups. In this study, individuals living with HIV presenting no evidence of fat redistribution did not demonstrate elevated 10-year CHD risk estimate compared with control subjects. Also, the CHD risk estimate was greatest in HIV-infected individuals with primary lipohypertrophy as compared to those with either lipohypertrophy or mixed fat redistribution. A severe subcutaneous fat loss is recognized as predisposing individuals to insulin resistance, diabetes, and dyslipidemia.

More recently, in 2007, Knobel et al. [22] described the cardiovascular risk factors in a cohort of 760 persons living with HIV. They compared the Framingham, Prospective Cardiovascular Munster (PROCAM) and SCORE equations. The authors observed that the Framingham equation categorized a higher proportion of HIV-infected males with moderate cardiovascular risk and a lower proportion of those with low risk (P < 0.0001) compared with PROCAM and SCORE. However, regardless of the equation used, the Knobel et al. study showed a high prevalence of HIV-infected individuals at low cardiovascular risk (between 76.6% and 90.1%).

In 2003, the French APROCO study group [18] compared the distribution of cardiovascular risk factors in 227 protease inhibitors treated HIV-infected individuals who were aged 35–44 years with 527 HIV-uninfected men from the Multinational MONItoring of trends and determinants in Cardiovascular disease (MONICA) project. Saves et al. found that HIV-1 infected individuals had a lower prevalence of hypertension, a lower mean high-density lipoprotein cholesterol concentration, a higher prevalence of smoking, a higher mean waist-to-hip ratio, and a higher mean triglyceride concentration. They found no difference for total plasma or low-density cholesterol concentrations, or for the prevalence of diabetes. The predicted risk of CHD was greater among HIV-1 infected men (RR 1.20) and women (RR 1.59; P < 10−6 for both) compared with in the uninfected cohort.

In the Swiss HIV Cohort Study [23], where 8033 individuals completed at least one cardiovascular risk factor questionnaire, Glass et al. found, in 2006, that the most common risk factors were smoking (57.0%), low high-density lipoprotein cholesterol concentration (37.2%), high triglycerides concentration (35.7%), and high blood pressure (26.1%). They reported the 10-year CHD risk as being high (>20%) in 2.7% of all participants and moderate (10–20%) in 13.8% of all participants. Over 6 years, they found the percentage of smokers decreased from 61.4% to 47.6% and the percentage of individuals with total cholesterol > 6.2 mmol/L decreased from 21.1% to 12.3%. They reported that prevalence of cardiovascular risk factors and CHD was higher in participants currently on ART than in either pre-treated or ART-naïve persons.

Among individuals living with HIV, the clinical presentation of CHD is similar to that in the general population, and includes silent ischemia, stable angina, and acute coronary syndrome (ACS). ACS is the main CHD clinical presentation in this young population, particularly ST-segment elevation myocardial infarction (Table 1). In six studies [24–29], (Table 1) comparing persons hospitalized for ACS with or without HIV infection, results showed that the most common profile of a person living with HIV presenting an ACS is a young man (90% male, ≤50 years), most often treated with ART (varying from 53% to 96%) and mainly taking protease inhibitors (>59%). When focusing on traditional cardiovascular risk factors, HIV-infected individuals are more frequently smokers and cocaine users, but are less likely to have hypertension or diabetes mellitus (Table 1). In studies looking about cause of sudden cardiac death (SCD) in HIV-infected individuals some discrepancy exists due to differences in definitions used. For example, in 2012 Tseng et al. [30] defined SCD as deaths meeting two criteria: the primary ICD-10 code for all cardiac causes and the World Health Organization stipulation of death within 24 hours of symptoms. However, the same year, Worm et al. [31] limited the time component to death within 6 hours. Subsequently, Tseng et al. [30] found mean SCD rate was 2.6 per 1000 person-years (95%CI 1.8–3.8) with SCDs accounting for 86% of all cardiac deaths while Worm et al. [31] calculated the sudden death rate as 0.33 cases per 1000 person-years (95%CI 0.26–0.41). In light of such issues around traditional cardiovascular risk factors and their clinical presentation, further studies investigating the underlying mechanisms of SCD and providing insight into causes of death are necessary.

Impact of antiretroviral therapy on coronary heart disease

Some antiretroviral drugs, particularly protease inhibitors, appear to be involved in the increased rate of CHD, including myocardial infarction. The first cases of myocardial infarction in HIV-infected individuals receiving protease inhibitors were reported in the late 1990s [32–35]. All the patients presented in these cases were aged ≤ 60 years, were heavy smokers and/or had an abnormal cholesterol concentration. Following these initial descriptions of myocardial infarction, several epidemiological studies [10,15,36–47] were conducted to assess whether ART could be implicated as a factor in the increased risk of CVD (Table 2). Some of these studies report no increased risk of CVD linked to ART exposure, while other set forward evidence of an association between the risk of CVD and exposure to ART (Table 2). Such disparities in the studies’ findings may be related to the fact that each of these studies differing in design and sample size, have
<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Period</th>
<th>Study Design</th>
<th>HIV+ vs. HIV−</th>
<th>Type of ACS, %</th>
<th>Age, y</th>
<th>Risk factors HIV+ vs. HIV−, %</th>
<th>Tobacco use</th>
<th>Cocaine use</th>
<th>Premature familial CHD</th>
<th>Hypertension</th>
<th>Diabetes mellitus</th>
<th>Dyslipidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matetzky et al. [24]</td>
<td>1998—2000</td>
<td>Prospective case-control</td>
<td>24 vs. 48</td>
<td>STEMI 58 vs. 58</td>
<td>47 ± 9 vs. 48 ± 7</td>
<td>58 vs. 48</td>
<td>0</td>
<td>50 vs. 44</td>
<td>29 vs. 44</td>
<td>12 vs. 19</td>
<td>58 vs. 56</td>
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<td>NSTEMI 42 vs. 42</td>
<td>88 vs. 88</td>
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<tr>
<td>Hsue et al. [25]</td>
<td>1993–2003</td>
<td>Database</td>
<td>68 vs. 68</td>
<td>STEMI 29 vs. 35</td>
<td>50 ± 8 vs. 61 ± 11</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>
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<td></td>
<td>NSTEMI 25 vs. 37</td>
<td>90 vs. 62</td>
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<td>UA 46 vs. 28</td>
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<tr>
<td>Boccara et al. [26]</td>
<td>2003–2006</td>
<td>Prospective case-control</td>
<td>103 vs. 195</td>
<td>STEMI 49 vs. 56</td>
<td>48 ± 9 vs. 50 ± 9</td>
<td>59 vs. 64</td>
<td>5 vs. 2</td>
<td>20 vs. 27</td>
<td>19 vs. 24</td>
<td>9 vs. 12</td>
<td>45 vs. 46</td>
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<td>NSTEMI 20 vs. 21</td>
<td>93 vs. 94</td>
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<td>UA 31 vs. 23</td>
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<td>Perelló et al. [27]</td>
<td>2006–2009</td>
<td>Prospective cohort</td>
<td>44 vs. 583</td>
<td>STEMI 59 vs. 24</td>
<td>47 ± 11 vs. 72 ± 21</td>
<td>59 vs. 20</td>
<td>11 vs. 0.3</td>
<td>21 vs. 5</td>
<td>18 vs. 65</td>
<td>16 vs. 28</td>
<td>36 vs. 49</td>
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<td>NSTEMI 23 vs. 38</td>
<td>92 vs. 67</td>
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<td>UA 18 vs. 38</td>
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<td>Pearce et al. [28]</td>
<td>1997–2006</td>
<td>Database</td>
<td>5984 vs. 2,501,904</td>
<td>STEMI 50 vs. 56</td>
<td>48 ± 0.3 vs. 54 ± 0.02</td>
<td>25 vs. 30</td>
<td>NA</td>
<td>NA</td>
<td>46 vs. 51</td>
<td>20 vs. 28</td>
<td>25 vs. 42</td>
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<td>NSTEMI 50 vs. 44</td>
<td>85 vs. 72</td>
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<td>Lorgis et al. [28]</td>
<td>2005–2009</td>
<td>Retrospective case-control</td>
<td>608 vs. 1216</td>
<td>STEMI 91 vs. 84</td>
<td>50 ± 10 vs. 68 ± 15</td>
<td>30 vs. 30</td>
<td>NA</td>
<td>NA</td>
<td>17 vs. 22</td>
<td>9 vs. 11</td>
<td>31 vs. 29</td>
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<td></td>
<td>NSTEMI 9 vs. 16</td>
<td>89 vs. 66</td>
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</table>

Adapted from Boccara et al. [56].

ACS: acute coronary syndrome; CHD: coronary heart disease; HIV: human immunodeficiency virus; NA: not available; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina.

*P < 0.05.
Table 2  Risk of cardiovascular diseases among HIV-infected individuals treated with cART.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study period</th>
<th>Study design</th>
<th>Events studied</th>
<th>Coronary events, n</th>
<th>ART-exposed subjects, n (PY)</th>
<th>Duration of follow-up with ART</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jütte et al.</td>
<td>1990–1998</td>
<td>Database on medical records</td>
<td>MI</td>
<td>1324 (1911)</td>
<td>373 (469)</td>
<td>10 months (median)</td>
<td>Incidence: 2.1/1000 PY in non-PI-treated patients vs. 10.6/1000 PY in PI-treated patients</td>
</tr>
<tr>
<td>Rickerts et al.</td>
<td>1983–1998</td>
<td>Database on medical records</td>
<td>MI</td>
<td>4993 (16,478)</td>
<td>1572</td>
<td>NA</td>
<td>OR 2.61 (95% CI 1.19–5.66) ART vs. no ART</td>
</tr>
<tr>
<td>David et al.</td>
<td>1999–2000</td>
<td>Database on medical records</td>
<td>MI</td>
<td>48</td>
<td>34</td>
<td>27 months for cases (median); 14 months for controls (median)</td>
<td>PIs not directly associated with greater risk of ischemic CVD</td>
</tr>
<tr>
<td>Holmberg et al.</td>
<td>1993–2002</td>
<td>Database on medical records</td>
<td>MI</td>
<td>5672 (17,712)</td>
<td>3247</td>
<td>49 months (mean)</td>
<td>Higher risk for PIs vs. non-Pis: HR 6.5 (95% CI 0.9–47.8)</td>
</tr>
<tr>
<td>Boznette et al.</td>
<td>1993–2001</td>
<td>Database on administrative data</td>
<td>CCVE</td>
<td>36,766 (121,935)</td>
<td>15,296 (26,957)</td>
<td>16 months (median)</td>
<td>HR 1.23 (95% CI 0.78–1.93) 24 months of PI exposure vs. no PIs</td>
</tr>
<tr>
<td>Klein et al.</td>
<td>1996–2002</td>
<td>Database on administrative data</td>
<td>MI</td>
<td>4408 (18,792)</td>
<td>2860 (10,686)</td>
<td>47 months (median)</td>
<td>4.0/1000 PY for no PIs vs. 3.9/1000 PY with PIs</td>
</tr>
<tr>
<td>Friis-Moller et al.</td>
<td>1999–2002</td>
<td>Specifically designed cohort</td>
<td>MI</td>
<td>23,468 (36,199)</td>
<td>17,484</td>
<td>22 months (median)</td>
<td>RR 1.26 (95% CI 1.12–1.41) PY of cART exposure</td>
</tr>
<tr>
<td>Mary-Krause et al.</td>
<td>1996–1999</td>
<td>Database on medical records</td>
<td>MI</td>
<td>34,976 men (88,029)</td>
<td>21,906 (39,023)</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>Study</td>
<td>Study period</td>
<td>Study design</td>
<td>Events studied</td>
<td>Coronary events, n (PY)</td>
<td>ART-exposed subjects, n (PY)</td>
<td>Duration of follow-up with ART</td>
<td>Results</td>
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<tr>
<td>d’Arminio et al. [43]</td>
<td>1999–2002</td>
<td>Specifically designed cohort</td>
<td>CCVE</td>
<td>36,145</td>
<td>CCVE 207; MI 126</td>
<td>NA</td>
<td>RR 1.26 (95% CI 1.14—1.38) PY of cART exposure</td>
</tr>
<tr>
<td>Friis-Moller et al. [44]</td>
<td>1999–2005</td>
<td>Validation of cases</td>
<td>MI</td>
<td>23,437 (94,469)</td>
<td>345</td>
<td>150,758 (83 months, median)</td>
<td>RR 1.16 (95% CI 1.09—1.23) PY of cART exposure</td>
</tr>
<tr>
<td>Obel et al. [45]</td>
<td>1995–2004</td>
<td>Database on medical records</td>
<td>Ischemic CVD</td>
<td>In non-cART period,</td>
<td>13,593 vs. 1,389,722</td>
<td>In non-cART period, 1.6 y; in cART period, 5.2 vs. 5.9 y</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>No validation of cases</td>
<td></td>
<td>9271 vs. 1,272,956; in cART period, 13,593 vs. 1,389,722</td>
<td>Before cART initiation 14 vs. 1946; after cART initiation 57 vs. 2817</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 years of cART</td>
<td></td>
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<tr>
<td>Worm et al. [46]</td>
<td>1999–2008</td>
<td>Specifically designed cohort</td>
<td>MI</td>
<td>33,308 (178,835)</td>
<td>580</td>
<td>NA</td>
<td>RR incidence 3.2/1000 PY (95% CI 3.0—3.5) RR cumulative exposure to IDV 1.12 (95% CI 1.07—1.18) RR cumulative exposure to LPV/RTV 1.13 (95% CI 1.05—1.21) RR recent exposure to ABC 1.70 (95% CI 1.17—2.47) RR recent exposure to DDI 1.41 (95% CI 1.09—1.82)</td>
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<tr>
<td>Study</td>
<td>Study period</td>
<td>Study design</td>
<td>Events studied</td>
<td>n (PY)</td>
<td>Coronary events, n</td>
<td>ART-exposed subjects, n (PY)</td>
<td>Duration of follow-up with ART</td>
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<tr>
<td>Lang et al. [43]</td>
<td>2000–2006</td>
<td>Case-control study nested in database</td>
<td>MI</td>
<td>74,958 (298,156)</td>
<td>289 MI vs. 884 controls</td>
<td>94%</td>
<td>79 vs. 84 months</td>
</tr>
<tr>
<td>Durand et al. [10]</td>
<td>1985–2007</td>
<td>Case-control study nested in database</td>
<td>MI</td>
<td>7053 (35,851)</td>
<td>125 MI vs. 1084 controls</td>
<td>76%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Adapted from Boccara et al. [56].

ABC: abacavir; ART: antiretroviral therapy; cART: combined antiretroviral therapy; CCVE: cardio- and cerebrovascular events; CI: confidence interval; CVD: cardiovascular disease; DDI: didanosine; EFV: efavirenz; HR: hazard ratio; IDV: indinavir; IV: intravenous; LVP: lopinavir; MI: myocardial infarction; NA: not available; OR: odds ratio; PI: protease inhibitor; PY: person-years; RR: relative risk; RTV: ritonavir; SMR: standardized morbidity ratio; SQV: saquinavir; NNRTI: non-nucleoside reverse transcriptase inhibitor.
used varying times of exposure to protease inhibitors, and that not all of them had an independent event committee.

**Exposure to protease inhibitors**

Only two studies with myocardial infarction as primary endpoint had a sufficient duration of exposure to protease inhibitors to possibly capture CHD manifestations [46,47]. In the 2010 FHDH study, cumulative exposure to any protease inhibitor, except for saquinavir, was associated with an increased risk of myocardial infarction (odds ratio [OR] 1.15, 95% CI 1.06–1.26, per year) [47]. Also published in 2010, in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study [46], cumulative exposure to indinavir or lopinavir/ritonavir was associated with an increased risk of myocardial infarction (relative rate per additional year 1.12, 95% CI 1.07–1.18 and 1.13, 1.05–1.21, respectively). This same study found no association for saquinavir or nelfinavir. In a systematic review published in 2013, Bavinger et al. demonstrated significant increased risks of myocardial infarction with cumulative indinavir use (RR 1.11, 95% CI 1.05–1.17) and cumulative exposure to lopinavir (RR 1.22, 95% CI 1.01–1.47) based on a pooled analysis of the two aforementioned studies [48]. D’Ascenzo et al. ’s 2012 meta-analysis of 11 studies found an overall significant risk of 2.68 (95% CI 1.89–3.89) in participants with early exposure to protease inhibitors based on the pooled analysis of two studies reporting the incidence of acute myocardial infarction in participants exposed to protease inhibitors [49]. No studies investigating each protease inhibitor individually reported an association between nelfinavir or saquinavir and the risk of myocardial infarction [46,47]. Concurrently, the 2013 Monforte et al. ’s study found there was no evidence of an association between cumulative exposure to atazanavir and myocardial infarction risk with a RR per year of 0.95 (95% CI 0.87–1.05) [50]. At present, no data are available describing the risk of myocardial infarction associated with exposure to darunavir, as this drug has only been available since 2009.

**Exposure to non-nucleoside reverse transcriptase inhibitors**

Neither the FHDH nor the D:A:D study found significant associations between cumulative exposure to efavirenz or nevirapine and the risk of myocardial infarction [46,47].

**Exposure to nucleoside reverse transcriptase inhibitors**

The pooled data from FHDH and D:A:D studies in Bavinger et al. ’s systematic review demonstrate that recent exposure to abacavir was associated with the risk of myocardial infarction, with a summary RR of 1.91 (95% CI 1.50–2.42). This finding suggests a harmful association between recent abacavir use and the risk of myocardial infarction [48]. However, as sensitivity analyses from the FHDH study revealed that the results for abacavir were unstable the authors subsequently concluded that no causal relationship could be established [47]. Regarding exposure to didanosine, recent exposure was associated with an increased risk of myocardial infarction in the D:A:D study (RR 1.41, 95% CI 1.09–1.82) but not in the FHDH study [46,47]. Using Fisher’s method of combining P-values to aggregate the results of the two aforementioned studies, Bavinger et al. found a harmful association (P = 0.001) [48].

**Exposure to integrase inhibitors**

For the moment, to our knowledge, no studies have evaluated the impact of these new agents because of their recent availability.

To conclude, as the increase in life expectancy conferred by combination ART far outweighs the associated risk of myocardial infarction, the benefit-risk ratio of receiving treatment remains positive.

**Other potential risk factors for coronary heart disease**

In the nested case-control study on myocardial infarction published in 2012, Lang et al. found that HIV replication, a low CD4 T-cell nadir and a high current CD8 T-cell count are associated with an increased risk of myocardial infarction independently of cardiovascular risk factors and antiretroviral therapy [51]. Likewise, Silverberg et al. have published that lower CD4 T-cell nadir seems to be independently associated with MIs, as HIV-infected individuals with recent CD4 T-cell or CD4 T-cell nadir ≥ 500 cells/mL had similar MI rates compared with uninfected individuals [52]. In fact, the results from the Strategies for Management of Antiretroviral Therapy (SMART) trial suggest that HIV itself can independently increase the risk of CHD [53]. This randomized trial found that HIV-infected individuals who discontinued ART had a higher rate of cardiovascular events than HIV-infected individuals who not discontinued ART, suggesting an indirect role of HIV viral rebound in the atherosclerosis process. Macrophages probably play a key role in HIV-related atherosclerosis. It is possible that HIV infection could affect all steps of atherosclerosis [54] through enhanced monocyte activation, viremia-induced interferon-alpha production and adaptive T-cell responses, altered reverse transendothelial migration of monocyte-derived macrophages, and defective cholesterol efflux by HIV infection which could lead to promotion of plaque expansion and instability. Moreover, claims have been made that inflammatory conditions accelerating atherogenesis are resultant from HIV induced alterations of HIV-infected individuals’ immunological response in addition to their exposure to various xenobiotics from HIV itself and other viral and bacterial infections. Endothelial dysfunction has also been reported in HIV infection [55]. As the current knowledge base is limited, the impact of HIV itself and related immune disorders on the coagulation system needs to be evaluated in the post-ART era.

**Conclusions**

After the impressive successes of cART in drastically decreasing fatal complications of severe immunodepression,
persons living with HIV taking cART are now facing challenges such as CVD and particularly CHD. Increased risk of CHD in HIV-infected populations compared with uninfected populations is associated with multiple factors including traditional cardiovascular risk factors, use of illicit drugs, and inflammatory and immunological disturbances. The new challenge for physicians involved in HIV care is promoting cardiovascular risk prevention, especially reinforcing smoking cessation support, for populations living with HIV who are at risk of CHD in order to reduce the number of coronary events. Assessing the risk of HIV-infected individuals may present its own set of challenges as numerous factors associated with CHD risk are not taken into account when calculating different risk equations. In this context, based on current best knowledge, CHD risk equations for HIV-infected patients should be modified.

Disclosure of interest

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References

Epidemiology of coronary heart disease in HIV-infected individuals


