Curr HIV/AIDS Rep (2015) 12:375–387
DOI 10.1007/s11904-015-0284-6

BEHAVIORAL-BIO-MEDICAL INTERFACE (JL BROWN AND RJ DICLEMENTE, SECTION EDITORS)

Risk of Cardiovascular Disease in an Aging HIV Population: Where Are We Now?

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Published online: 30 September 2015

Abstract With more effective and widespread antiretroviral treatment, the overall incidence of AIDS- or HIV-related death has decreased dramatically. Consequently, as patients are aging, cardiovascular disease (CVD) has emerged as an important cause of morbidity and mortality in the HIV population. The incidence of CVD overall in HIV is relatively low, but it is approximately 1.5–2-fold higher than that seen in age-matched HIV-uninfected individuals. Multiple factors are believed to explain this excess in risk such as overrepresentation of traditional cardiovascular risk factors (particularly smoking), toxicities associated with cumulative exposure to some antiretroviral agents, together with persistent chronic inflammation, and immune activation associated with HIV infection. Tools are available to calculate an individual's predicted risk of CVD and should be incorporated in the regular follow-up of HIV-infected patients. Targeted interventions to reduce this risk must be recommended, including life-style changes and medical interventions that might include changes in antiretroviral therapy.

This article is part of the Topical Collection on *Behavioral-Bio-Medical Interface*

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Keywords Cardiovascular Risk · HIV · Acute myocardial infarction · Antiretroviral therapy · Cerebrovascular disease

Introduction

Over the last two decades, the prognosis for HIV-positive individuals in developed countries has tremendously improved due to the availability of potent and well-tolerated combination antiretroviral therapy (cART), achieving virological suppression in most cases [1]. This has lead to an important improvement in life expectancy, which—in subjects without hepatitis C virus (HCV) infection or other comorbidities—is now similar to that of the general population [2, 3].

Consequently, the HIV-infected population is aging—50 % of HIV-infected subjects in Europe and in the USA are aged 50 years or older—and the focus of clinical care has changed dramatically, from facing severe opportunistic complications associated with advanced immunodeficiency in the earlier days of the epidemic to the present focus on prevention and management of age-related comorbidities and cART-related complications, such as cardiovascular disease (CVD).

As in the general population, CVD is emerging as one of the most frequent causes of death among HIV-infected patients [2]. This review will address the current evidence on CVD risks in HIV-infected individuals and the implications on clinical prevention and management.

Evolvement of the Risk of Cardiovascular Disease in the HIV-Infected Population

Several large observational cohort studies have consistently demonstrated increased rates of CVD, including acute myocardial infarction (AMI) among HIV-infected compared with

matched uninfected controls, with an approximate 1.5- to 2-fold increased relative risk (RR) over the last decade [4–10, 11•, 12•, 13••, 14]. However, some recent studies suggest that this increased risk may now be diminishing [13••]. An overview of the main epidemiologic studies on CVD in the HIV population is presented in Table 1. Similar studies have also observed that HIV infection confers an increased risk of heart failure [15], ischemic stroke [16], and sudden cardiac death [17].

A recent meta-analysis reported that the adjusted RR of CVD was 1.61 (95 % CI=1.43–1.81) among HIV-positive individuals compared with HIV-uninfected controls. The RR of CVD increased to 2.00 (95 % CI=1.70–2.37) when the analysis was restricted to HIV-infected patients on ART compared with HIV uninfected subjects, while it was 1.52 (95 % CI=1.35–1.70) compared with treatment naïve HIV-infected people [18].

Similarly, two recent large cohort studies with demographically and behaviorally matched HIV uninfected controls have also reported solid evidence of an association of HIV status and AMI [11•, 12•, 13••, 14]. The Kaiser Permanente group reported a RR of AMI of 1.44 (95 % CI=1.3–1.6), after adjusting for traditional CVD risk factors (CVDRF). However, the risk was no longer increased when the analysis was restricted to those with recent or nadir CD4+ cell count≥ 500 cells/ml (RR=0.85, 0.55–1.33) [12•]. In the most recent update of the study (calendar period from 1996 to 2011), the AMI risk was similar among HIV-infected individuals compared to matched HIV uninfected subjects in the latest period from 2010 to 2011 (RR=1.0, 95 % CI=0.7–1.4). The CVDRF profile for both groups was similar in this period, even more favorable in the HIV-positive group [13••]. However, Paisible et al. recently assessed the association between HIV and AMI by burden of CVDRF and found an increase in risk of AMI in the HIV group compared to uninfected individuals in all the strata, including those with no major CVDRF, with a 2-fold increased risk of MI, but low CD4+ cell count and unsuppressed viremia were more common in this subgroup [14].

The majority of the participants in these studies are men, so predictors of CVD in HIV-infected women are less well examined.

Additional evidence is collected from studies examining surrogate measures of subclinical atherosclerosis through arterial imaging. Carotid ultrasound assessing carotid artery intima-media thickness (cIMT), coronary CT to assess coronary artery calcium (CAC), coronary artery plaques and wall thickness, brachial artery ultrasound to evaluate endothelial function, pulse wave velocity (PWV) to evaluate artery stiffness, and more recently, FDG-PET to evaluate arterial inflammation have provided important insights into the prevalence and pathophysiology of HIV-associated CVD. However, final results from these studies are somewhat mixed.

Several studies have found coronary artery wall thickness [19], coronary artery plaque [20, 21], cIMT, and cIMT progression changes [22–24] to be associated with HIV disease, suggesting an increased risk of CVD. Increased cIMT and cIMT progression and increased coronary artery plaque have unexpectedly been reported also among elite-controllers despite spontaneous virological and immunological control, supporting that other factors than ART and high viral replication are involved in the atherogenic process [25, 26].

Taken in aggregate, the current evidence supports the presence of an increased rate of CVD among HIV-infected individuals, likely more clinically evident with the aging of the HIV-infected population. Some cohorts report unchanging CVD rates, which may be attributable to intensive preventive efforts.

Traditional CVD Risk Factors

Framingham was the first study to establish the concept of CVRF in the background population. This study found that the three modifiable risk factors (RF) most strongly related to coronary risk were cigarette smoking, elevated blood pressure, and total cholesterol (TC). Findings of main modifiable risks in HIV-infected persons are consistent.

One of the most important conventional modifiable RF for CVD is cigarette smoking. In this respect, a dose-effect relationship of smoking and CVD risk is well described [27], and high smoking prevalence has been reported in HIV-infected populations [11•, 12•, 28]. The risk of CVD and mortality attributable to smoking has also been found to be considerable in HIV-infected patients [29•, 30•].

In an analysis from the D:A:D study, smoking cessation showed to decrease the risk of CVD in HIV-infected patients with increasing time since stopping smoking, further encouraging efforts to motivate smoking cessation in this population [31••].

Hypertension is another key RF for CVD in HIV patients as in the general population. The prevalence in different HIV-infected cohorts has been reported from 4 to 54 %. In the pre-cART era, elevated blood pressure was uncommon and mainly seen in association with HIV-related renal complications. However, after the introduction of cART and with the aging of the HIV-infected population, hypertension has become more prevalent and probably more intensively monitored [32, 33]. A number of recent studies have suggested an association with some antiretroviral agents, including Indinavir and Nevirapine [32, 34–36].

Diabetes and impaired insulin sensitivity are becoming an increasing problem among HIV-infected patients, and the risk of CVD increases with longer duration of diabetes [37, 38]. Although traditional RF plays a role, HIV-infection per se, chronic inflammation, lipodystrophy, and some antiretroviral

Table 1 Schematic resume of main epidemiologic studies on CVD in the HIV population

Cohort study	N (HIV)	Follow up py	Age HIV	Male (%)	Period	Outcome	Effect size
Kaiser[a] (Klein 2002) [4]	4159	14,823	Median 42	100	1996–2001	CVD in HIV vs. matched controls	1.7
CA Medicaid[b] (Currier 2003) [5]	28,513	71,286	68.5 % under 45 years	72.7	1994–2000	CVD in HIV vs. matched controls	Men 18–24 years: 6.76 25–34 years: 2.16 Women 18–24 years: 2.47 25–34 years: 1.67
						CVD in HIV exposed to cART vs not exposed to cART	2.06
FHDH[c] (Mary-Krause 2003) [6]	34,976	88,029	Mean 38	100	1996–1999	MI in HIV exposed to PI vs. estimated rates from population registries	2.56
Partners HIV cohort[d] (Triant 2007) [7]	3851	16,983	Median 38	69.6	1996–2004	MI in HIV vs. matched controls	1.75
Danish HIV cohort[e] (Obel 2007) [8]	3953	Non-cART period: 9271 cART period: 13,593	Median 36.8	76.8	1995–2004	First hospitalization for IHD vs. population based matched controls	Non-cART period: 1.39 cART period: 2.12
FHDH (Lang 2010) [9]	74,958	298,156	Median 47	89	2000–2006	MI in HIV vs. estimated rates from population registries	1.5
Quebec RAMQ[f] (Durand 2011) [10]	7043	35,851	Median 37	78	1985–2007	MI in HIV vs. matched controls	2.11
VACS cohort[g] (Freiberg 2013) [11]	27,350	Median follow-up 5.9 years	Median 48	97.3	2003–2009	MI in HIV vs. matched controls	1.48
Kaiser Permanente[h] (Silverberg 2014) [12]	22,081	99,090	68 % under 45 years	90.6	1996–2009	MI in HIV vs. matched controls	1.4
Kaiser Permanente (Klein 2015) [13]	24,768	119587	Mean 41 years	91	1996–2011	MI in HIV vs. matched controls	1996–1999: 1.8 (1.3–2.6) 2000–2003: 1.7 (1.4–2.1) 2004–2007: 1.3 (1.0–1.6) 2008–2009: 1.3 (0.9–1.7) 2010–2011: 1.0 (0.7–1.4)
VACS cohort (Paisible 2015) [14]	26,831	Median follow-up 5.9 years	Optimal CVD RF profile: mean 45 years	99.9	2003–2009	CVD in HIV vs. matched controls by similar CVD RF profile	2.0 (Optimal CVD RF profile)

[a] Kaiser Permanente Northern California (KPNC) database

[b] From the California's Medicaid population

[c] French Hospital Database on HIV (FHDH) is an ongoing, nationwide, hospital-based cohort of HIV-infected individuals in France created in 1989

[d] Partners HIV cohort included patients who presented on at least two occasions to one of two Boston health care facilities, Brigham and Women's Hospital or Massachusetts General Hospital

[e] Danish HIV Cohort Study is an ongoing, nationwide, prospective, population-based cohort study of all Danish HIV-infected individuals treated at Danish hospitals since 1995, who are matched by gender, age, and municipality of residence to a population control group

[f] Database from the *Régie de l'assurance-maladie du Québec* (RAMQ) including HIV-positive patients and HIV-negative individuals matched by age, gender, entry date, and adequate period of pharmaceutical insurance coverage

[g] Veterans Aging Cohort Study Virtual Cohort (VACS VC) is a prospective longitudinal cohort of HIV-infected individuals who are age, gender, race/ethnicity, and clinical site matched to HIV-uninfected individuals enrolled in the same calendar year. Participants have been enrolled since 1998 from the US Department of Veterans Affairs administrative data

[h] Kaiser Permanente Medical Care Program of Northern and Southern California (KPNC and KPSC, respectively), two large integrated healthcare delivery systems providing care to more than 6 millions members. HIV-positive individuals are identified using HIV registries that include all known HIV/AIDS cases since the early 1980 for KPNC and 2000 for KPSC. HIV-negative member is matched to HIV-positive individuals by sex, age, medical center, and initial calendar year of follow-up

agents may be directly implicated in the development of insulin resistance. Particularly, some PI and NRTI have been associated with impaired insulin sensitivity; however, newer ART induces less insulin resistance and has a better metabolic profile [38–41].

Antiretroviral Treatment as an Independent Cardiovascular Risk Factor

The pathogenesis of premature atherosclerosis and increased risk of CVD in HIV-infected patients is not fully explained by the overrepresentation of traditional CV RF in this population. Current belief is that multiple factors drive this excess risk, including traditional CVDRF, toxicities associated with cumulative exposure to ART, either direct or via associated metabolic disorders, together with chronic inflammation, and immune activation associated with HIV infection. Other factors such as the metabolic syndrome, renal disease, or HCV coinfection may also contribute to this risk.

The Intrinsic Cardiovascular Risk Factor of Some ARV Drugs

Current evidence stems mainly from large observational registry-based cohort studies with the potential bias and confounders that are inherent to this kind of research, many lacking information on important RF such as smoking or renal disease, and channeling or prescription bias.

The D:A:D is a large prospective multi-cohort study designed to address the potential association between cART and CVD. This ongoing international collaboration of 11 cohorts was initiated in 1999 and is prospectively following 49,734 HIV-infected patients at 212 clinics in Europe, Argentina, the USA, and Australia. The D:A:D was one of the first studies to describe the excess risk of CVD associated with ART, reporting a 26 % relative increase in the rate of AMI per year of exposure during the first 4 to 6 years of cART [42]. With a longer follow-up, the study was able to analyze the effect of drug classes [43•] and subsequently the inherent risk of individual drugs [44]. Some of the drugs analyzed in those studies are no longer preferred, potentially explaining part of the decrease observed in CVD rates with the availability of newer and less toxic agents.

Many studies have shown strong evidence of association between PI exposure and increased risk of CVD [6, 43•, 44–46]. However, studies assessing the potential association of individual NRTIs and increased CV events have shown more divergent results [44, 47–49].

Although exposure to ART with those drugs was associated with increased risk of CVD, findings from the SMART study clearly demonstrated a benefit in overall mortality and CVD events in subjects treated with ART compared to those interrupting therapy [50, 51], which strengthen the potential influence of chronic inflammation and immune activation.

Protease Inhibitors

In the D:A:D study, the incidence of AMI increased from 1.53 per 1000 person-years in those not exposed to PI to 6.01 per 1000 person-years in those with more than 6 years of PI exposure. After adjusting for exposure to other ART classes and traditional CVDRF (excluding lipid levels), the RR of AMI per year of PI exposure was 1.16 (95 % CI=1.10–1.23), and after additional adjustment for lipids, this risk decreased to 1.10 (95 % CI=1.04–1.18), indicating that the increased risk of MI was partly but not fully explained by dislipidemia [43•].

Later analyses showed that only indinavir and lopinavir/ritonavir were associated with an excess risk of MI, increasing with longer cumulative exposure, whereas such an association was not seen for other PIs, particularly saquinavir and nelfinavir [44].

More recently, the D:A:D group has been able to explore newer PI drugs such as atazanavir, reporting no increased risk of AMI or stroke, either boosted or unboosted with ritonavir. This suggests a more "detailed" picture with only increased risk associated with exposure to individual PI-drugs typically associated with a worse metabolic profile and not with the whole PI class [52]. Data on the newer PI darunavir are still lacking.

Analyses of the French Hospital Database confirmed the association with individual PIs observed in the D:A:D study and also found a higher risk of MI with fosamprenavir. The overall exposure to PI was associated with an OR of AMI of 1.15 (95 % CI=1.06–1.26) per year of PI exposure, similar to that found in the D:A:D study [47].

The mechanisms behind this excess of CVD associated with PI exposure might be dislipidemia, pro-thrombotic effects or mediated by direct effects on endothelial function.

Nucleoside Reverse Transcriptase Inhibitors (NRTI's)

Originally, D:A:D was one of the first to describe an increased risk of AMI with exposure to some individual NRTI drugs, such as didadosine and abacavir. While the hypothesis was an expected increased risk with thymidine analogues, such association was not found. The results showed an association between recent exposures to abacavir with increased rates of AMI of 1.89. The association appeared reversible upon discontinuation of the drug, and the risk was present in all strata of underlying CVD risk [53].

Since then, a number of other groups have evaluated whether the finding was reproducible in their studies, and the issue is still a matter of hot debate. Some additional studies

have confirmed the increased risk described in the D:A:D [10, 18, 44, 49, 54–56]; however, other studies have not found evidence of such association [47, 48, 57–60] (Table 2).

The ANRS cohort found an increased risk of AMI only while on abacavir for the first year of therapy, but additional analyses suggested that preferential use of abacavir in patients with impaired renal function or in drug users might have confounded the association [47, 58].

The D:A:D study also conducted analyses to explore this issue. A slightly higher proportion of renal function impairment was seen in patients receiving abacavir than other NRTIs, but the association was still seen after adjusting for low eGFR (RR=1.89) [61].

No excess of risk of AMI with abacavir was observed in the pooled analysis of randomized clinical trials (RCT) database maintained by the manufacturer of abacavir. However, the study had few events and short follow-up, and thus a limited power to address the question. Furthermore, information on key CVRF was lacking, and analysis was unadjusted [48].

Recently, two additional meta-analyses and an observational cohort of subjects randomized to ACTG RCT did not find evidence of increased risk of CVD with abacavir exposure; however, the median age of patients included in the RCTs was significantly lower than in cohort studies [57, 59, 60].

A recent study from the North American Cohort (NA-ACCORD) has rekindled the debate. The study compared subjects with recent abacavir exposure with those starting a non-abacavir regimen [62]. Baseline characteristics of the two groups were different, many of them known to be strong CVDRF. Carrying out the analysis as done in the initial D:A:D, they found similar results (HR=1.71). In the full study population, the main study endpoint, when repeating the analysis and adjusting for traditional CVRF and renal impairment, no significant association was found. However, in an analysis restricted to subjects naïve to ART when starting abacavir, they reported a significant association of AMI in those starting abacavir (HR=1.96).

Overall, an increased risk of AMI in patients treated with abacavir has been observed in many studies. While weighing the evidence of the observations from the different studies, the central issue to consider is the study design, and uncertainty about existing bias or confounding remains. For now, the causal relationship between exposure to abacavir and the risk of MI can neither be confirmed nor refuted.

The potential biological mechanisms of how abacavir might increase the risk of AMI are discussed below.

Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI's)

Clinical data are limited regarding risks from the NNRTI class. Three large observational studies have investigated the relationship of NNRTI exposure (primarily nevirapine and efavirenz) with CV risk, and neither identified any excess risk with NNRTI use [43•, 44, 47, 63].

Metabolic and Thrombotic Complications Associated with cART

Initial ART induces lipid changes, which partly represent a restoration of abnormal levels, usually observed in patients with low weight and an advanced HIV disease.

Most PIs increase plasma levels of both TC and low-density lipoprotein-cholesterol (LDL-C), as well as levels of triglycerides (TG). However, darunavir and atazanavir have shown to have a more favorable lipid profile than older PI, without significant differences among them [64–66]. Of interest, raltegravir produced the most favorable lipid profile when compared with once-daily ritonavir-boosted darunavir and atazanavir [66].

Unboosted atazanavir has been associated with a significantly better lipid profile than ritonavir-boosted atazanavir [67]. On the other hand, similar lipid profiles were observed with atazanavir being boosted with ritonavir or cobicistat [68, 69]

NNRTIs have been found to increase TC and high-density lipoprotein-cholesterol (HDL-C), with an improvement of the TC/HDL ratio. In a recent study, efavirenz was associated with increases in TC, LDL-C, but not TC/HDL compared to atazanavir-ritonavir [70]. Therapy with rilpivirine is associated with lower increases in TC, HDL, LDL, and TG compared with efavirenz; however, the TC/HDL ratio is similar in both groups [71]. Nevirapine is the NNRTI associated with the safer lipid profile so far.

Integrase inhibitors have a more favorable lipid profile as a class, with a lipid neutral profile. In the STARTMRK study, raltegravir showed lower TG, TC, HDL, and LDL cholesterol increases compared with efavirenz in treatment naïve patients [72]. Switching a PI/r (usually ritonavir-boosted lopinavir or atazanavir) to a raltegravir-based cART in virologically suppressed HIV-infected patients was associated with an overall improvement in lipid profile, including a shift to a less atherogenic LDL phenotype in a RCT [73]. In the same way, switching to raltegravir was associated with greater reductions in serum lipid concentrations than was continuation of lopinavir/ritonavir in another RCT [74]. Dolutegravir has shown a similar lipid profile as raltegravir in a RCT [75]. Coformulated cobicistat-boosted elvitegravir-emtricitabine-tenofovir seems to have a similar lipid profile to atazanavir-ritonavir and induces smaller increases in TC, LDL but also HDL than efavirenz [76, 77]. Some drugs of the NRTI drug class have an impact on lipid concentrations.

Abacavir-lamivudine was recently compared to tenofovir-emtricitabine, combined either with efavirenz or atazanavir-

Table 2 Summary of main studies assessing the association between abacavir use and risk of CVD

Study	N	Events n	Study design	Time period	Exposure	Endpoint	Effect size (CI 95 %)
Studies showing association between exposure to abacavir and risk of CVD							
D:A:D Sabin et al.[61]	33,347	517	Cohort	1999–2005	Recent exposure to abacavir (current or in the past 6 months)	MI	1.89 (1.47, 2.45)
D:A:D Worm et al. [44]	33,308	580	Cohort	1999–2008	Recent exposure to abacavir	MI	1.70 (1.17, 2.47)
Danish HIV Cohort Obel et al.[49]	2952	67	Cohort	1995–2005	Exposure to abacavir	First-time hospital diagnosis of MI	2.0 (1.07, 3.76)
Quebec RAMQ Durand et al. [10]	1209 (7053)	142	Nested case–control	1985–2007	Exposure to abacavir	MI	1.79 (1.16, 2.76)
STEAL study Martin et al.[55]	360	9 (4 MI)	RCT	2005–2006	TDF-FTC vs. ABC-3TC regimen	CVD[a]	Less CV events in TDF-FTC group HR 0.12 (0.02, 0.98)
SMART/INSIGHT [54]	4544	MI 19	Cohort (after inclusion in an RCT)	2002–2006	Current exposure to abacavir	MI	4.25 (1.39, 13.0)
		Major CVD 70				Major CVD[b]	1.8 (1.04, 3.11)
		Expanded CVD 112				Expanded CVD[c]	1.91 (1.25, 2.92)
Islam et al. [18]	–	–	Meta-analysis[d]	1983–2009	Abacavir exposure	CVD	Pooled RR 1.80 (1.43, 2.26)
US Veteran Health Administration Choi et al. [56]	10,931	501	Cohort	1997–2007	Recent exposure to abacavir	CVD	1.48 (1.08, 2.04)
NA-ACCORD[e] Palella et al. [62]	16,733	301	Cohort	1995–2010	Recent exposure to abacavir	MI	1.71 (1.11, 2.64)
NA-ACCORD Palella et al. [62]	6485	93	Cohort (Only ART naïve persons included)	1995–2010	Recent exposure to abacavir	MI	1.96 (not given)
Studies showing no association between exposure to abacavir and risk of CVD							
GlaxoSmithKline-sponsored clinical trial Brothers et al. [48]	3262	11	12 RCT with respect to abacavir[f]	1997–2004	–	MI	0.52 (0.2, 1.8)
FHDH Lang et al. [47]	1173 (74,958)	289	Nested case–control	2000–2006	Past, cumulative and recent exposure to abacavir	MI	1.60 (0.89, 2.85) 0.88 (0.74, 1.04) 1.62 (0.93, 2.81) [g]
US Veterans Health Administration Bedimo et al. [58]	19,424	278	Cohort	1996–2004	Cumulative exposure to abacavir	MI	1.18 (0.92, 1.50) for each year of abacavir use
ACTG A5001/ALLRT Ribaudo et al. [57]	5056	36	Cohort (after inclusion in an RCT)	1998–2009	Short term (1 year-period) and long term (6 years) exposure to abacavir	MI	0.6 (0.3, 1.4) 0.7 (0.2, 2.6)
Cruciani et al. [59]	7054	31	Meta-analysis of 28 RCT[h]	1996–2010	–	MI	0.73 (0.39, 1.35)
Ding et al. [60]	9868	46	Meta-analysis of 26 RCT	1996–2010	_	MI	1.02 (0.56, 1.84)

[a] CVD: MI, peripheral artery disease, coronary artery bypass surgery, ischemic stroke, and deep venous thrombosis

[b] Major CVD: MI, stroke, surgery for coronary artery disease, and death from CVD

[c] Expanded CVD: major CVD plus congestive heart failure, peripheral vascular disease, coronary artery disease requiring drug treatment, and witnessed deaths

[d] Three cross-sectional studies, two case–control studies, 16 cohort studies, and two RCT

[e] The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is a regional collaboration of multiple independent cohorts that includes over 130,000 HIV-infected and 150,000 HIV-negative participants from more than 200 sites throughout the USA and Canada

[f] HIV Data Repository, an aggregated clinical trials database maintained by GSK. Data from 52 adult trials were assessed, 36 were randomized trials, 12 randomized with respect to abacavir therapy

[g] No association found with cumulative exposure to abacavir. Recent exposure to abacavir was associated with increased risk of MI (OR=2.01, CI 95 %=1.11–3.64) but the association disappeared when analysis was restricted to cocaine and intravenous drugs non-users

[h] MI data were only available from 18 RCT

ritonavir, reporting higher lipid levels in the abacavir group but similar TC/HDL ratio [78], findings beings also reported in other studies [79–81]. However, decreases in TG and increases in HDL-C were greater with abacavir/lamivudine than with tenofovir/emtricitabine when combined with raltegravir [82].

Altered platelet reactivity has been described in HIV-infected patients. However, the role of different ART drugs on platelet dysfunction is not fully clarified. Abacavir has been shown to enhance some in vivo markers of platelet activation and induce platelet hyper-reactivity in some studies, which might lead to an increased risk of CVD [83]. Intensification of ART with raltegravir has shown to suppress residual viral replication and reduce inflammatory and coagulation biomarkers and has been associated with a reduction in platelet hyper-reactivity and platelet-monocyte aggregation [84–86].

The Role of HIV Infection in Itself in the Pathogenesis of Cardiovascular Risk

Immune dysfunction and persistent inflammation are important underpinnings among patients with HIV and are not completely restored despite maintained virological suppression. HIV is associated with T-cell activation; translocation of microbial products from the gut; monocyte-, and macrophage-related inflammation; inflammatory cytokines; dysfunctional immunoregulatory responses; endothelial activation; and hypercoagulation, all potentially contributing to an increased risk of CVD. All these mechanisms are incompletely understood and are the focus of active research. Other pathogens, such as cytomegalovirus, might also contribute to this T-cell activation [87].

HIV infection causes damage of the gut epithelium resulting in a chronic translocation of microbial products (such as lipopolysaccharide (LPS)) contributing to persistent systemic inflammation. Markers of microbial translocation correlate with markers of inflammation (such as hsCRP and IL-6), innate immune activation (such as sCD14 and sCD163), and coagulation (d-dimer) which are elevated in HIV-infected individuals and are predictive of morbidity (including CVD) and mortality [87–92].

HIV viremia correlates with d-dimer levels in untreated patients and initiation of cART diminishes d-dimer levels, though it probably does not restore normal levels. Intensification strategies with raltegravir have shown to decrease d-dimer levels even further [85].

Elevated soluble urokinase-type plasminogen activator receptor (suPAR) is an inflammation marker and has recently been identified as a predictor of MI in HIV-infected patients [93].

Inflammation may also affect CVD risk through proatherogenic effects on lipid metabolism. HIV seroconversion results in decreased levels of TC, LDL-C, and HDL-C [94]. The progressive immunosuppression and inflammation in untreated patients is associated with hypoalphalipoproteinemia, altered HDL metabolism redirecting cholesterol to apo-B containing lipoproteins, HDL with increased TG content, and high levels of TG, leading to predominance of atherogenic very-low-density lipoprotein-cholesterol (VLDL-C) and LDL-C, which is associated with increased risk of CVD in the background population [95].

Findings from studies assessing the potential association between CD4+ cell count and risk of CVD are somewhat divergent. While some have found an increased risk [12•, 96–98] in individuals with lower nadir or recent CD4+ counts, a strong independent association was not clear in other studies [99]. However, patients with incomplete or declining immunological recovery despite virological successful cART have a higher risk of CVD [100, 101].

The recent results from the START study showed a marked advantage for early ART-initiation [102], with reduced risk of AIDS and non-AIDS outcomes. However, no difference in CVD risk was observed between treatment arms in a median follow-up of 3 years. All the same, it is likely that earlier initiation of cART will also further reduce the potential endothelial damage associated with chronic inflammation.

Cardiovascular Risk Estimation in HIV-Infected Individuals

Current guidelines for CVD risk reduction in the HIV population recommend assessment of CVD risk using conventional risk prediction models, such as Framingham, SCORE, or other national prediction models [103]; or by using a prediction model tailored to the HIV-infected population, such as the D:A:D prediction model [104, 105]. Cardiovascular risk prediction equations developed in non-HIV populations may be inaccurate to estimate the CVD risk in HIV-infected individuals [103, 106], as they do not take into account HIV-related features that likely contribute to the increased risk, including ART, chronic inflammation, immune activation, or HCV co-infection [107]. However, the models can be recalibrated to provide better estimates.

HIV-specific CV risk-prediction equations have been developed, incorporating traditional CVRF and HIV-specific measures such as exposure to individual ART and CD4+ cell count [104, 108, 109]. Assessment of conventional CV models, and the D:A:D HIV-specific model, that was derived primarily from European populations, were all found to underestimate the risk of CVD in the US HOPS population

[110]. Recently, the D:A:D group has developed updated CVD-risk prediction models to facilitate the identification of high-risk patients at the clinic. A full model incorporates CD4+ count and exposure to ART, and a reduced model is based on conventional CVRF and CD4+ count only [108].

There is a need to further assess and calibrate the prediction models in demographically diverse populations of HIV-infected individuals, including in non-white populations, in women, and in elderly.

Further, future studies may show whether bio-markers of inflammation or thrombosis can contribute with additional predictive value in HIV.

Clinical Implications

Primary and secondary prevention of CVD in the HIV population is of paramount importance and mainly based on guideline recommendations from the general population, which may not be fully fitting for HIV-positive persons.

Recommended preventive measurements should be targeted to individuals at increased risk of CVD and include smoking cessation, lipid-lowering therapy, anti-hypertensive therapy, and treatment of glucose disorders, while the value of exercise and dietary modification is less well examined in the HIV-positive population.

Early ART-initiation is recommended based on the effect in preventing AIDS and non-AIDS clinical outcomes, and may be helpful in decreasing the risk of CVD. Choice of ART in patients at moderate to high risk of CVD should include drugs with improved lipid and metabolic profiles, and limited potential of drug–drug interactions with co-medications [111].

With regard to management of dyslipidemia, updated ACC/AHA guidelines for the US general population were recently published [112]. With the newer recommendation, more HIV-infected persons are now eligible for statin therapy [113, 114]. However, the European guidelines are more conservative with higher thresholds for recommending statin-initiation [115] (Fig. 1).

Statins have lipid-lowering and anti-inflammatory properties and have been shown to reduce the risk of CVD. Drug–drug interactions with ART should be taken into consideration before statin-initiation. Serum levels of simvastatin and lovastatin are markedly increased when co-administrated with inhibitors of CYP3A4, such as ritonavir and cobicistat, and should be avoided. Atorvastatin levels are modestly increased when co-administrated with boosted-PIs can be used initiating at the lowest dose with gradual up-tittering to goal lipid levels. In contrast, CYP3A4 inducers (e.g., EFV) may result in decreased atorvastatin serum concentrations. Rosuvastatin and pitavastatin are not metabolized via CYP3A4, and no significant drug interactions are expected. Pravastatin can also be used, with dose down-adjustment when administrated with darunavir. There are no drug–drug interactions between unboosted integrase-inhibitors and any of the statins.

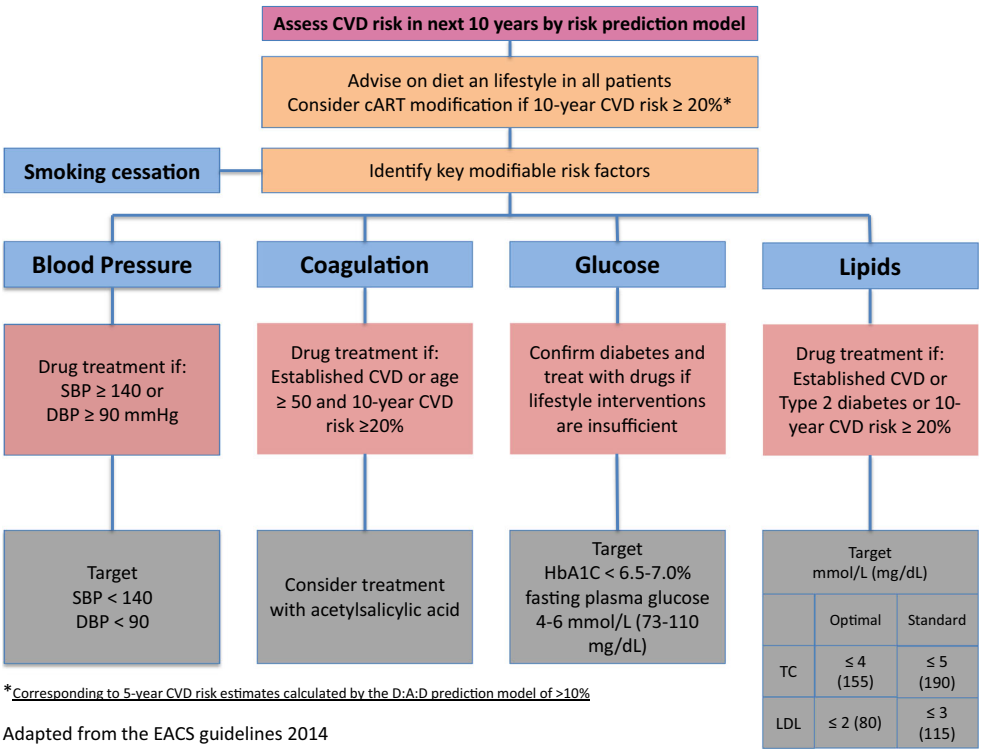

Fig. 1 Prevention of CVD in HIV-infected patients. *SBP* systolic blood pressure, *DBP* diastolic blood pressure. Source: European AIDS Clinical Society

Fibrates can be used in HIV similarly to uninfected patients [116].

Data on effect of statin therapy on clinical outcomes in the HIV-population are scarce, but a large ongoing RCT assessing the effect of pitavastatin—the REPRIEVE study—is likely to inform the field, and additional newer lipid-lowering and anti-inflammatory drugs are being evaluated by other ongoing clinical trials.

Rosuvastatin has shown to halt progression of cIMT in HIV-infected patients on ART with low LDL-cholesterol [117]. A recent study assessed the effect of atorvastatin versus placebo in HIV-infected individuals with increased arterial inflammation and low LDL showing no significant difference in FDG-PET uptake but a reduction in non-calcified plaque volume [118].

Conclusions and Future Perspectives

As HIV-infected patients with controlled HIV-1 viremia are aging, CVD has emerged as an important cause of death. The incidence of CVD overall in HIV is relatively low, but it is approximately 1.5-fold higher than in age-matched HIV-uninfected individuals. The absolute risk of CVD is expected to increase paralleling aging, and more patients will get to the situation where interventions are required. Both HIV-related factors and ART might contribute independently to an increased risk of CVD, together with an overrepresentation of CVDRF (including smoking).

Protease inhibitors currently recommended as first-line therapy in some guidelines have a worse metabolic profile than new integrase inhibitors. There are still concerns about abacavir use and the risk of CVD, although an increased risk of CVD has not been found consistently across studies. While some major guidelines include precaution for the potential increased risk of CVD with abacavir use [105], others have removed this warning.

There are data to suggest that interventions to modify CVDRF in HIV-infected persons have increased over the years and have in some settings contributed to curbing CVD rates. It remains paramount to include assessment of CVDRF and predicted CVD risk in the regular follow-up of HIV-infected persons.

Many questions remain unanswered regarding CVD in the HIV-population, a continuously evolving field. Future research should include demographically diverse populations ensuring equal representation according to gender and ethnicity. Further understanding of HIV-related mechanisms involved in CVD and the potential benefits of anti-inflammatory and antithrombotic therapy are of important value. Challenge remains in early risk identification and prevention strategies in this population. As the HIV population continues to age, the efforts in CVD prevention will increase and have a more seminal role in HIV care. Therefore, more precise and detailed recommendations on antiretroviral treatment choice and pro-active changes to further benefit the CVD profile will be needed.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Martin-Iguacel has nothing to disclose. Dr. Llibre reports personal fees from Janssen-Cilag, personal fees from Merck, personal fees from Sharp & Dohme, personal fees from ViiV Healthcare, personal fees from Gilead Sciences, personal fees from Bristol Myers Squibb, outside the submitted work. Dr. Friis-Møller has nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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