

HIV infection, aging and cardiovascular disease: epidemiology and prevention

Kathy Petoumenos^{A,C} and Signe W. Worm^B

^AThe Kirby Institute, University of New South Wales, Sydney, NSW 2010, Australia.

^BCopenhagen HIV Program (CHIP), University of Copenhagen, Copenhagen DK-2200, Denmark.

^CCorresponding author. Email: Kpetoumenos@kirby.unsw.edu.au

Abstract. In the developed world, HIV infection is now well managed with very effective and less toxic antiretroviral treatment. HIV-positive patients therefore are living longer, but are now faced by challenges associated with aging. Several non-AIDS associated morbidities are increased in this population, including cardiovascular disease (CVD). It is suggested that CVD occurs earlier among HIV-positive patients compared with HIV-negative patients, and at a higher rate. Several factors have been proposed to contribute to this. First, the traditional CVD risk factors are highly prevalent in this population. High rates of smoking, dyslipidaemia and a family history of CVD have been reported. This population is also aging, with estimates of more than 25% of HIV-positive patients in the developed world being over the age of 50. Antiretroviral treatment, both through its effect on lipids and through other, sometimes less well understood, mechanisms, has been linked to increased CVD risk. HIV infection, especially untreated, is a further contributing factor to increased CVD risk in HIV-positive patients. As the HIV-positive population continues to age, the risk of CVD will continue to increase. Guidelines for the management and prevention of CVD risk have been developed, and are largely modelled on those used in the general population. However, the data currently suggest that these interventions, such as the use of lipid-lowering medications and smoking cessation programs, remain quite low. A better understanding of the mechanisms of CVD risk in this aging population and further efforts in improving uptake of prevention strategies will remain an important research area.

Additional keywords: AIDS, antiretroviral treatment, dislipidaemia, heart disease, myocardial infarction.

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Introduction

Successfully treated HIV-positive patients in developed countries are now experiencing increased rates of several non-AIDS related complications. Cardiovascular disease (CVD) is among the major non-AIDS complications, with between 9% and 20% of HIV-positive patients in developed countries reported to have a moderate to high 10-year risk of myocardial infarction (MI).^{1–4} Multiple factors contribute to this increased risk. First, this population is now aging, with increasing rates of patients over the age of 50.⁵ In Australia, more than 25% of the HIV-positive patients in clinics are now aged over 50 years.^{6,7} In the USA, it is estimated that by 2015, for example, 50% of HIV-positive patients will be over the age of 50.⁸ Studies have shown that among older patients, the risk of CVD, as well as many other non-AIDS conditions, increases for HIV-positive patients, as it does for HIV-negative patients, but the risk is greater in HIV-positive patients.^{9–12} Lifestyle factors such as smoking and substance misuse are much higher in HIV-positive patients,^{13,14} and HIV-positive patients are also more likely to experience dyslipidaemia and often have other chronic conditions that increase the risk of severe non-AIDS morbidity.¹⁵ Furthermore, antiretroviral treatment (ART)

increases the rates of dyslipidaemia, insulin resistance and diabetes.^{16,17} Finally, HIV infection itself appears to be associated with age-related complications.¹⁸

The risk of CVD in HIV-positive patients is more complex than in the general population, with potential interactions between traditional cardiovascular risk factors, which are highly prevalent in this now aging population; genetics and family history; the effect of ART; and the HIV virus itself. Rates of MI events have been reported in various studies to range between 3.5 per 1000 person-years and 11.13 per 100 person-years among HIV-positive patients;^{9,11,16,19} substantially greater than in the HIV-negative population.⁹ In the Data Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study, the largest prospective study of HIV-positive patients, the rate of MI increased from 0.27 per 1000 person-years in patients aged 25–30 years to 16.99 per 1000 person-years in patients aged over 70 years.¹⁶ Even in countries with lower overall MI risk, such as France, HIV-positive men and women are at increased risk compared with age- and sex-matched HIV-negative patients.²⁰ This review will focus on the traditional risk factors of CVD, as well as the impact of ART and, to a lesser extent, HIV infection on CVD and, finally, prevention.

Traditional risk factors

In the developed world, HIV-positive patients are largely male, aging and, to a smaller extent, have a family history of CVD,^{4,21,22} accounting for several of the non-modifiable CVD risk factors. Indeed, age is among the strongest factors associated with CVD risk in both HIV-positive and HIV-negative populations, with the risk of MI increasing by 6–9% for every year aged in both populations as previously described.²³ Among the modifiable CVD risk factors, smoking, dyslipidaemia, and hyperglycaemia are also highly prevalent among HIV-positive patients.^{2,4,22} In a cross-sectional analysis of the D:A:D study population, almost 25% were in an older age group (over 45 years for males; over 55 for females), 11.4% had a family history of coronary heart disease, 51.5% were current cigarette smokers, more than 8% had hypertension and the overall prevalence of diabetes mellitus was 2.5%.²¹ In a USA registry-based study, HIV-positive patients had significantly higher proportions of hypertension (21.2% v. 15.9%) and diabetes (11.5% v. 6.6%) compared with HIV-negative patients.⁹ In another USA study, the prevalence rates of current smoking and hyperlipidaemia were significantly higher among HIV-positive cases than HIV-negative controls (18.8% v. 9.5% for smoking and 21% v. 16% for hyperlipidaemia), whereas the prevalence rates of hypertension (18% v. 24%) and diabetes (7.2% v. 8.8%) were lower among HIV-positive cases.¹¹

The contribution of smoking on the risk of CVD is significant and, in some cases, greater than many other CVD risk factors.^{19,24} Current smoking has been reported in 40% to 70% of HIV-positive patients, two- to three-fold greater than the general population.^{4,22,25–31} Compared with non-smokers, smokers have a two-fold or greater increased risk of MI¹⁹ and CVD.^{24,32} Although two studies have reported decreasing rates of smoking over time, in part suggesting that in an aging cohort, smoking rates are decreasing,^{4,5} few data are available on actual rates of smoking as HIV-positive patients age. In the Swiss HIV Cohort Study, the prevalence of current smoking was lower among men older than 40 years compared with younger men (52.5% v. 64.3%, respectively), but not in women (53.4% v. 53.9%).⁴

Cocaine use has also been linked to CVD.³³ The mechanism for this association is beyond the scope of this review; however, it may be of relevance in the setting of HIV, as cocaine use, and injecting and illicit drug use more generally, is prevalent across several HIV subpopulations. In the USA, up to 20% of all HIV-positive patients are thought to use cocaine and more than 40% among African Americans.³⁴ Among women participating in the Women's Interagency HIV Study (WIHS), ~25% reported intermittent cocaine use.³⁵ In Australia, among men who have sex with men, the prevalence of illicit drug use is over 60%, and 17% have reported using cocaine at least once.¹⁴ Cocaine use is also associated with poorer adherence and consequently poorer immunological and virological control.^{35,36} Long-term cocaine use has been linked to silent coronary artery disease in HIV-positive African Americans;³⁴ however, to date, there has been no large study in the setting of HIV that has proven that use of cocaine is associated with an increased risk of MI.

Hypertension or raised blood pressure has been reported in up to 28% of HIV-positive patients.^{4,21,22} As these patients age,

the prevalence of hypertension is also expected to increase, with data from the USA reporting hypertension in 12–20% of patients below the age of 40, and in 35–41% of patients over the age of 40.³ In the D:A:D study, older age was significantly associated with hypertension, along with several other traditional risk CVD factors such as male gender, a higher body mass index and higher blood pressure, as well as regimens excluding non-nucleoside reverse transcriptase inhibitors (NNRTI).³⁷

Between 2% and 14% of HIV-positive patients have been diagnosed with diabetes mellitus or other glucose disorders, and this proportion is also increasing over time, due at least in part to the aging of patients.^{2,4,21,22} In the D:A:D study, increasing age was significantly predictive of incident diabetes mellitus, even after adjustment for other CVD risk factors and ART.³⁸ Further, data from this study suggested that the risk of coronary heart disease (CHD) increased with longer duration of diabetes mellitus.³⁹ Elevated triglycerides, decreased total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) have been increasingly observed among HIV-positive patients; and these changes have been attributed to multiple factors, including ART,^{40–42} as well as HIV infection.^{41,43} Combination ART (cART) use and worsening lipid concentrations is well documented, with protease inhibitor (PI) use having the most profound effect on lipids.^{21,44} Plasma triglycerides increase, as does TC and LDL cholesterol,^{40–42} and both PI and nucleoside(tide) reverse transcriptase inhibitor (NRTI) use have been linked with causing abnormal fat distribution.^{45,46} In particular, stavudine and didanosine have been linked with the development of lipodystrophy syndrome (LDS).^{46,47} As these drugs are now seldom used, it is anticipated that the incidence of LDS will decline. Studies have reported high frequencies of impaired glucose tolerance in patients with LDS or fat accumulation, for example, 35% are reported to have impaired glucose tolerance compared with 5% in healthy matched controls, and 7% are reported to have diabetes mellitus compared with 0.5% of healthy matched controls.⁴⁸ The presence of LDS has not been shown to be an independent risk factor for MI,¹⁶ and it remains unclear whether dyslipidaemia worsens with age among HIV-positive patients. In the D:A:D study, rates of dyslipidaemia remained relatively stable for each calendar year between 2000 and 2006,⁵ while data from the Veteran's Affairs study reported dyslipidaemia to be more common among older HIV-positive patients who are also male and of white ethnicity.⁴⁹ As this population is living longer, HIV-positive patients will be receiving cART for much longer, and the independent effect of aging on dyslipidaemia will continue to be confounded by the direct effect of ART, other CVD risk factors and increases in the use of lipid-lowering medication.

HIV infection

HIV infection itself has been associated with CVD risk, with increased rates of CVD shown in many HIV-positive versus HIV-negative studies.^{9,50,51} The independent role of untreated HIV infection was most notably demonstrated following the outcomes of the Strategies for Management of Antiretroviral Therapy (SMART) study. Patients in the SMART study who

were randomised to the drug conservation arm (intermittent therapy guided by CD4 cell counts) had a 60% increased risk of CVD over a mean of 16 months of follow-up compared with those in the viral suppression arm (continuous therapy). As a result of these findings, it was proposed that a combination of HIV viral load, immunological factors and inflammation as a result of discontinuing ART all contribute to CVD risk.¹⁸

The link between immunodeficiency and CVD is still unclear. Much of the literature reporting associations between low CD4 cell count and CVD are from registry-based studies, some of which do not account for or lack sufficient information for several important confounders such as smoking and family history of CVD. In one USA health care system database, the latest CD4 cell counts below 200 cells μL^{-1} was independently associated with a 74% increased risk of MI, although smoking data were not available in this analysis.⁵² Data from the HIV Outpatient Study (HOPS) cohort reported a 28% and 58% increased risk of CVD for patients with baseline CD4 cell counts between 350–499 cells μL^{-1} and <350 cells μL^{-1} , respectively, compared with counts >500 cells μL^{-1} . In a nested case-control study, the HOPS group also reported that a latest CD4 cell count below 500 cells μL^{-1} was independently associated with an increased incidence of CVD, but baseline or nadir CD4 cell counts were not.⁵³ In contrast, results from the prospective D:A:D study with clinical end-points have consistently reported no association between immunodeficiency and CVD risk.^{16,19} In the Aquitaine study investigating hospitalisation rates among HIV-positive patients between 2000 and 2004, a trend with CD4 was shown for several non-AIDS events, yet, little association was shown with CVD events.⁵⁴ Data from Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) suggest a stronger association with HIV RNA and CVD death than with CD4 cell count.⁵⁵

HIV-induced inflammation might also explain this increased risk in CVD in part, particularly given that it is well established that inflammation is major factor in the development of atherosclerosis in the general population.⁵⁶ The risk of CHD is also likely to be higher in patients with chronic inflammation.⁵⁷ Carotid artery intima-media thickness (cIMT), a surrogate marker of atherosclerosis, has been associated with vascular inflammation in HIV-positive patients;^{58,59} and HIV-positive patients are at increased risk for progression of cIMT compared with sex- and age-matched controls.^{50,60} However, others have not shown an increased cIMT in HIV-positive patients compared with HIV-negative controls.^{61,62} Whether HIV infection is independently associated with increased cIMT remains uncertain. Elevated C-reactive protein (CRP) and interleukin-6 (IL-6) are both predictors of CVD events in the general population.^{63,64} The Multicenter AIDS Cohort Study (MACS) showed an elevated CRP level in HIV-positive patients that was associated with AIDS, negatively correlated with CD4 cell count and positively correlated with HIV RNA levels.⁶⁵ Higher D-dimer levels were also associated with increased CVD risk in the general population.⁶⁶ In the SMART study, 1 month after stopping treatment, HIV RNA levels were associated with increases in D-dimer and IL-6 levels, and baseline D-dimer and IL-6 levels were strongly associated with an increased risk of all-cause mortality.⁶⁷ Compared with HIV-negative patients, treated HIV-

positive patients have higher levels of inflammatory markers such as high sensitivity CRP, IL-6, D-dimer and cystatin C.¹⁵ Higher CRP levels are reported in ART-treated versus naïve patients,⁶⁸ and data from the Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) showed an increase in fibrinogen and CRP compared with HIV-negative patients, and among patients on PIs compared with patients receiving NNRTIs.⁶⁹ Although these markers of inflammation are higher in untreated HIV infection, they do not seem to be fully reversed with effective cART.⁶⁷

The association between immune status, inflammation and CVD risk remains the subject of ongoing research. How aging might also influence these associations is also still being investigated. Changes in the immune system caused by normal aging are similar to changes observed due to HIV infection, such as declining CD4 cell counts with age. In one study, levels of naïve cells in HIV-positive patients were equivalent to those seen in HIV-negative patients 20–30 years older.⁷⁰ It is also increasingly hypothesised that HIV infection results in the premature aging of the immune system, known as immunosenescence.^{71,72} Future research is likely to clarify whether these factors may result in increased rates of CVD among HIV-positive patients compared with HIV-negative patients and at an earlier age.

Antiretroviral treatment and CVD

The increasing rates of dyslipidaemia and other metabolic changes among HIV-positive patients receiving ART have led to many studies investigating the link between ART use and CVD. The largest prospective cohort study specifically designed to investigate the impact of ART on CVD is the D:A:D study, including more than 33 000 patients from Europe, the USA and Australia. Initial findings from this study reported a relative rate for MI of 1.26 per year of ART exposure and 1.16 after adjustment for individual lipids.¹⁹ These results demonstrated a higher risk of CVD among HIV-positive patients receiving ART. PI use in particular has been linked to increased CVD risk. In the D:A:D study, the rate of MI was 1.53 per 1000 person-years among patients not exposed to PI and 6.01 per 1000 person-years for patients exposed to PIs for more than 6 years.¹⁶ The risk per additional year of exposure to PIs was 13% NRTI and 16% PI respectively, similar to that also reported by others.⁷³ This risk was reduced to 10% per year in the D:A:D study after adjustment for NRTI exposure as well as diabetes mellitus, hypertension, TC, triglycerides and HDL,¹⁶ suggesting that lipid changes explains some of the elevated risk of CVD, but not all. Several other studies have also reported an association between PI and CVD,^{24,51,74,75} although others have not.⁷⁶ Data on the association between NRTI and NNRTI use and CVD are more limited. In the D:A:D study, NNRTI was not associated with increased MI risk,¹⁶ and data from the Veterans Affairs also were unable to demonstrate an association.⁷⁶ However, in these studies, the overall duration on NNRTI is considerably less than duration of PI use and may require longer exposure time to fully elucidate if there is an association. NRTI use has also been linked to increased CVD risk.¹⁹

While earlier studies focussed on the impact of ART class overall and CVD, individual antiretrovirals and their association

with CVD have been increasingly investigated. Even after adjusting for lipid changes, some PIs are still associated with CVD. Cumulative exposure to indinavir and lopinavir-ritonavir, for instance, was significantly associated with an increased risk of MI in the D:A:D study, and although these risks were attenuated after adjustment for lipids, this association still remained significant (Fig. 1).⁷⁷ Among the NRTIs, the thymidine analogues zidovudine and stavudine are thought to be linked with increased CVD due to their associations with dyslipidaemia, insulin resistance and other metabolic complications. Data from the D:A:D study failed to demonstrate this association between zidovudine and stavudine use and MI risk, but found that recent exposure to abacavir and didanosine were associated with a significant increased risk of MI, even after adjustment for the predicted 10-year risk of CHD, with the risk virtually unchanged.¹⁷ The abacavir finding was unexpected, and since then, several others have also found an association between abacavir and CVD,^{78–80} while others have not.^{81–83} Recent analyses from the USA Food and Drug Administration (FDA)⁸² and the AIDS Clinical Trial Group (ACTG) group⁸³ both demonstrated no association between the increased risk of MI and abacavir use in this young HIV population with no CVD risk factors,⁸² a finding consistent with other studies exploring use of abacavir in patients at low CVD risk.^{17,81} The association between abacavir use and increased MI risk therefore remains uncertain. A randomised clinical trial with MI as a clinical endpoint would be ideal to address this question, although a large enough trial is unrealistic. In the absence of such a trial, it remains important to understand the potential underlying mechanisms. Recent research has suggested that increased platelet aggregation^{84,85} and certain inflammatory processes⁸⁶ explain the increased risk of MI seen with use of abacavir.

Prevention

Achieving and maintaining HIV viral suppression is the fundamental goal of commencing ART treatment. Despite

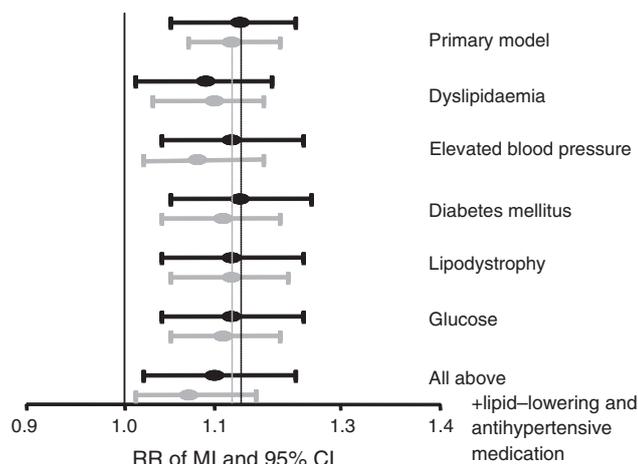


Fig. 1. Lopinavir-ritonavir (black lines) and indinavir (grey lines): effect of adjustment for latest metabolic factors on estimates of cardiovascular disease risk (source: the D:A:D study⁷⁷). CI, confidence interval; MI, myocardial infarction; RR, relative rate.

the increased risk of CVD in the population receiving cART, the absolute risk is small and the benefits of cART outweigh the risks;²¹ stopping ART therefore is not an option. Moreover, results from the SMART study demonstrated that stopping ART did not reduce the risk for CVD, or any other ART related toxicities; in fact, there was a borderline significant increase in CVD risk.¹⁸ Lipid and thrombotic factors may also be affected by discontinuing ART.^{73,87} Nevertheless, which ART to commence with (or change to) needs to be considered in terms of the patient's lifelong use of ART and their future CVD risk.

Assessing an individual patient's future cardiovascular risk is a useful tool for guiding the prevention and management of CVD risk. Recently, several cardiovascular risk equations have been developed for HIV-positive patients.^{88,89} Although these vary somewhat, they mostly agree that the risk factors in HIV-positive patients are broadly similar to those seen in the general population, with the additional contribution of ART use and HIV infection itself, factors not accounted for in the general risk equations.¹ As HIV-positive patients are living longer and aging, prevention and management of CVD risk is increasingly relevant, but may also be more complex than in the general population, as HIV-positive patients are also more likely to have other competing comorbidities. Key prevention strategies include management of dyslipidaemia and hypertension, smoking cessation, diet and other lifestyle factors, as well as the treatment and management of their HIV infection.

Guidelines for the management of dyslipidaemia in HIV-positive populations⁹⁰ mostly follow those for the general population, particularly the National Cholesterol Education Program Adult Treatment Panel-III (ATP-III) recommendations.⁹¹ The guidelines recommend the evaluation of patients in terms of their future risk of CHD and MI as determined by a risk assessment tool. Patients with the highest risk are treated most aggressively. Based on their risk, patients are either to initiate therapeutic lifestyle changes including diet, smoking cessation and hypertension medication, or, if necessary, to commence lipid-lowering medication. Lipid measures are also to be evaluated before commencing ART, then within 3–6 months of starting a new regimen and then yearly, unless abnormal and therapeutic interventions are commenced.^{90,92} Possible drug–drug interactions with ART need to be considered when lipid-lowering treatment is initiated.

To date, there is little or no evidence to suggest that HIV-positive patients need to be offered more aggressive interventions than those used in the general population. Although not in controlled trial settings, the benefit of lipid-lowering drugs and the prevention of CVD in HIV-positive populations have been demonstrated;¹ however, a large randomised clinical trial with clinical endpoints in the setting of HIV is needed to clarify this. Furthermore, the literature also suggests that the use of lipid-lowering medication may be underprescribed in the HIV positive population. In the D:A:D study, at the time of any cardiovascular event, only 23% were receiving lipid-lowering medication and a further 45% were treated in the following 6 months.⁹³ Even when lipid-lowering drugs are used, more than 50% do not reach the levels recommended

by the ATP-III guidelines in two cohort studies^{94,95} and one randomised trial.⁹⁶

The management of hypertension and diet are components of the management and prevention of dyslipidaemia and CVD.^{90,92} In the general population, dietary interventions are effective in reducing hypertension. In the HIV setting, one study involving intensive lifestyle intervention, including dietary and physical activity counselling, showed a significant reduction in blood pressure.⁹⁷ As with the management of dyslipidaemia, guidelines used in the general population to prevent or treat hypertension and reduce CVD should also be considered for HIV-positive patients. Again, the impact of ART on hypertension and possible interactions between ART and blood pressure pharmacotherapy should be considered before commencement.

The health benefits of stopping smoking are well known in the general population, with the risk of coronary heart disease and mortality considerably reduced within the first 2 years of stopping smoking.^{98–103} Similarly, recent findings from the D:A:D study demonstrated a decreasing risk in CVD with increasing years of having stopped smoking.³¹ Nevertheless, preventing smoking in HIV-positive patients is challenging. Despite the known risks associated with smoking, HIV-positive patients continue to smoke. Several reasons have been suggested, including social conditions, polysubstance abuse, psychiatric comorbidities, physical and mental distress, lack of access to smoking cessation interventions and adherence to such treatments.^{27,29,104} Pilot data have shown that existing smoking cessation interventions are feasible in HIV care settings,^{105–107} although these interventions have yet to be confirmed in large clinical trials. More research is needed to evaluate the efficacy and generalisability of smoking cessation programs in HIV-positive patients, and to gain a better understanding of the complex needs of HIV-positive patients,¹⁰⁸ as well as research on the potential interaction of pharmacotherapies and ART.

Conclusion

In summary, as HIV-positive patients live longer CVD is expected to continue to increase. The risk of CVD in HIV-positive patients is a complex mix of the traditional cardiovascular risk factors, which are highly prevalent in this aging population, ART use and HIV infection. How these risk factors might interact and how aging may also contribute to this increased CVD risk remains the subject of ongoing research. Finally, the assessment and prevention of CVD risk in this population is increasingly becoming important. However, viral control remains the number one priority in the clinical management of HIV-positive patients. The evaluation of an individual's CVD risk should be assessed routinely, and the prevention of CVD should therefore be considered in terms of the patient's overall CVD risk and HIV disease stage.

Conflicts of interest

None declared.

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