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HIV and cardiovascular disease

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Abstract

HIV-related cardiovascular disease research is predominantly from Europe and North America. Of the estimated 37·9 million people living with HIV worldwide, 25·6 million live in sub-Saharan Africa. Although mechanisms for HIV-related cardiovascular disease might be the same in all people with HIV, the distribution of cardiovascular disease risk factors varies by geographical location. Sub-Saharan Africa has a younger population, higher prevalence of elevated blood pressure, lower smoking rates, and lower prevalence of elevated cholesterol than western Europe and North America. These variations mean that the profile of cardiovascular disease differs between low-income and high-income countries. Research in, implementation of, and advocacy

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for risk reduction of cardiovascular disease in the global context of HIV should account for differences in the distribution of traditional cardiovascular disease risk factors (eg, hypertension, smoking), consider non-traditional cardiovascular disease risk factors (eg, access to antiretroviral therapy with more benign cardiovascular disease side effect profiles, indoor air pollution), and encourage the inclusion of relevant risk reduction approaches for cardiovascular disease in HIV-care guidelines. Future research priorities include implementation science to scale up and expand integrated HIV and cardiovascular disease care models, which have shown promise in sub-Saharan Africa; HIV and cardiovascular disease epidemiology and mechanisms in women; and tobacco cessation for people living with HIV.

Introduction

People living with HIV have an excess risk of cardiovascular disease compared with people without HIV.[1,2] The mechanisms driving this risk include HIV-specific, and traditional and non-traditional cardiovascular disease risk factors. Data linking HIV and clinical cardiovascular disease, risk factors, and risk assessment come predominantly from Europe and North America. Of the estimated 37·9 million people living with HIV worldwide, 25·6 million live in sub-Saharan Africa, where less is known about incidence of cardiovascular disease and the burden of risk factors driving cardiovascular disease.

Epidemiology of HIV and cardiovascular disease

With access to life-preserving combination antiretroviral therapy (ART), people with HIV are living longer and could have increased risk for diseases of ageing, such as cardiovascular disease. A model based on the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort showed that the median age of people with HIV on ART will increase from 43·9 years in 2010, to 56·5 years in 2030, by which time 78% of people with HIV will have been diagnosed with cardiovascular disease.[3]

The increase in relative risk of myocardial infarction among people with HIV ranges from 20% to 100%, compared with people without HIV (table 1). This increased relative risk persists among those with viral suppression,[14] exists for type 1 and type 2 acute myocardial infarction events;[15] and might be more pronounced in women than in men (for coronary heart disease).[16] Although the absolute rates of acute myocardial infarction are lower among people with fewer risk factors for this condition, the relative risk of acute myocardial infarction remains higher among people with HIV including those with good cardiac health.[17] Ischaemic stroke accounts for approximately 80% of all strokes in people with HIV,[18] with the rest accounted for by haemorrhagic stroke.

The scope and presentation of heart failure in HIV has evolved with improved uptake and access to ART. Overt AIDS cardiomyopathy has become less common while other causes of heart failure, including preserved ejection fraction, ischaemic post-myocardial infarction, and reduced ejection fraction heart failure, have become more common. The excess in HIV-associated risk could be greater for reduced than for preserved ejection fraction heart failure.[8]

Peripheral artery disease is relatively understudied among people with HIV. Peripheral artery disease in the USA is one of the most common clinical presentations of atherosclerosis. The few available studies on the association between HIV and peripheral artery disease report inconsistent results.[6,10,12,19] Estimates from South Africa on peripheral artery disease suggest a prevalence of 7% in HIV populations with a mean age 46 years,[20] compared with the general population with prevalence estimates of 3·9% in people aged 40–49 years.[21] The largest study examining HIV infection as a risk factor for peripheral artery disease involved over 90 000 participants from the Veterans Aging Cohort Study in the USA and reported a 19% increase in risk of incident peripheral artery disease among people with HIV versus without HIV.[10]

In a recent meta-analysis,[2] people living with HIV had more than twice increased risk of cardiovascular disease overall. All the cohorts analysed, except one from Tanzania, were either from western Europe or North America. The distribution of cardiovascular disease risk factors varies by geographical location and by HIV prevalence. Sub-Saharan Africa has the greatest prevalence of HIV, along with a younger population, higher elevated blood pressure prevalence, lower tobacco smoking rates, and lower prevalence of elevated cholesterol than western Europe and North America (figure 1).[22,23] In addition, several unique exposures such as indoor air pollution and repeated exposure to infectious agents might compound the effect of HIV on cardiac and pulmonary health[24,25] in sub-Saharan Africa, but could have minimal relevance in high-income settings.

Cardiovascular disease mechanisms in HIV

Virus-related mechanisms

Virus-related mechanisms include pro-inflammatory effects of HIV proteins released from the HIV virus, $CD4^+$ T-cell depletion, increased intestinal permeability, microbial translocation, and altered cholesterol metabolism (figure 2). Biomarkers of chronic inflammation, monocyte activation, and altered coagulation are elevated in people living with HIV compared with people without HIV.[26] Many of these biomarkers are associated with atherogenesis, an inflammatory process, leading to atherosclerotic cardiovascular disease (eg, myocardial infarction). Importantly, sex-based differences in response to an acute HIV infection might persist into chronic infection, resulting in increased immune activation in women compared with men.[16] These sex-based differences could explain higher rates of myocardial infarction among women,[16] which is an important reason for greater inclusion of women and sex-stratified analyses in this field. Greater inclusivity should extend to pre-menopausal and post-menopausal women, and gender minorities for whom sex hormone profiles might (independently and synergistically with HIV) be important drivers of cardiovascular disease risk.

$CD4^+$ T-cell depletion among people with HIV is associated with higher rates and risk of incident acute myocardial infarction, heart failure, peripheral artery disease, and ischaemic stroke (table 1). Weakened adaptive immunity could lead to opportunistic infections, which in turn drive an inflammatory response that might lead to cardiovascular disease (eg, infectious myocarditis).[27] A study by Grody and colleagues[28] also suggests that HIV itself can cause cardiomyopathy via direct infection of cardiac myocytes.[29] The depletion of $CD4^+$

T cells in the gut mucosa, caused by HIV infection, damages the lining of the gut and increases its permeability to microbial translocation products. Microbial translocation is a process whereby microbial products from the gut leak across the disrupted gut lining and into the portal circulation on the way to the liver. This process leads to chronic immune activation and inflammation.[30] HIV, like other viral infections, is associated with altered cholesterol metabolism resulting in atherogenic lipid and cholesterol profiles.[31]

In the CNS, HIV could alter the blood–brain barrier through infected monocytes, which routinely surveil the brain from the peripheral circulation. In the closed brain compartment, HIV can infect perivascular macrophages, microglial, and mural support tissue, and establish a reservoir.[32,33] This microenvironment of HIV-infected cells can accentuate inflammatory mediators and contribute to endothelial dysfunction, and vessel wall remodelling.[33,34] Whether the mechanism in the brain differs from the periphery is yet to be established, but clinical stroke phenotypes suggest differences do exist.[35]

ART-related mechanisms

Any adverse effect of ART on cardiovascular disease risk should be balanced against the life-preserving effects of ART and the effects of these drugs on reducing HIV viraemia.[36] Older ART regimens (eg, abacavir, lopinavir, and ritonavir) used in low-income settings had side-effect profiles detrimental to cardiovascular health such as altered glucose and lipid metabolism, mitochondrial toxicity and subsequent cardiac myopathy, or impaired left ventricular function.[37] Other regimens (eg, dolutegravir or atazanavir) might have less detrimental effects on cardiovascular health.[38,39] Whether these cardiotoxic-ART effects differ by sex is unclear.[40]

Weight gain after initiation of ART and HIV viral suppression in part reflects ART side-effects[41] and a return to health after resolution of overt HIV replication (a catabolic state).[42] It also reflects fluctuating trends in weight gain in low-income and high-income settings, which are not unique to HIV. Combined, these sources of weight gain have been associated with incident diabetes, a cardiovascular disease risk factor, and this association is dependent on body physique before starting ART.[42]

People ageing with HIV have multiple chronic comorbidities often requiring multidrug regimens and resulting in polypharmacy.[43] The potential for drug–drug interactions increases with increasing number of medications which in turn could contribute to QT interval prolongation.[44] Prolonged QT intervals are associated with HIV infection and increased risk of sudden cardiac death. People with HIV have a 4-times increased risk of a sudden cardiac death compared with people without HIV.[11]

Non-HIV specific mechanisms

Non-HIV specific mechanisms contributing to increased risk of cardiovascular disease include traditional and non-traditional cardiovascular disease risk factors. Traditional risk factors include smoking, diabetes, dyslipidaemia, hypertension, and biological sex. Although not unique to people living with HIV, populations in some regions might have greater exposure to these risk factors (figure 1). Women with HIV might have higher odds of developing metabolic syndrome than men.[40] When these risk factors are absent, the relative

risk of acute myocardial infarction among people with HIV compared with people without HIV is still 2-times higher, but the absolute rates of acute myocardial infarction are low. Increasing exposure to these risk factors leads to an exponential increase in cardiovascular disease risk regardless of HIV status.[17]

These risk factors in combination with HIV infection have been variably associated with subclinical atherosclerosis including carotid intima-media thickness, coronary artery calcification, and other structural and functional vascular alterations.[45–49] In addition to variability in the geographical distribution of traditional cardiovascular disease risk factors, variability in the association of these risk factors with subclinical cardiovascular disease highlight the need for geographically diverse studies for HIV-related cardiovascular disease risk reduction globally.

Non-traditional cardiovascular disease risk factors are also accentuated in HIV and include unhealthy alcohol consumption, depression, hepatitis C, and possibly cytomegalovirus co-infection. Unhealthy alcohol consumption, independent of HIV infection, can cause microbial translocation, activating Kupffer cells, which drive chronic inflammation. Liver fibrosis can itself be associated with increased heart failure risk.[50] Unhealthy alcohol consumption is also associated with ART non-adherence,[51] which causes increased HIV viral replication and might consequently increase cardiovascular disease risk.

Major depressive disorder can affect between 5% and 10% of people with HIV. Depression is a risk factor for both acute myocardial infarction and heart failure among people with HIV.[52,53] Although the exact mechanism is unknown, some reports link depression with autonomic nervous system dysregulation, inflammation, and platelet activation.

Hepatitis C and cytomegalovirus are common co-infections among people with HIV. In many, but not all, studies, hepatitis C has been linked to incident cardiovascular disease events.[14,54] Underlying mechanisms are thought to be related to chronic inflammation, endothelial dysfunction, and exacerbating microbial translocation through hepatic damage. The role of cytomegalovirus as a risk factor for cardiovascular disease is less clear. Observational studies in the general population link cytomegalovirus antibody status to incident cardiovascular disease.[55] Among people with HIV, no such studies exist, although some evidence links cytomegalovirus status to immunosenescence,[56] which might predispose to cardiovascular disease risk.

Disparities in cardiovascular care occur with studies reporting that people with HIV are less likely to receive aspirin for primary cardiovascular disease prevention, HMG-CoA reductase inhibitor therapy for diabetes, cardiovascular disease, or dyslipidaemia;[57] and invasive procedures for myocardial infarction compared with people without HIV.[58] These disparities by HIV status might be worsened by substance use disorders, female sex,[40] and among racial and ethnic minorities.

Clinical guidelines for treating cardiovascular disease in HIV

Scarce data on HIV and cardiovascular disease risk, from sub-Saharan Africa, are the reason for insufficient cardiovascular disease risk stratification tools and guidelines tailored for

this setting.[59,60] Most existing cardiovascular disease risk calculators are derived from HIV uninfected populations in high-income countries. Although an HIV-specific risk estimation model exists, it is derived from a largely white European population and relies on data from before the modern ART era, therefore limiting its current applicability.[61] Cardiovascular disease risk prediction for people living with HIV in sub-Sahara Africa faces another problem in that the epidemiology of traditional cardiovascular disease risk factors is unique from that in high-income countries. The results of studies including REPRIEVE (NCT02344290), SEARCH (NCT01864603), and EVERLAST[48] might provide important incidence and risk factor data to inform cardiovascular disease risk prediction for people with HIV in low-income and middle-income countries.

The American Heart Association (AHA) recently provided guidance[62] on applying the atherosclerotic cardiovascular disease risk calculator in people living with HIV (table 2). For patients with HIV-related cardiovascular disease risk-enhancing factors (eg, prolonged viraemia, fatty liver disease), clinicians might adjust the calculated risk estimate upward by 1·5–2 times on the basis that most risk calculators tend to underestimate cardiovascular disease risk in this group,[76] and that specific HIV-related factors (eg, low nadir and current CD4 count) are associated with cardiovascular disease risk elevation. Traditional and non-traditional atherosclerotic cardiovascular disease risk factors should be considered. Intervention involves a combination of lifestyle optimisation regardless of risk and consideration of pharmacotherapy with rosuvastatin, atorvastatin, pravastatin, or pitavastatin for people at sufficiently high risk.

This risk adjustment approach in the AHA scientific statement on HIV is also incorporated in the European Society for Cardiology guidelines[71] that consider people with HIV at high risk for cardiovascular disease and suggest treating LDL-cholesterol to a goal of less than 70 mg/dL. These guidelines seem reasonable to apply in low-income and middle-income countries in the absence of a clear alternative. However, in South Africa, people living with HIV are considered to be at low risk for atherosclerotic cardiovascular disease and guidelines applicable to the general population are suggested for people living with HIV with no upward adjustment in risk.[64]

The 2010 South African guidelines[72] for the management of ischaemic stroke and transient ischaemic attack have provided comprehensive guidance, but they were not specific about HIV infection and the risk of stroke. Extrapolating AHA guidance to existing cardiovascular risk scores for stroke risk prediction in low-income and middle-income countries is reasonable, considering previously discussed limitations.[73] An additional caveat is that intracranial, large to medium sized ischaemic strokes might be driven by non-traditional vascular risk factors and therefore might not be applicable.[74]

Combining stroke epidemiology with cardiovascular disease, an oversight to be rectified in the *International Classification of Diseases and Related Health Problems*-11,[75] reduces emphasis on stroke in high-income settings.[76] The AHA acknowledged that the cause of stroke is dependent on the stage of HIV infection, transitioning from opportunistic infection, coagulopathy, and HIV-associated vasculitis in advanced disease, to atherosclerosis and an undefined (non-vasculitic, non-atherosclerotic) vasculopathy among those with stable

disease and on ART.[35,62,77] In high-income countries, the stage of HIV is less advanced than in low-income countries but opportunistic infections can still arise when ART fails, or in the late presentation of HIV.[78] An inflammatory vasculopathy can occur in the context of a cerebrospinal fluid HIV escape syndrome, among those with stable disease and those on ART.[79] Although antiplatelets, statins, antiglycaemic drugs or antihypertensive drugs are the main therapies for primary and secondary prevention of cardiovascular disease in high-risk groups, other targeted therapies might be required after a stroke (eg, antithrombotic drugs, antiviral drugs for co-infection, and ART in those with more potent CNS penetration to manage cerebrospinal fluid HIV escape syndrome).

No guidelines exist for HIV-related heart failure prevention and treatment, given the absence of clinical trial data and few observational data on heart failure in the modern ART era. Accordingly, the 2019 AHA scientific statement suggests that heart failure examination and therapy for people with HIV should be similar to that for those without HIV, given the uncertainty about the mechanisms of heart failure in HIV. Diuretics, renally-excreted β blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs), with the exception of losartan and irbesartan, do not appear to have prohibitive drug–drug interactions with most ART. Providers should be aware of heart failure medication metabolised by the cytochrome P450 3A4 enzyme because of potential interactions with ART that can inhibit this enzyme, such as ritonavir and cobicistat. People living with HIV should be offered surgical, device, and mechanical therapies for heart failure on the basis of clinical indications applicable to the general population.[62]

Experts recommend following the guidelines for peripheral artery disease and sudden cardiac death provided by the American College of Cardiology, AHA,[80] European Society for Vascular Surgery, and European Society of Cardiology.[81] These guidelines recommend full assessment and screening of patients, and a physical examination. If the assessment is suggestive of peripheral artery disease, additional testing (eg, ankle-brachial index) is needed. Revascularisation, assessment of left ventricular ejection fraction, and consideration of electrophysiology and an implantable cardiac defibrillator can be considered as preventative strategies for reducing the risk of sudden cardiac death.[80]

Cardiovascular disease risk reduction in HIV

Sub-Saharan Africa and low-income and middle-income countries

Country-level HIV programmes helped transition health systems that were traditionally focused on acute, episodic care to develop some of the first chronic care programmes. As a result, much of the effort to reduce coronary heart disease risk in low-income and middle-income countries has been deployed and evaluated in these national HIV programmes. Most approaches to cardiovascular disease risk reduction in people with HIV begin with HIV management while also addressing coronary heart disease risk screening, referral, and risk factor management to varying degrees. Active HIV replication and immune dysfunction are important drivers of coronary heart disease risk. Strengths and weaknesses of screening programmes at the community-level and clinic-level have been described.[82] Using HIV platforms to incorporate comprehensive chronic-disease management and exploring population health approaches is key.[83]

Lessons learned include the importance of efficiently testing new deployments of existing resources in sub-Saharan Africa.[84] Recent illustrative examples come from Malawi[85] and Uganda.[86] Following population-based integrated HIV and non-communicable disease screening in Uganda,[86] people with HIV and hypertension were referred to receive integrated care with 45% successful linkage to care. Among factors linked to care, blood pressure control increased from 15% at baseline to 46% over subsequent follow-up. In a Malawi HIV-care programme,[85] 29 359 people living with HIV were screened for hypertension over a 1-year period revealing an 11% prevalence. Subsequently, 85% of people with HIV and hypertension received treatment, or lifestyle modification advice, or both, with blood pressure control rates at 6 months of 38% in people with HIV who had mild hypertension and 30% in people with HIV who had moderate hypertension.

These risk reduction strategies also apply to stroke in people with HIV. Antiplatelet therapy is added as a secondary preventive agent in individuals with haemorrhagic stroke and brain imaging can help to risk-stratify these patients. Effective prevention and treatment of heart failure in people with HIV in low-income and middle-income countries are scarce. Use of ACE inhibitors, ARBs, β blockers, or mineralocorticoid antagonists is low, and diuretics are prescribed in only 51–67% of cases.[87,88] Data on the application of device and mechanical therapies for heart failure in people with HIV are insufficient, as are concerted efforts of heart failure prevention.[89]

Risk reduction approaches for coronary heart disease also apply to peripheral artery disease. A 2009 South African study[90] of patients with advanced peripheral artery disease and poor HIV control used $CD4^+$ T-cell count to guide vascular intervention decisions. Lower CD4 counts led to more conservative surgical approaches. Standard surgical techniques were used, except for patients with AIDS for whom broad spectrum antibiotics and fluconazole were used prophylactically instead of the standard cefazolin prophylaxis. Smoking rates in this study were high (79%) and are an important intervention point. Little availability of services to diagnose and treat cardiac arrhythmias in several low-income countries in sub-Saharan Africa exists,[91] which further limits our ability to prevent sudden cardiac death in these settings.

High-income countries

Coronary heart disease and stroke prevention might not be adequately addressed in the current primary care of people with HIV. A large international study which surveyed people with HIV found that only 19% discussed cardiovascular disease with their providers, and only 31% had ever discussed hypertension, hypercholesterolaemia, family history of cardiovascular disease, or smoking.[92] In the USA, rates of statin prescription among people with HIV who are most likely to benefit from these drugs remain low.[93] Under-prescription is particularly evident in racial and ethnic minorities in people with HIV.[94] However, low rates of appropriate cardiovascular disease risk-factor management could relate more to poor risk factor control, rather than HIV-specific shortfalls. Studies in the USA[95] and sub-Saharan Africa[96] have shown better control of coronary heart disease risk factors presumably affected by access to care for people without HIV than for people without HIV. Whether or

not individuals with HIV will benefit from lower thresholds for lipid, blood pressure, or glucose control remains unknown.

In high-income countries most stroke patients with HIV will be managed in stroke units. With the rapid patient assessment now required to offer life-saving and disability-saving therapy, stroke interventions will frequently be offered without knowledge of a HIV diagnosis. Although no high-quality studies to give guidance on the safety and effectiveness of these therapies exist, retrospective studies indicate no substantial harm is caused.[97]

Despite the considerable improvement in HIV life expectancy and promising outcomes of advanced heart failure therapies (including transplantation) for people with HIV, many health centres lack experience and expertise caring for people with HIV who have advanced heart failure. Some clinicians still consider HIV as a contraindication to heart transplantation.[98] Strategies to prevent or treat heart failure with preserved ejection fraction in HIV remain undefined.

The risk of peripheral artery disease is highest among those with unsuppressed HIV viraemia or low CD4 T-cell counts, suggesting that HIV management is an important factor in reducing risk. Traditional risk factors such as smoking and diabetes are also strongly associated with peripheral artery disease.

All data on approaches to reducing sudden cardiac death are from the general population and not specific to people with HIV. Among individuals who have ischaemic heart disease, electrophysiological evaluation and consideration of an implantable cardiac defibrillator are recommended in some clinical scenarios.[80] Individuals with particular infiltrative conditions such as sarcoidosis might be considered for an implantable cardiac defibrillator based on clinical history, structural heart disease, or cardiac MRI findings.[80] Whether or not HIV-infected individuals will benefit from different defibrillator thresholds will require further research.

Current approaches to reducing cardiovascular disease risk and their effectiveness

Sub-Saharan Africa and low-income and middle-income countries

Prevalence of coronary heart disease risk factors for people with HIV in low-income and middle-income countries varies—eg, hypertension (21%), elevated LDL cholesterol (23%), hypertriglyceridaemia (27%), low LDL cholesterol (52%), overweight (21%), and obesity (8%).[99] Underdiagnosis of these risk factors continues and screening programmes have identified 33–47% undiagnosed hypertension cases[100] and 66% elevated cholesterol cases. Studies with coronary heart disease-related clinical endpoints in low-income and middle-income countries are needed.

Models for integrating HIV care and coronary heart disease risk reduction include facility-based and community-based integrated care.[85,101] Although preliminary findings on their feasibility and effect on existing HIV-care delivery are promising,[100,102] data on clinical outcomes in general, including coronary heart disease risk reduction, are unavailable.

Reducing stroke burden among people with HIV is not the current focus of attention in many low-income and middle-income countries especially as progress is needed to reduce stroke burden in the general population. Although stroke incidence and disability decreased globally over the last 20 years, stroke incidence in southern Africa has increased.[103] Given that HIV infection is attributable to 15–25% of incident stroke cases in this region,[5,62] developing stroke preventive strategies for people with HIV at a policy-level might improve the disproportionate increase of stroke incidence in HIV endemic regions.

Precursors to heart failure are common among people living with HIV in low-income and middle-income countries. Hypertensive heart disease, rheumatic heart disease, and cardiomyopathy account for approximately two-thirds of cases of heart failure among hospitalised patients; however, ischaemic heart disease is much less common.[104] Hypertension is a recognised risk factor for heart failure. The age-standardised prevalence of hypertension increased by 8% in low-income and middle-income countries between 2000 and 2010.[105] Heart failure outcomes are worse for people with HIV in low-income and middle-income countries than in the general population. The sub-Saharan Africa Survey of Heart Failure (THESUS-HF)[106] showed that HIV infection conferred a 62% greater risk of all-cause mortality at 180 days after a heart failure admission.

Little is known about the burden of peripheral artery disease over time among people with HIV in low-income and middle-income countries. Presentation for peripheral artery disease among people with HIV in places such as South Africa might be delayed. In one study, 90% of largely untreated HIV patients admitted to a vascular unit presented with advanced stage vascular disease (rest pain or gangrene, corresponding to Fontaine stage III or IV) resulting in a high primary limb amputation rate of 32%.[90] A study from Nigeria suggested higher peripheral artery disease prevalence among people with HIV, but similar prevalence in virologically-suppressed people with HIV, compared with people without HIV.[107]

Few studies of sudden cardiac death have been reported. A study in Cameroon[108] reported a 9·4% rate of sudden cardiac death with crude incident rate of 31·3% per 100 000 person-years. Thus, it remains challenging to establish how approaches to reduce ischaemic heart disease are affecting sudden cardiac death risk for people with HIV.

High-income countries

Few data exist regarding temporal trends of clinical coronary heart disease incidence among people with HIV (table 3). A study in Europe[112] followed up 8762 people with HIV since 2000, and showed that coronary heart disease risk factor burden is high, but that modification of risk factors such as hypertension appears to be improving over time. Identifying the role of coronary heart disease risk-factor management in temporal changes in cardiovascular disease mortality for people with HIV is difficult given concomitant changes in ART timing and regimens which affect absolute and relative risks for coronary heart disease (table 3).

Absolute rates of cardiovascular disease mortality for people with HIV have declined since 1999, primarily because of improved HIV treatment uptake and related continued improvement in CD4 cell count.[113] However, the relative contribution of cardiovascular

disease to mortality is increasing because of the ageing population of people with HIV in high-income countries and decreasing risks of AIDS-related deaths.[114] Between 1997 and 2006, a US-based longitudinal analysis showed that despite the increasing uptake of ART, and accounting for health disparities, the rate of ischaemic stroke increased by 60% for people living with HIV.[115] This finding was supported by reports which showed that global HIV-associated cardiovascular disease tripled between 1990 and 2015.[2]

In high-income settings, the epidemiology of HIV-associated heart failure has most likely shifted in the ART era from severe left ventricular systolic dysfunction in the setting of uncontrolled HIV replication and AIDS, to diastolic and systolic dysfunction in the setting of chronic, cumulative comorbidities. How heart failure risk factors interact with HIV-related cardiovascular disease risk factors to drive myocardial dysfunction and heart failure is unknown. The prognosis of HIV-associated heart failure has also shifted from shortened survival among people living with HIV or AIDS to outcomes comparable with people without HIV.

Future studies are needed to ascertain the effect of HIV control and risk factor control on peripheral artery disease risk in HIV. Ischaemic heart disease is the most common underlying condition associated with sudden cardiac death. In the general population, the incidence of sudden cardiac death in the setting of ischaemic heart disease is decreasing.[116] By contrast, structural heart disease including cardiomyopathy associated with myocardial fibrosis and left ventricular hypertrophy are increasing.[117] Scarce data on sudden cardiac death in HIV make it challenging to assess how the approaches to reduce ischaemic heart disease are affecting sudden cardiac death risk in people with HIV.

Future approaches to reducing cardiovascular risk

Sub-Saharan Africa and low-income and middle-income countries

First, coronary heart disease risk factor screening should be part of routine care for people with HIV.[84] Given few resources and the absence of cost-effective data on routine coronary heart disease risk factor screening in facility-based HIV-care programmes,[118] it might be advisable to reserve routine screening for people with HIV older than 40 years for whom feasibility has been shown.[119] This is a practical approach, although barriers to scale up and expand into other low-income and middle-income countries still exist.[119] Contextually appropriate innovations such as targeted screening of people with HIV at high risk for coronary heart disease, task redistribution, and the use of point-of-care diagnostics would help to overcome some of these barriers.[119] Improving risk awareness for coronary heart disease among treated people with HIV might also augment surveillance efforts.[120] In addition, early diagnosis could attenuate the need for pharmacotherapy in most cases, which is an important consideration for low-income and middle-income health-system resources.[121]

Second, there should be a pathway to care for people with HIV who screen positive for coronary heart disease risk factors including factors unique to or dominant in low-income and middle-income countries.[84,122] This pathway should also improve access to essential medicines for coronary heart disease risk factors.[60] An integrated care approach (ie,

providing coronary heart disease care in the same clinic visit as HIV care) is feasible[102] and would be optimal to improve linkage and retention in care, which is crucial for chronic disease management.[123] Uptake of this approach remains slow in low-income and middle-income countries,[100,124,125] and data on cost-effectiveness and clinical outcomes are sparse.[101,102,118]

Third, timely policy interventions for people with HIV can decrease exposure to coronary heart disease risk factors such as tobacco, high cholesterol diets, and excessive alcohol usage. The prevalence of cigarette smoking, dyslipidaemia, and obesity are lower in many low-income and middle-income countries than high-income countries, although these factors are on the rise because of urbanisation.[99] Public education, tobacco-product taxation, and legislation to reduce availability of trans-fatty acids are effective and cost-effective methods that are urgently required in low-income and middle-income countries as part of primary prevention for coronary heart disease with potential effects beyond HIV populations.[126,127] Fourth, rigorous implementation approaches are required to inform how best to scale up and scale out interventions for preventing coronary heart disease among people with HIV in low-income and middle-income countries.[102,128] These recommendations apply to other cardiovascular disease causes discussed in this Review (figure 3).

We should leverage large HIV-population cohorts in sub-Saharan Africa and low-income and middle-income countries to develop tailored risk scores for stroke prevention. In regions with the highest burden of HIV infection in sub-Saharan Africa, priority should be given to developing stroke diagnostic and treatment pathways, centred around stroke units where brain imaging is available, and where complex management and rehabilitation can be provided. Government-operated stroke units are not commonplace in sub-Saharan Africa and are currently clustered in South Africa, Nigeria, and Ghana.[129,130] Early admission to a stroke unit saves lives and reduces disability.[131] Important barriers such as financial constraints, delay in presentation, sociocultural factors, and denial of a stroke are more frequent factors encountered in sub-Saharan Africa.[132]

Research to understand the disparity in heart failure outcomes for people with HIV is needed. Screening of individuals at greatest risk for heart failure[62] should occur in the same environment as the screening for HIV and related conditions. Care delivery for heart failure could thus mimic some of the successful innovations from the HIV-care framework such as task redistribution. In Rwanda, nurses have been successfully deployed for decentralised heart failure diagnosis and care delivery since 2006, showing their ability to apply basic echocardiography skills to diagnose common presentations of heart failure.[133] By using tailored algorithms to manage heart failure, patients in this nurse-led programme had a 36% 5-year mortality rate.[134]

Public education about the signs and symptoms of peripheral artery disease should be targeted toward people with HIV in low-income and middle-income countries to reduce the occurrence of late disease presentation and incidence of avoidable amputations. Increased awareness of sudden death and underlying mechanisms is needed. The development of tools for risk stratification and symptom identification as a preventive strategy[135] is warranted.

High-income countries

First, more research is needed to identify optimal thrombotic risk reduction strategies for HIV in regions where the comorbid burden of cardiovascular disease and HIV is greatest. Second, lifestyle modification, particularly smoking cessation and reduction, should be emphasised in HIV care to reduce atherosclerotic cardiovascular disease risk. Similarly maintaining a healthy diet is essential to avoiding excess weight gain and related metabolic complications, particularly after ART initiation.[42] Implementing these lifestyle optimisation strategies is challenging, but an opportunity exists to embed such strategies with HIV primary care. Third, appropriate management of cardiovascular disease risk factors is essential for diabetes, hypertension, and dyslipidaemia, in particular, with pharmacotherapy as indicated. Improved understanding of HIV-related cardiovascular disease risk factors is also important. Fourth, the impact of anti-inflammatory strategies, which might decrease atherosclerotic cardiovascular disease in the general population,[136] merit additional investigation in the setting of HIV. Attention should be paid to sex-based differences in response to HIV and the potential effect on cardiovascular disease risk. Strategies to lower inflammation that could be HIV-specific include therapies aimed at limiting or repairing intestinal barrier dysfunction, co-infection with cytomegalovirus, or HIV cure. Fifth, the cardiovascular benefit of early initiation of ART, and cardiovascular disease risk associated with newer ART regimens remain unknown.

Recognising stroke as a separate outcome to cardiovascular disease, in line with the 2017 WHO International Classification of Diseases reclassification,[75] will help to focus risk scores and population effect metrics from clinical trials and cohort studies in people with HIV. Additionally, mechanistic studies with a focus on intracranial HIV-associated vasculopathy are needed to guide drug discoveries.

It is important to supplement existing epidemiological data on increased heart failure in HIV with deeper clinical phenotyping of heart failure presentations and triggers among people with HIV. These studies would enable identification of targets for prevention and early interventions aimed at controlling the onset and progression of heart failure in HIV. Effective therapies for heart failure with preserved ejection fraction are still absent in the general population. Investigating the immunopathogenesis of HIV-associated heart failure might inform broader understanding and targeting of immunological and inflammatory contributors to heart failure with preserved ejection fraction.

A more complete estimation of the prevalence, incidence, and severity of peripheral artery disease among people with HIV is needed. Mechanistic studies should evaluate the mediators of increased peripheral artery disease and sudden cardiac death for people with HIV. Such studies provide insight for treatment modalities beyond ensuring HIV viral suppression, immune restoration, and management of traditional risk factors for atherosclerosis. Smoking is a strong modifiable risk factor for peripheral artery disease. Efforts to reduce smoking in people living with HIV are almost certain to reduce peripheral artery disease incidence and progression. Additionally, increased awareness about peripheral artery disease and sudden cardiac death is needed. One approach to increase awareness that is worth investigating is routine ankle-brachial index screening.

Conclusion

In summary, a geographical imbalance between HIV disease burden and the populations included in published HIV-related cardiovascular disease research exists. There is strong evidence linking HIV infection to myocardial infarction, stroke, and heart failure. There are scarce data that also link HIV infection to peripheral artery disease and sudden cardiac death. Although mechanisms for these associations might be the same for all people with HIV, the distribution of cardiovascular disease risk factors varies by geographical location. These variations result in different profiles of cardiovascular disease risk in low-income and middle-income countries compared with high-income countries. To reduce cardiovascular disease risk globally among people with HIV calls for thoughtful balancing of public and individual health approaches, evidence-informed strategies, expert health-care and patient opinions, and basic translational and implementation research in areas with the highest HIV burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Search strategy and selection criteria

References for this Review were identified by PubMed searches from June 10, 2019, to Nov 1, 2019, for HIV or AIDS and types of cardiovascular disease. Search terms included “HIV”, “human immunodeficiency virus”, “AIDS”, “acquired immunodeficiency syndrome”, “myocardial infarction”, “stroke”, “coronary heart disease”, “heart failure”, “peripheral artery disease”, “ankle brachial index”, “sudden cardiac death”, “atherosclerosis”, “Africa”, “Kenya”, “Uganda”, “Malawi”, “Nigeria”, “Thailand”, “India”, “China”, “Russia”, “Asia”, “South America”, “low income country”, “middle income country”, “LMIC”, and “meta-analysis”. Manuscripts that were from the last 5 years and assessed incident clinical events, or included meta-analyses comprehensively summarising existing data were preferred. Only papers published in English were reviewed.

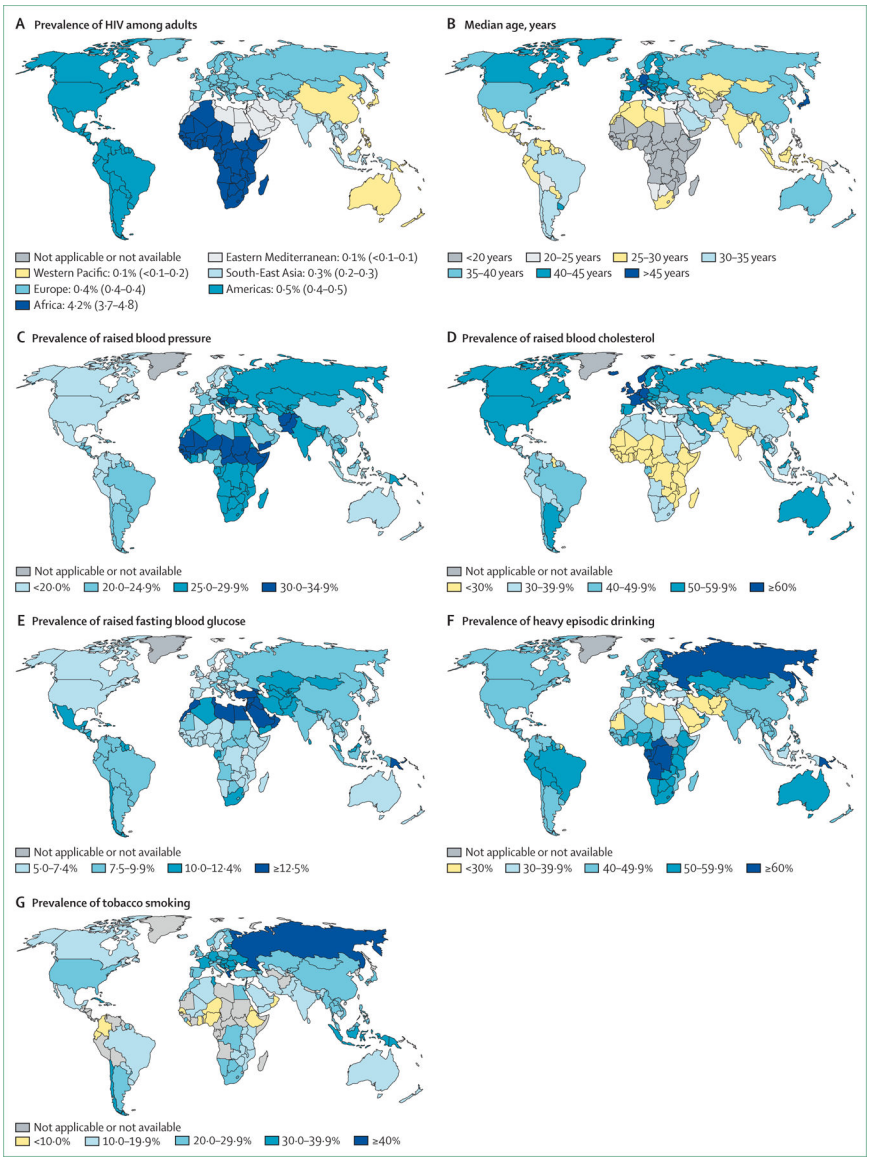

Figure 1: Prevalence distribution of HIV and risk factors for cardiovascular disease

World maps showing increased HIV prevalence, age, raised blood pressure, raised blood cholesterol, raised fasting blood glucose, heavy episodic drinking, and tobacco smoking. Permission from WHO and the Institut National d'Etudes Démographiques. (A) Prevalence of HIV among adults aged 15–49, 2016 classified by WHO regions. Global prevalence of HIV: 0·8 (average 0·7–0·9). Numbers in brackets show global prevalence of HIV on average. (B) Median age (years), 2017. (C) Prevalence of raised blood pressure (systolic blood pressure ≥140 mm Hg; diastolic blood pressure ≥90 mm Hg), ages over 18 years, 2015. Age-standardised estimate for both sexes. (D) Prevalence of raised blood cholesterol (≥5·0 mmol/L), ages over 25 years, 2008. Age-standardised estimate for both sexes. (E) Prevalence of raised fasting blood glucose (≥7·0 mmol/L or on medication for raised blood glucose), ages over 18 years, 2014. Age-standardised estimate for both sexes. (F) Prevalence of heavy episodic drinking among both sexes, ages over 15 years and older,

2016. (G) Prevalence of tobacco smoking among people aged 15 years and older, 2016. Age-standardised estimate.

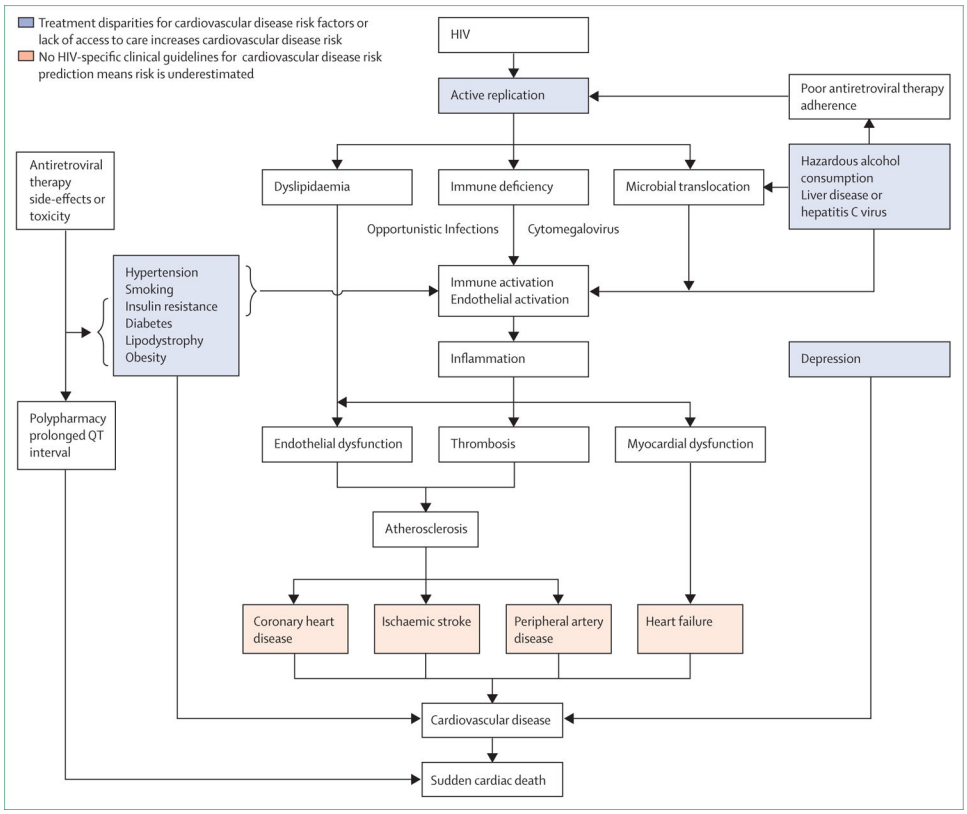

Figure 2:
Mechanisms of HIV-associated cardiovascular disease

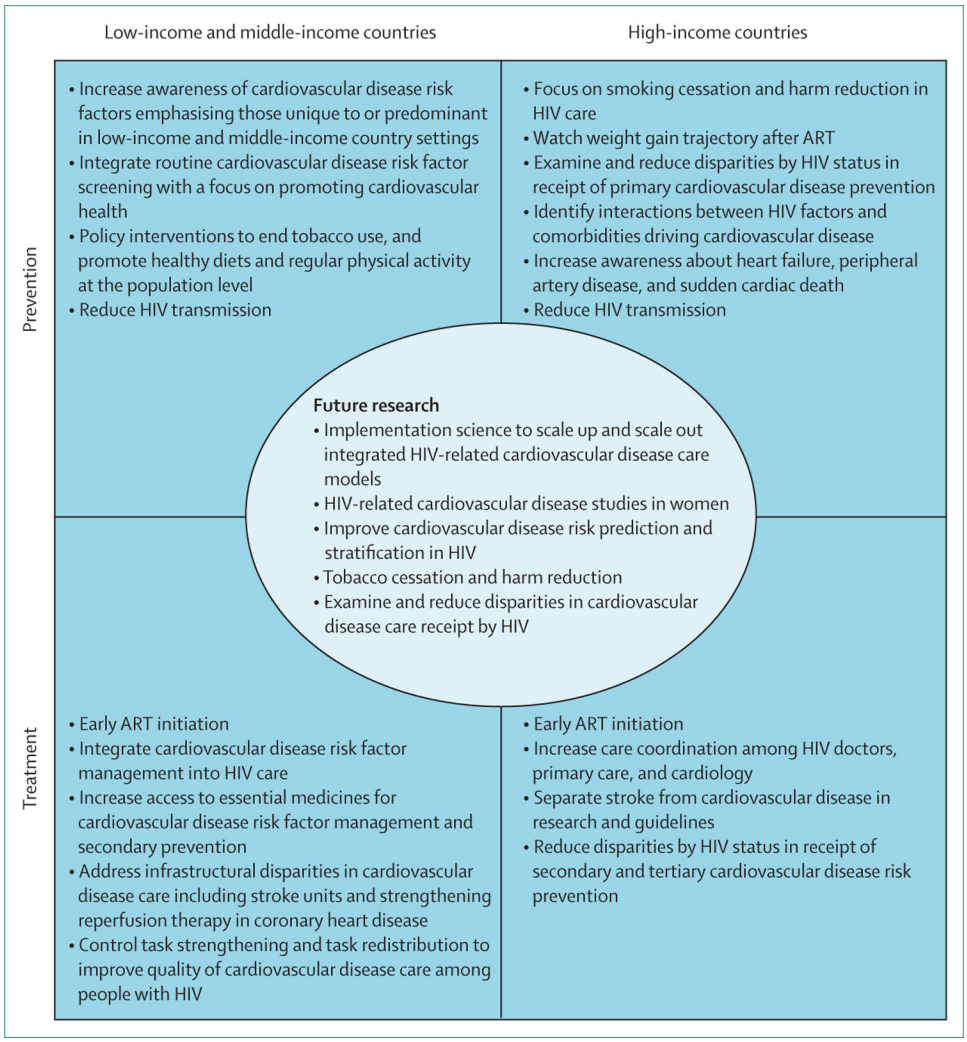

Figure 3: Intervention points to reduce HIV-associated cardiovascular disease risk stratified by income status

ART=antiretroviral therapy.

Table 1:

Studies on the association of HIV status and clinical cardiovascular disease

	Location	Number of participants	Number of HIV cases	Number of CVD events	Mean age (SD)	Outcome	Measure of effect	Effect estimate (95% CI)
Stroke								
Qureshi et al (1997)	Grady Memorial Hospital, USA	236	113	68	35 (6)	Cerebral infarction	Odds ratio	3·2 (1·1–8·9)
Cole et al (2004)	Baltimore-Washington Cooperative Young Stroke Study, USA	386	6	386	36	Ischaemic stroke	Odds ratio	13·70 (6·10–30·80)
Chow et al (2012)	Massachusetts General Hospital and Brigham and Women's Hospital, USA	36 731	4308	914	41 (12)	Ischaemic stroke	Hazard ratio	1·21 (1·01–1·46)
Mateen et al (2013)	Multicenter AIDS Cohort Study, USA	3945	1776	114	42	All stroke	Relative risk	2·16 (1·39–3·31)
Walker et al (2013)	Rural Hai district in northern Tanzania and urban Dar-es-Salaam, Tanzania	201	25	201	61 (13)	All stroke	Odds ratio	5·61 (2·41–13·09)
Marcus et al (2014)[4]	Kaiser Permanente Southern California and Northern California, USA	282 368	24 768	1279	40 (10)	Ischaemic stroke	Incidence rate ratio	1·4 (1·2–1·7)
Rasmussen et al (2015)	Danish HIV Cohort Study	58970	5897	1785	Median 37 (IQR 31–44)	Stroke	Incidence rate ratio	1·84 (1·60–2·13)
Sico et al (2015)	Veterans Aging Cohort Study, USA	76 835	25 434	910	49 (9)	Ischaemic stroke	Hazard ratio	1·17 (1·01–1·36)
Benjamin et al (2016)[5]	Malawi urban hospital; stroke cases and community controls	725	69	222	59	All stroke	Odd ratio	3·28 (2·05–5·25)
Alonso et al (2019)[6]	Truven Health MarketScan Commercial Claims and Encounter and the Medicare Supplemental and Coordination of Benefits databases, USA	79 100	19 798	93	43 (13)	Stroke	Hazard ratio	2·3 (1·5–3·6)
Myocardial infarction								
Triant et al (2009)	Massachusetts General Hospital and Brigham and Women's Hospital, USA	70 357	487	..	Mid-50s	Acute myocardial infarction	Odds ratio	1·93(1·21–2·93)
Lang et al (2010)[7]	French hospital database on HIV	74 958	74 958	360	Not provided	Myocardial infarction	Standardised morbidity ratio	1·5 (1·3–1·7) men; 1·4 (1·3–1·6) women
Durand et al (2011)	Régie de l'Assurance maladie du Québec, Canada	27 734	7053	365	40 (11)	Acute myocardial infarction	Hazard ratio	2·11 (1·69–2·63)

	Location	Number of participants	Number of HIV cases	Number of CVD events	Mean age (SD)	Outcome	Measure of effect	Effect estimate (95% CI)
Klein et al (2015)	Kaiser Permanente Southern California and Northern California, USA	282 368	24 768	2803	40	Myocardial infarction	Incidence rate ratio	1·40 (1·20–1·60)
Althoff et al (2015)	Veterans Aging Cohort Study, USA	83 527	56 274	689	Mid-50s	Acute myocardial infarction	Hazard ratio	1·76 (1·49–2·07)
Rasmussen et al (2015)	Danish HIV cohort	58 970	5897	1238	Median 37 (IQR 31–44)	Myocardial infarction	Incidence rate ratio	2·02 (1·71–2·38)
Alonso et al (2019)[6]	Truven Health MarketScan Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits databases, USA	79 100	19 798	154	43 (13)	Myocardial infarction	Hazard ratio	1·2 (0·8–1·8)
Heart failure								
Freiberg et al (2017)[8]	Veterans Aging Cohort Study, USA	98 015	31 523	2636	48 (10)	Congestive heart failure	Hazard ratio	1·41 (1·29–1·54)
Feinstein et al (2018)[9]	HIV Electronic Comprehensive Cohort of CVD Complications (Northwestern Medicine), USA	7371	4640	152	40 (11)	Adjudicated heart failure	Hazard ratio	2·10 (1·38–3·21)
Alonso et al (2019)[6]	Truven Health MarketScan Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits databases, USA	79 100	19 798	223	43 (13)	Heart failure	Hazard ratio	2·8 (2·0–3·8)
Peripheral artery disease								
Alonso et al (2019)[6]	Truven Health MarketScan Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits databases, USA	79 100	19 798	98	43 (13)	Peripheral artery disease	Hazard ratio	0·9 (0·5–1·4)
Beckman et al (2019)[10]	Veterans Aging Cohort Study, USA	91 953	28 714	7708	48 (10)	Peripheral artery disease	Hazard ratio	1·19 (1·13–1·25)
Lai et al (2018)	Taiwan Centers for Disease Control, HIV Surveillance Database	2 000 000	26 272	55	32 (10)	Peripheral artery disease	Standardised Incidence rate	0·87 (0·65–1·13)
Sudden cardiac death								
Tseng et al (2012)[11]	HIV specialty clinic in San Francisco, California, USA	2860	2860	30	Median 39 (IQR 33–45)	Sudden cardiac death	Standardised mortality ratio	4·46
Lai et al (2018)[12]	Taiwan Centers for Disease Control, HIV Surveillance Database	General population	26272	82	32 (10)	Sudden cardiac death	Standardised Incidence rate	3·01 (2·39–3·73)

	Location	Number of participants	Number of HIV cases	Number of CVD events	Mean age (SD)	Outcome	Measure of effect	Effect estimate (95% CI)
Alvi et al (2019)[13]	Bronx Lebanon Hospital Center, Icahn School of Medicine at Mount Sinai, USA	2149	344	191	60 (9)	Sudden cardiac death	Odds ratio	3·0 (1·78–4·24)
Tseng et al (CROI 2019, unpublished)	HIV specialty clinic in San Francisco, California, USA	552	47	552	51–63	Sudden cardiac death	Incidence rate ratio	1·86 (1·39–2·50)
Freiberg et al (CROI 2019, unpublished)	Veterans Aging Cohort Study, USA	144 336	43 407	3035	50 (11)	Sudden cardiac death	Hazard ratio	1·14 (1·04–1·25)

For cardiovascular disease types where data are sparse, studies using population-based HIV-negative groups and conference abstracts are included. Studies with references were not included in a meta-analysis by Shah and others.[2] All other studies (appendix p 1) were included in this meta-analysis. CVD=cardiovascular disease. CROI=conference on retroviruses and opportunistic Infections.

Table 2:

Guidelines on cardiovascular disease prevention, prediction, and risk reduction

	Cardiovascular disease risk prediction	Tobacco	Hypertension	Diabetes	Dyslipidaemia	Drug interactions
Kenya National Guidelines for cardiovascular disease management (2018)[63]	No HIV-specific recommendation	No HIV-specific recommendation	As in general population with exceptions on interactions of antihypertensive drugs with ART	Assess glucose at baseline and then annually	Assess fasting lipids at baseline and annually if abnormal	Yes; antihypertensive drugs interacting with ART
South African dyslipidaemia guideline (2018) and National Consolidated HIV Guidelines (2015)[64,65]	"There is no validated risk score for HIV-infected black South Africans; Framingham risk tables may be used to aid decision-making"	No HIV-specific recommendation	No HIV specific recommendation	No HIV-specific recommendation	Full lipogram recommended after ART initiation; repeated at 3 months after starting protease inhibitor and periodically thereafter	Yes; lipid lowering drugs interacting with ART
Malawi HIV Testing Services Guidelines (2016)[66]	Not addressed	Recommends stopping smoking	Assess blood pressure at ART initiation; repeat annually; identified specific blood pressure thresholds; lifestyle changes or pharmacotherapy management	Recommends screening as part of hypertension management	Not addressed	Not addressed
Infectious Diseases Society of America HIV Guidelines (2013)[67]	Coronary heart disease risk assessment recommended but not specified; Framingham risk scores assumed given reference to NCEP guidelines	Recommends smoking cessation as part of regular patient education	Blood pressure check annually in all patients	Consider NHANES HbA1c cutoff of 5·8%; check fasting plasma glucose and HbA1c every 6–12 months	Recommends fasting lipid profile 1–3 months after and before ART initiation; management per NCEP guidelines	Yes; lipid lowering drugs interacting with ART
American Heart Association Statement on HIV and Cardiovascular Disease[62]	Proposes upward adjustment of risk assessment by 1·5–2-times using ACC, AHA ASCVD risk estimator in the presence of risk-enhancing factors	Smoking cessation and online resources	No HIV-specific recommendation	No HIV-specific recommendation	Lifestyle optimisation; pharmacotherapy with a start low, go slow strategy because of side-effects	Mentioned with reference to online resource; interaction of lipid lowering drugs, anticoagulant, and ART
European AIDS Clinical Society Guidelines Version 9·1 (2018)[68]	Framingham score every two years in men (>40 years) and women (>50 years) without cardiovascular disease; HIV-specific calculators as alternatives	Provides screening algorithm, treatment strategies motivational, cognitive behavioural counselling, and pharmacotherapy	Extensive risk assessment algorithm; includes drug sequencing algorithm	Diagnostic criteria, risk assessment algorithm, and management algorithm	Risk assessment algorithm	Yes; antihypertensive drugs and cholesterol lowering drugs interacting with ART
British HIV Association guidelines (2019 interim update)[69]	QRISK2 for patients aged >40 years annually if no vascular disease	Auditable targets include patients with a smoking history documented in the last 2 years (90%) and blood pressure recorded in the last 15 months (90%)	Annual screens for those with cardiovascular disease and at increased risk (10-year risk >10%)	Annual screens for those with cardiovascular disease and at increased risk (10-year risk >10%)	Annual screens for those with established cardiovascular disease and at increased risk (10-year risk >10%); high-dose (80 mg) atorvastatin for	Recommend all medications to be reviewed and documented at each clinic visit to identify potential drug–drug interactions

	Cardiovascular disease risk prediction	Tobacco	Hypertension	Diabetes	Dyslipidaemia	Drug interactions
					established cardiovascular disease	

Recommendations in selected HIV-care guidelines from sub-Saharan Africa, North America, and Europe. ART=antiretroviral therapy. NCEP=National Centers for Environmental Prediction. NHANES=National Health and Nutrition Examination Survey. ACC=American College of Cardiology. AHA=American Heart Association. ASCVD=atherosclerotic cardiovascular disease. QRISK2=Quality Cardiovascular Risk Score 2.

Table 3:

Time trends of myocardial infarction incidence among people with HIV in high-income countries

	Number of people with HIV	Number of AMI events	HIV positive effect estimate	HIV negative effect estimate	Relative effect estimate by HIV (95% CI)
Kaiser Permanente Southern California and Northern California health plans [*] [109]					
1996–2011 [†]	24 768	2803	268	165	1·4 (1·2–1·6)
1996–1999	..	..	276	136	1·8 (1·3–2·6)
2000–2003	..	..	324	162	1·7 (1·4–2·1)
2004–2007	..	..	270	178	1·3 (1·0–1·6)
2008–2009	..	..	245	167	1·3 (0·9–1·7)
2010–2011	..	..	195	165	1·0 (0·7–1·4)
French hospital database on HIV [*] [110]					
2000–2002 early cART era	43 628	132 men	196	148·0	1·35 (1·14–1·61)
2003–2005 intermediate cART era	51 007	205 men	229·5	133·4	1·74 (1·51–1·99)
2006–2009 late cART era	58 866	259 men	185·2	161·1	1·12 (0·99–1·27)
2000–2002 early cART era	43 628	15 women	68·4	25·5	2·81 (1·58–4·64)
2003–2005 intermediate cART era	51 007	16 women	47·6	23·6	2·18 (1·25–3·55)
2006–2009 late cART era	58 866	36 women	67·5	32·9	1·99 (1·39–2·75)
Cohort of HIV adults of the AIDS research network (Spain) [‡] [111]					
2004–2009	10 760	18 (HIV)	279 (265, 293)	199 (188, 209)	1·41 (1·26–1·55)
2010–2015	10 760	34 (HIV)	222 (211, 233)	173 (163, 183)	1·28 (1·15–1·43)

[*] Measure of effect was the incidence rate per 100 000 person-years.

[†] The total number of people with HIV for the entire period (1996–2011) was 24 768. During this time period, 2803 AMI events occurred (320 among people with HIV and 2483 among people without HIV).

[‡] Measure of effect was the standardised incidence rate in men (*vs* general Spanish male population). AMI=acute myocardial infarction. cART=combination antiretroviral therapy.