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Global Burden of Atherosclerotic Cardiovascular Disease in People Living With HIV

Systematic Review and Meta-Analysis

Editorial, see p 1113

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BACKGROUND: With advances in antiretroviral therapy, most deaths in people with HIV are now attributable to noncommunicable illnesses, especially cardiovascular disease. We determine the association between HIV and cardiovascular disease, and estimate the national, regional, and global burden of cardiovascular disease attributable to HIV.

METHODS: We conducted a systematic review across 5 databases from inception to August 2016 for longitudinal studies of cardiovascular disease in HIV infection. A random-effects meta-analysis across 80 studies was used to derive the pooled rate and risk of cardiovascular disease in people living with HIV. We then estimated the temporal changes in the population-attributable fraction and disability-adjusted life-years (DALYs) from HIV-associated cardiovascular disease from 1990 to 2015 at a regional and global level. National cardiovascular DALYs associated with HIV for 2015 were derived for 154 of the 193 United Nations member states. The main outcome measure was the pooled estimate of the rate and risk of cardiovascular disease in people living with HIV and the national, regional, and global estimates of DALYs from cardiovascular disease associated with HIV.

RESULTS: In 793 635 people living with HIV and a total follow-up of 3.5 million person-years, the crude rate of cardiovascular disease was 61.8 (95% CI, 45.8–83.4) per 10 000 person-years. In comparison with individuals without HIV, the risk ratio for cardiovascular disease was 2.16 (95% CI, 1.68–2.77). Over the past 26 years, the global population–attributable fraction from cardiovascular disease attributable to HIV increased from 0.36% (95% CI, 0.21%–0.56%) to 0.92% (95% CI, 0.55%–1.41%), and DALYs increased from 0.74 (95% CI, 0.44–1.16) to 2.57 (95% CI, 1.53–3.92) million. There was marked regional variation with most DALYs lost in sub-Saharan Africa (0.87 million, 95% CI, 0.43–1.70) and the Asia Pacific (0.39 million, 95% CI, 0.23–0.62) regions. The highest population-attributable fraction and burden were observed in Swaziland, Botswana, and Lesotho.

CONCLUSIONS: People living with HIV are twice as likely to develop cardiovascular disease. The global burden of HIV-associated cardiovascular disease has tripled over the past 2 decades and is now responsible for 2.6 million DALYs per annum with the greatest impact in sub-Saharan Africa and the Asia Pacific regions.

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Clinical Perspective

What Is New?

- Recent studies have identified plausible biological mechanisms, including endothelial dysfunction and arterial inflammation, to explain the association between HIV infection and atherosclerotic disease.
- This article represents a systematic analysis to evaluate the association between HIV and cardiovascular disease and estimate the burden of HIV-associated cardiovascular disease at a national, regional, and global level.
- We report that the risk of cardiovascular disease is increased 2-fold in people living with HIV, and the global burden of HIV-associated cardiovascular disease has tripled over the past 2 decades with the majority of the burden experienced in sub-Saharan Africa and the Asia Pacific region.

What Are the Clinical Implications?

- The combined burden of HIV and cardiovascular disease, especially in high-prevalence regions, has important implications with respect to regional health policies, guidelines, and resource allocation.
- Risk stratification and identification of patients at risk of future cardiovascular disease are already challenging in these regions.
- Whether patients living with HIV should be considered high-risk and appropriate primary prevention pharmacotherapy such as statin therapy should be implemented remains unclear.
- Our estimates have important policy implications for implementing appropriate cardiovascular risk stratification and treatment strategies across healthcare systems, especially in low- and middle-income nations where both HIV and cardiovascular disease remain highly prevalent.

Currently, >35 million people are infected with HIV, with two-thirds being resident in sub-Saharan Africa.[1] Although the global incidence for HIV has stabilized, the provision and widespread distribution of combined antiretroviral therapy[2] has dramatically improved survival with the prevalence of HIV steadily increasing over the past 2 decades.[3] This improvement in survival has been primarily attributed to a reduction in opportunistic infections, especially in the low- and middle-income nations.[1,4] Indeed, most deaths now arise from noncommunicable illnesses, especially cardiovascular disease.[5–7]

Cardiovascular disease is the leading cause of morbidity and mortality worldwide.[8,9] The past 2 decades have seen a substantial increase in the morbidity attributable to cardiovascular disease, with a significant proportion of the burden borne by low- and middle-income nations.[10,11] The highest prevalence rates of HIV have been observed in sub-Saharan Africa. This region has also seen a steady increase in the burden of cardiovascular disease over the past 2 decades.[2,12] Recent studies have shown a link between the development of cardiovascular disease and HIV infection with multiple potential mechanisms, including direct vascular inflammation,[13,14] dyslipidemia,[15] and insulin resistance.[16,17]

The aim of this systematic analysis was to review and to meta-analyze the rate of cardiovascular disease in people living with HIV, to determine the association between HIV infection and the risk of cardiovascular disease, and to estimate the national, regional, and global burden of HIV-associated cardiovascular disease.

METHODS

Data and the corresponding R analysis code will be available at https://github.com/anoopsshah/hiv_cvd.

Databases, Sources, and Searches

We searched MEDLINE, EMBASE, Global Health, Cumulative Index to Nursing and Allied Health Literature, and Web of Science by using the following key words: myocardial infarction, stroke, cerebrovascular disease, cardiovascular disease, and HIV (Text I in the online-only Data Supplement). Bibliographic reference lists of studies selected for inclusion in our meta-analysis and relevant review articles were manually searched (Figure 1). We limited our search to studies published between 1948 and August 30, 2016.

Selection of Articles, Extraction of Data, and Data Synthesis

All longitudinal studies, including case-control, cohort, and randomized controlled trials, were included. There were no language restrictions, and only peer-reviewed original articles were included. Many studies provided data on the same cohort at extended follow-up time points. In such cases, we selected the published study with the longest follow-up period. Data were extracted independently, and any discrepancies were adjudicated by 4 investigators (A.S.V.S., D.S., K.K.L., and S.A.). We contacted authors for additional data or clarification where required. The study methodology, results, and presentation were conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Table I in the online-only Data Supplement).[18]

Crude Rate

The pooled incident crude rates of cardiovascular disease studies were only included if they provided the number of cardiovascular events (fatal or nonfatal myocardial infarction or stroke) and the follow-up period. Crude incidence rates were pooled per 10 000 person-years and presented for all incident cardiovascular events and deaths. The analysis was substratified by etiology classified as either myocardial infarction or cerebrovascular disease, where applicable.

Risk Ratio

For estimating the pooled risk ratios of cardiovascular disease, cases were defined as any hospitalization with,

or mortality from, cardiovascular events (fatal or nonfatal myocardial infarction or stroke) in individuals with and without HIV. Studies were also included if the outcome was defined as a cardiovascular event and included but was not exclusive to myocardial infarction or stroke. Risk ratio estimates for disease incidence and case fatality for cardiovascular events in HIV-infected populations in comparison with populations not infected by HIV were pooled and presented with 95% CIs.

Pooled risk ratio estimates were assessed for publication bias by visually assessing funnel plots and for asymmetry by using the Egger regression test.[19] The trim-and-fill method was used to adjust for selection bias attributable to potential unpublished studies or bias attributable to small-study effects.[20] Sensitivity analysis was performed by removing studies where adjustment for important confounders was omitted (Table II in the online-only Data Supplement). Across both the pooled rate and risk ratios, subgroup analysis was only performed where ≥3 estimates were available. Studies providing estimates for the risk ratio were further stratified by type of event and publication year.

Regional and Global Estimates for HIV Prevalence and Cardiovascular Disability-Adjusted Life-Years

Global and regional estimates of cardiovascular disease attributable to HIV were derived annually from 1990 to 2015.

Cardiovascular Disability-Adjusted Life-Years

National disability-adjusted life-year (DALY) estimates for cardiovascular disease (consisting of the sum of DALYs attributable to ischemic heart disease and stroke) were available from the Institute of Health Metrics and Evaluation. Countries were grouped into Joint United Nations Programme on HIV/AIDS (UNAIDS) regions (Table III in the online-only Data Supplement). The DALYs for cardiovascular disease in each country were summed to derive the regional cardiovascular burden. These data were available at 5-year intervals, from 1990 to 2015, with intervening years obtained via linear interpolation.

Regional Prevalence of HIV

Prevalence estimates for HIV were available from 1990 to 2015, for the population from 15 to 49 years of age, from UNAIDS at a global and regional level.

Population-Attributable Fraction and HIV-Attributable Cardiovascular DALYs

At the global and regional levels, we applied the HIV prevalence estimates for the 15- to 49-year age group across the entire adult population. As such, the calculated population-attributable fraction was applied to the entire adult population when calculating the cardiovascular DALYs attributable to HIV at global and regional levels.

National Estimates for HIV Prevalence and Cardiovascular DALYs

National estimates of HIV prevalence and cardiovascular burden were available from 160 and 179 countries, respectively, of the 193 United Nations member states, and both were available from 154 countries. National HIV prevalence estimates were available for the >15-years age group for 2016, and national DALY estimates for cardiovascular disease were available for 2015.

We also calculated estimates of burden in the nations with a high HIV prevalence by combining data for the UNAIDS-defined 21 Global Plan priority countries (Table III in the online-only Data Supplement).[21,22] National-level data for cardiovascular DALYs for 2015 and HIV prevalence for 2016 were available for 20 of the 21 Global Plan priority countries (Table III in the online-only Data Supplement).

Statistical Analysis

Using the pooled risk ratio for cardiovascular disease in people living with HIV and the prevalence of HIV, we estimated the population-attributable risk fraction at national, regional, and global levels. At regional and global levels, we further estimated the yearly changes in attributable risk to take into account temporal changes in the population prevalence of HIV. The population-attributable fraction for HIV for cardiovascular disease was calculated as described previously:[23,24]

$$\textit{Population Attributable Fraction}=\frac{\textit{Prevalence}*(\text{Risk Ratio}-1)}{1+\textit{Prevalence}*(\text{Risk Ratio}-1)}$$

We anticipated heterogeneity between studies when estimating both the crude incidence rates and the risk ratio because of different study designs, methods of analysis and varying adjustment, and geographical and population differences. We therefore used a random-effects model with the maximum likelihood estimator to account for both within- and between-study heterogeneity.[25] Heterogeneity, when estimating the pooled estimate of the risk ratio, was examined using the standard I^2 test. Publication or small-study bias was assessed using the regression test, and the trim-and-fill method was used for correcting funnel plot asymmetry. Risk of bias was assessed at a study level according to the level of adjustment undertaken (Table II in the online-only Data Supplement). Studies at low risk of bias were defined if adjustment of age, sex, and at least 1 other covariate was undertaken. Moderate risk was defined as adjustment of at least age or sex, and studies were classified as high-risk if no adjustment was undertaken. Full statistical methods are explained in the online-only Data Supplement (Text II in the online-only Data Supplement, Figure IA and IB in the online-only Data Supplement). All analyses were performed in R Version 3.2.3 with the estimates derived using the meta-for package. Statistical significance was taken as a 2-sided $P<0.05$.

RESULTS

A total of 80 studies were identified to estimate the rate and risk ratio of cardiovascular disease in people living with HIV. One hundred twenty-two estimates from 73 studies were used to calculate the pooled crude incident rates of fatal and nonfatal cardiovascular disease in people living with HIV (Table IV in the online-only

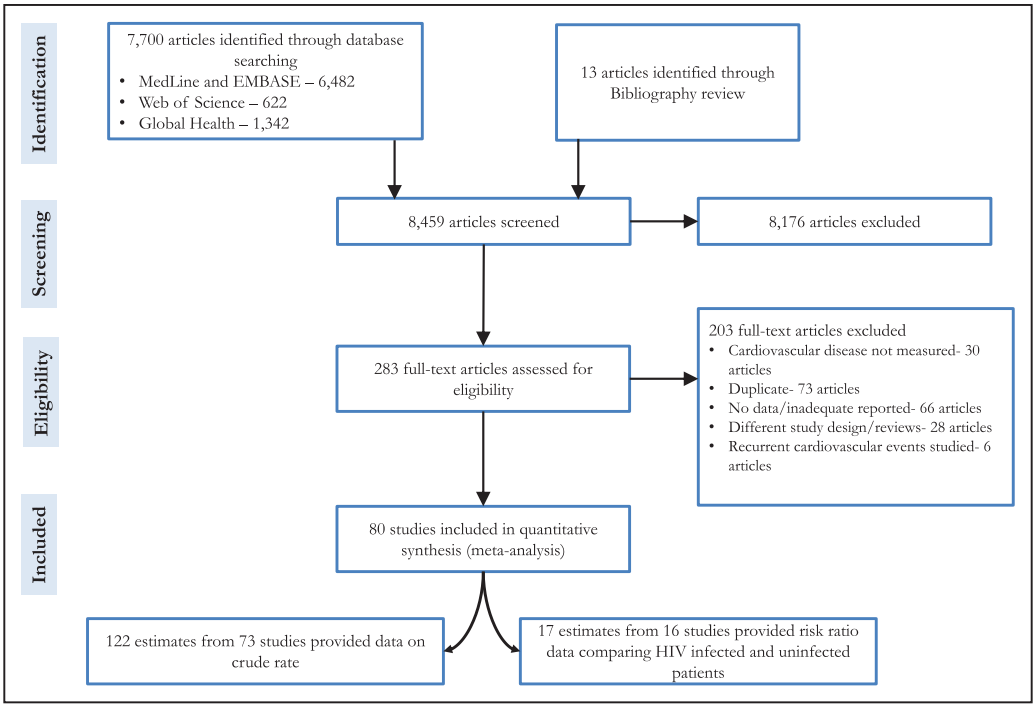

Figure 1. Flow chart.
Flow chart of studies meeting the inclusion criteria of the systematic review and meta-analysis.

Data Supplement; Figure 1). This comprised 793 635 people with HIV and a total follow-up of 3.5 million person-years. The crude incidence rate for cardiovascular disease per 10 000 person-years was 61.8 (95% CI, 45.8–83.4). When stratified by incident myocardial infarction and stroke, the rate was 25.9 (95% CI, 20.3–33.0) and 17.9 (95% CI, 13.2–24.3), respectively (Figure IIA through IIC in the online-only Data Supplement). The cardiovascular mortality rate was 14.1 per 10 000 person-years (95% CI, 10.3–19.4) (Figure IID through IIF in the online-only Data Supplement). Of the 122 estimates, only 12 (9.8%) estimates (across 11 studies) provided information on crude rates in the non-HIV population (Table V in the online-only Data Supplement).

A further 17 estimates from 16 studies were identified to estimate the pooled risk ratio of incident cardiovascular disease in individuals with HIV infection (Table, Figure 2B). Studies originated mainly from Europe, North America, and the Asia Pacific region with few studies from low- and middle-income nations (Table) and primarily involving black and white participants (Table VI in the online-only Data Supplement). The majority of studies used physician diagnosis or the *International Classification of Diseases* coding system to define cardiovascular disease. The pooled risk ratio was 2.16 (95% CI, 1.68–2.77) (Figure 2B). The risk ratio when stratified by type of event was 2.36 (95% CI, 1.50–3.70) for any cardiovascular disease (including myocardial infarction and stroke), 1.79 (95% CI, 1.54–2.08) for myocardial infarction, and 2.56 (95% CI, 1.43–4.61) for stroke. Risk ratios for older studies, those with moderate/high risk of bias, and those with longer follow-up were larger (Table VII in the online-only Data Supplement). Selection bias attributable to potential unpublished studies or to small-study effects was noticed for the overall risk ratio. Imputing for asymmetry using the trim-and-fill method did not alter the effect direction, but, as expected, did attenuate the effect size (Table VII in the online-only Data Supplement and Figure III in the online-only Data Supplement). We observed substantial heterogeneity for the overall estimate (Figure 2).

Trends in the Global and Regional Burden of Disease

Globally, the population-attributable fraction for cardiovascular disease associated with HIV infection increased from 0.36% (95% CI, 0.21%–0.56%) in 1990 to 0.92% (95% CI, 0.55%–1.41%) in 2015. This was associated with a >3-fold increase in DALYs from HIV-associated cardiovascular disease from 0.74 million (95% CI, 0.44–1.16) in 1990 to 2.57 million (95% CI, 1.53–3.92) in 2015 (Figure 3A). Similar temporal increases were seen when stratified by sex (Figure 3B, Table VIII in the online-only Data Supplement).

There was marked regional variation in the temporal change in the DALYs because of cardiovascular disease attributable to HIV (Figure 3C). In 2015, East and Southern Africa, Asia and the Pacific, and West and Central Africa accounted for over two-thirds of all DALYs (Figure 3C). The largest annual increase across the 26-

Table. Baseline Characteristics of Studies Providing Estimates of Risk Ratio

Author	Cohort Name	Country	Study Type	Data Source	Outcome Classification	Male (%)	Age at Baseline (y)	From	To	Outcome
Qureshi et al, 1997[26]	Atlanta, GA	USA	CCS	Clinical database	ICD-9	58	35	1990	1994	Stroke*
Gardner et al, 2003[27]	HERS	USA	Cohort study	Hospital database	NA	0	38	1993	2000	CVD*†
Cole et al, 2004[28]	BW-CYSS	USA	Cohort study	Clinical database	ICD-9	83	35	1988	1991	Stroke*
Triant et al, 2009[29]	RPDR	USA	Cohort study	Clinical database	ICD-9	63	38	1997	2006	MI*
Aldaz et al, 2011[30]	Navarre, Spain	Spain	Cohort study	AIDS case register	NA	68	NA	1999	2006	CVD† (mortality)
Durand et al, 2011[31]	Quebec	Canada	Cohort study	Quebec public health insurance database and clinical database	ICD-9	78	37	NA	2007	MI*
Chow et al, 2012[32]	RPDR	USA	Cohort study	Research Patient Data Registry	ICD-9	69	42	1996	2009	Stroke (incident) *
Helleberg et al, 2012[33]‡	Danish HIV	Denmark	Cohort study	Danish Civil Registration System, National registry of cause of death	ICD-10	75.8	36	1995	2008	CVD† (mortality)
Walker et al, 2013[34]	Tanzania	Tanzania	CCS	Verbal autopsy	WHO definition	55	62	2003	2006	Stroke*
Mateen et al, 2013[35]	MACS	USA	Cohort study	MACS database	ICD-9	100	41	1996	2011	Stroke
Tripathi et al, 2014[36]	South Carolina Medicaid program	USA	Cohort study	HIV reporting system Surveillance Database	ICD-9	57	39	1994	2011	CVD*†
Womack et al, 2014[37]	VACS-VC	USA	Cohort study	Medicare/IHD Quality Enhancement Initiative	ICD-9	0	44	2003	2009	CVD† (incident)
Sico et al, 2015[38]	VACS-VC	USA	Cohort study	Medicare/IHD Quality Enhancement Initiative	ICD-9/ICD-10	100	48	2003	2009	Stroke
Rasmussen et al, 2015[39]§	Danish HIV	Denmark	Cohort study	Danish Civil Registration System, National registry of cause of death	ICD-10	76	37	1995	2014	MI (incident)
Althoff et al, 2015[40]	VACS	USA	Cohort study	Medicare/IHD Quality Enhancement Initiative	ICD-9	NA	48	2003	2010	MI*
Klein et al, 2015[41]‖	KPNC KPSC	USA	Cohort study	HIV registry; electronic medical record	ICD-9	91	41	1996	2011	MI*

CCS indicates case control study; CVD, cardiovascular disease; HIV, human immunodeficiency virus; HR, hazard ratio; ICD, *International Classification of Diseases*; MI, myocardial infarction; and NA, not available.

*Outcome data determined from hospital databases and, therefore, may exclude fatal events occurring in the community and not resulting in hospitalization.

†CVD in these studies was defined as follows: in Gardner et al[27]: ischemic heart disease, cardiomyopathy, ventricular arrhythmias, transient ischemic attack, congestive cardiac failure, deep vein thrombosis, stroke; in Aldaz et al[30]: ICD-10 codes from I00 to I99; in Helleberg et al[33]: ICD-10 codes from I00 to I99; in Tripathi et al[36]: acute myocardial infarction, angina, percutaneous intervention, and nonhemorrhagic stroke; and in Womack et al[37]: acute myocardial infarction, unstable angina, ischemic stroke, and heart failure.

‡Helleberg et al[33] provided the risk ratio for cardiovascular disease for the year of 1995 only in comparison with an age- and sex-matched reference general population.

§Rasmussen et al[39] provided a risk ratio for both myocardial infarction and stroke.

‖Klein et al[41] provided an adjusted HR of 1.4 (95% CI, 1.2–1.6) for the period of 1996 to 2011; however, this risk estimate has decreased over time to 1.0 (95% CI, 0.7–1.4) for 2010 to 2011.

year period was observed in East and Southern Africa (15 870 DALYs per year [95% CI, 7600–32 660]) with the lowest increases observed in the Middle East and North Africa (530 DALYs per year [95% CI, 280–950]) and Western and Central Europe and North America (700 DALYs per year [95% CI, 410–1070]) (Table IX in the online-only Data Supplement).

National Estimates

National estimates of prevalence and cardiovascular burden were available for 154 countries. The highest population-attributable fraction was observed in countries within sub-Saharan Africa, with HIV accounting for >15% of the cardiovascular burden in Swaziland,

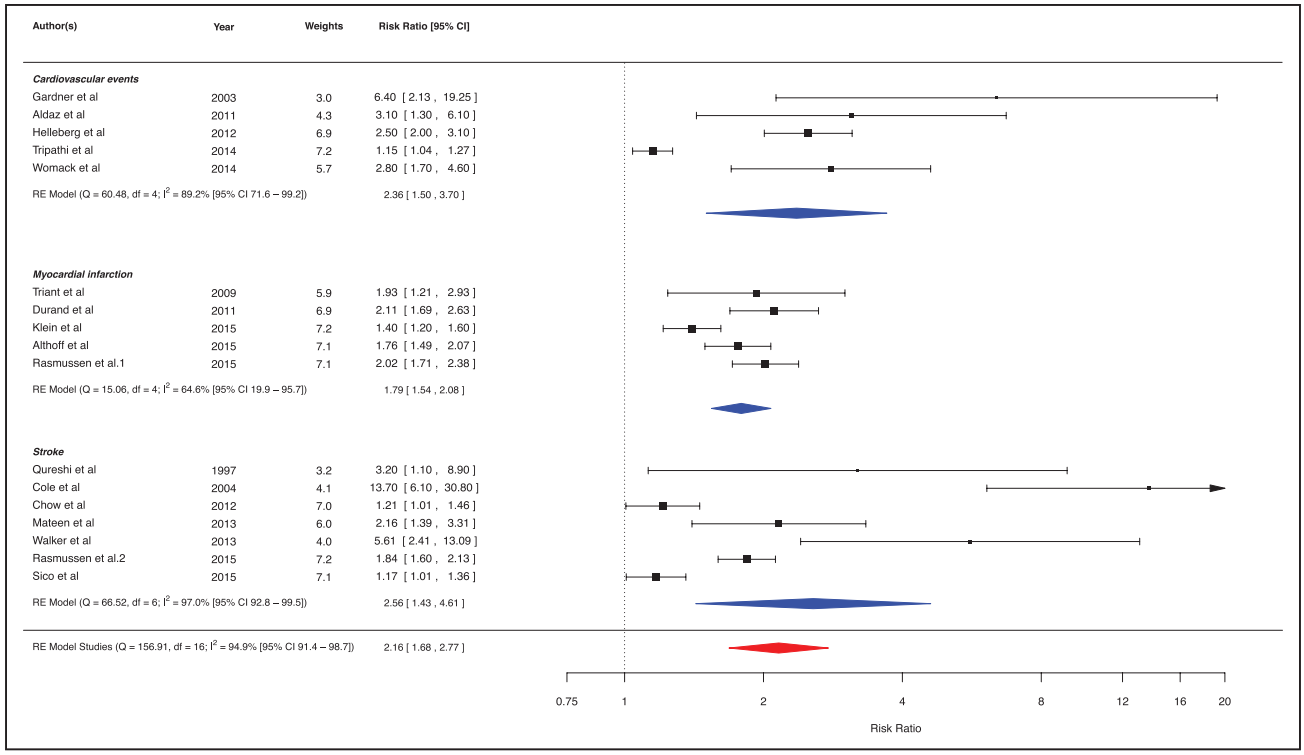

Figure 2. Forest plot.
Pooled risk ratio for risk of cardiovascular disease in people living with HIV in comparison with those without stratified by type of event.[26–41] Both Aldaz et al[30] and Helleberg et al[33] evaluated cardiovascular mortality defined as an ICD code range from I00 to I99. ICD indicates *International Classification of Diseases*; and RE, random-effects.

Botswana, Lesotho, and South Africa (Figure 4A, Table X in the online-only Data Supplement). Similarly, the largest burden was observed in sub-Saharan Africa (Figure 4B). In the UNAIDS Global Plan priority countries, the population-attributable fraction was comparable to other traditional cardiovascular risk factors (Table XI in the online-only Data Supplement).

Data for the burden of cardiovascular DALYs attributable to HIV were available for 20 of the 21 priority countries from sub-Saharan Africa in the UNAIDS Global Plan.[22] HIV-associated cardiovascular DALYs across these countries increased from 0.21 million (95% CI, 0.11–0.38) in 1990 to 0.74 million (95% CI, 0.39–1.37) in 2015 (Figure IV in the online-only Data Supplement).

DISCUSSION

In this systematic review, meta-analysis, and burden assessment, we evaluated the association between HIV infection and cardiovascular disease, and estimated the national, regional, and global burden of cardiovascular disease attributable to HIV infection. We make a number of important and novel observations. First, the crude rate for incident cardiovascular disease was 60 per 10 000 person years and is comparable to other high-risk cardiovascular groups, such as diabetes mellitus.[42] Second, the risk of incident cardiovascular disease was 2-fold higher in people living with HIV. Third, the number of DALYs attributable to HIV-associated cardiovascular disease has increased 3-fold over the past 2 decades, but has now plateaued. Finally, there were major regional variations in both the attributable fraction and the rates of cardiovascular disease attributable to HIV, with much of the burden seen in sub-Saharan Africa, followed by Asia and the Pacific.

Many factors may have affected the estimates that we have derived and are based on several assumptions that merit discussion. First, the pooled risk ratios used to calculate the population-attributable fraction and the subsequent cardiovascular burden were primarily obtained from developed nations but were applied to all regions. This approach is ubiquitous in these types of analyses[43,44] and highlights the paucity of data from these regions. In a recent analysis evaluating the global burden of cardiovascular disease attributable to hypertension and obesity, <10% of cohorts originated from low- and middle-income nations.[44,45] Second, the incidence rate does not consider competing risk from non-cardiovascular mortality. This would further underestimate the rate of cardiovascular disease in people living with HIV, especially in earlier studies when antiretroviral therapy was not widely available. Third, although many of the individual studies evaluating the risk ratio of cardiovascular disease adjusted for important traditional risk factors, there remains the risk of residual confounding. Previous studies have already shown higher fre-

quencies of both modifiable and nonmodifiable cardiovascular risk factors in people living with HIV.[17] As such, a higher prevalence of factors that do not lie on the causal pathway may have influenced the overall association between HIV and cardiovascular events. Fourth, the pooled relative risk estimates used to calculate the

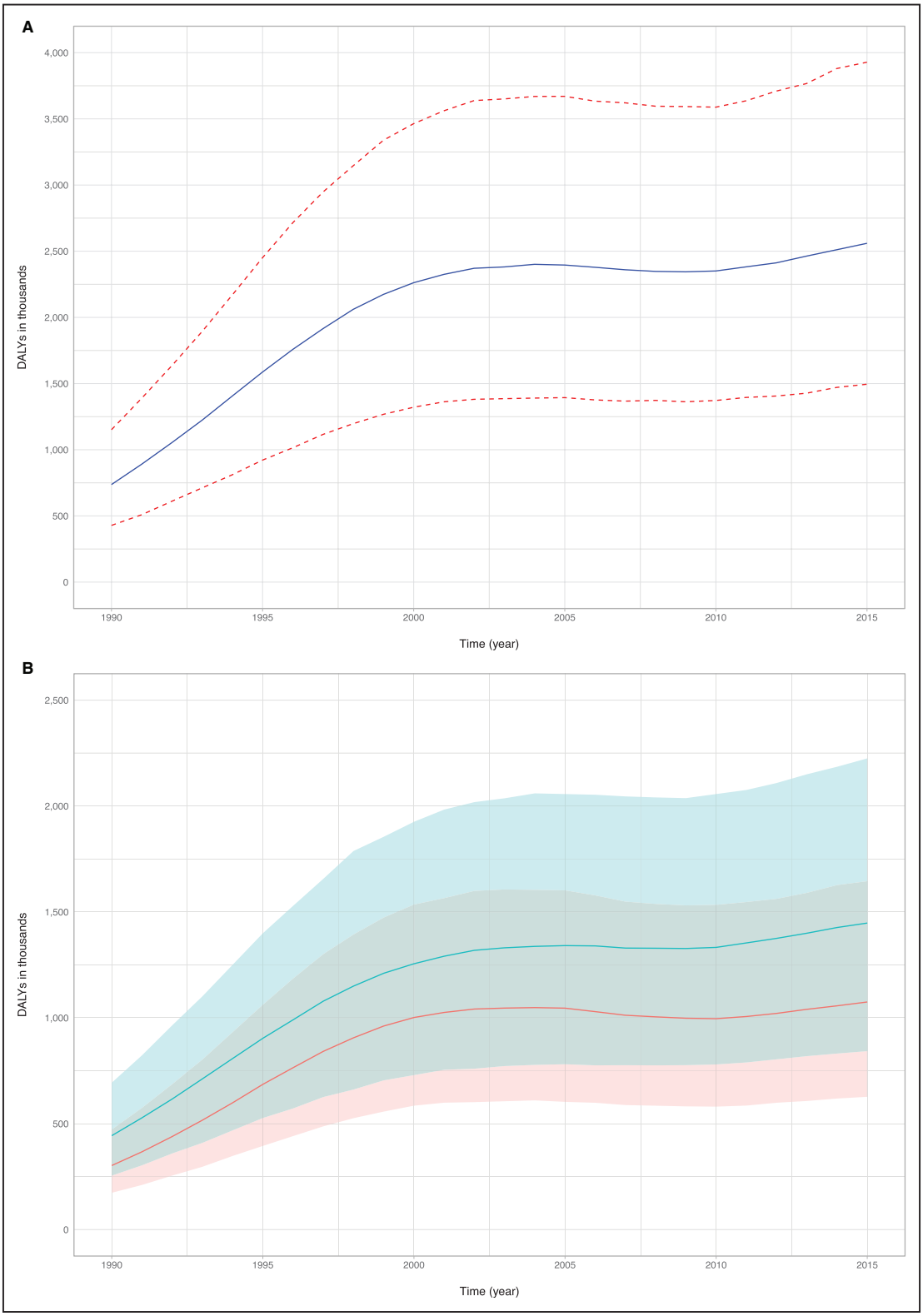

Figure 3. Disability-adjusted life-years.
Temporal change in the disability-adjusted life-years (DALYs) of HIV-associated cardiovascular disease globally (**A**) and stratified by sex (**B**); red line represents central estimate, and blue dashed lines represent the 95% CI. (*Continued*)

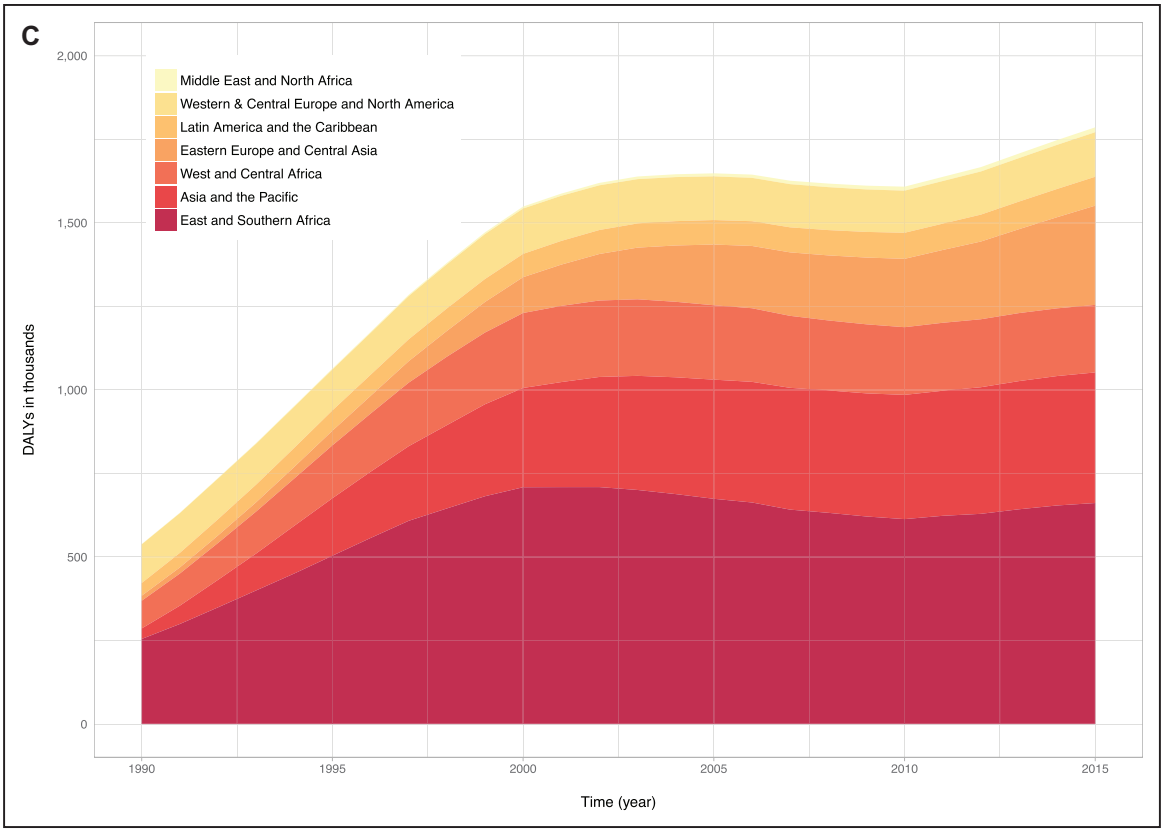

Figure 3 Continued. **C**, Stack-plot showing the central estimate by UNAIDS region and time. UNAIDS indicates Joint United Nations Programme on HIV/AIDS.

population-attributable fraction for DALY for ischemic heart and cerebrovascular disease was obtained solely from studies including acute myocardial infarction or stroke and so did not specifically include estimates for angina pectoris or other chronic manifestations of atherosclerotic disease. However, relative to the overall cardiovascular DALY attributable to ischemic heart disease, the burden from angina is minimal.[10] Therefore, the impact of this limitation on the overall burden estimate is likely to be small. Fifth, the majority of studies evaluating the risk of cardiovascular disease in people living with HIV have recruited participants before 2010, with a large number conducted in the previous century. The epidemiology of HIV diagnosis and care has changed significantly over the past 2 decades, with better provision of antiretroviral therapy and improved survival, resulting in an increased prevalence of HIV.[46] Sixth, when calculating the burden at a global and regional level, we have made the assumption that the prevalence of HIV infection in the younger age group (15–49 years old) is consistent across the entire age range. There is a paucity of data in the prevalence of HIV in the older population, especially in high-prevalence regions such as sub-Saharan Africa.[47] However, analysis of the populations in these regions shows that the prevalence in the older population remains similar to that of the 15- to 49-year group.[47] Finally, we noticed substantial heterogeneity for our overall pooled risk ratios. The source for this degree of heterogeneity is likely to be multifactorial and reflect differences in population demographics, sample size and small-study effect, patient characteristics, selection or publication bias, and case ascertainment bias because the majority of data were based on national statistics.

Many studies have evaluated the association between HIV infection and the risk of atherosclerotic disease including the potential role of antiretroviral therapy.[17,48–50] This is the first study to review and meta-analyze systematically the association between HIV infection and cardiovascular disease, and to estimate the burden of cardiovascular disease attributable to HIV. The mechanisms underlying this association remain poorly understood.[17] Possible mechanisms include endothelial dysfunction[51] and increased systemic[13] and coronary arterial inflammation[14] associated with elevated inflammatory markers.[13] Furthermore, patients with HIV have more traditional metabolic risk factors for cardiovascular disease[17] including dyslipidemia,[15] insulin resistance and abnormal glucose homeostasis,[16] and abnormalities in body fat composition.[52–54] The increased risk of cardiovascular disease in people living with HIV is thus a consequence of both accelerated atherosclerosis attributable to chronic infection and the increased prevalence of traditional risk factors.

The global burden of cardiovascular disease attributable to HIV infection has tripled over the past 2 decades,

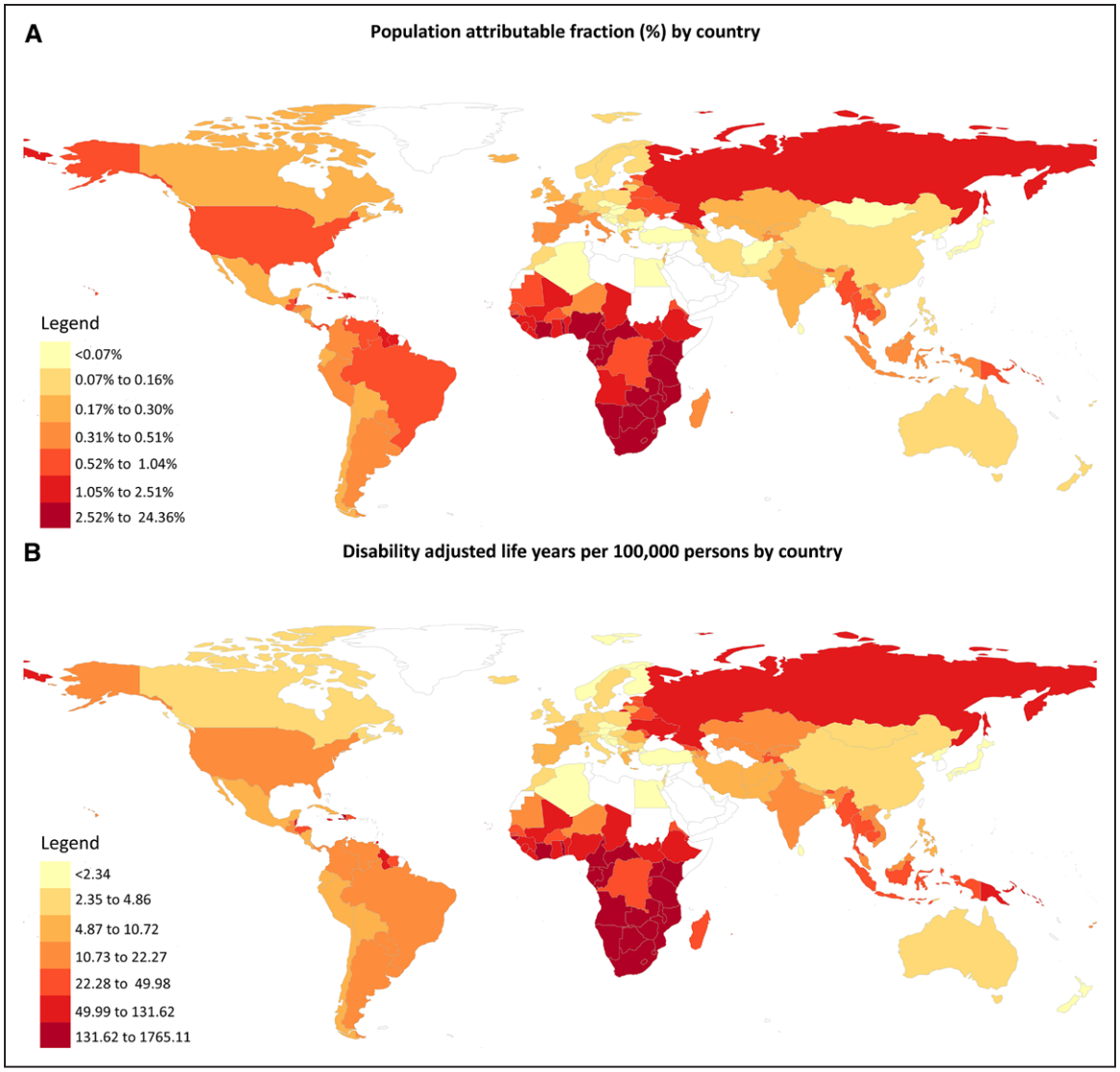

Figure 4. Cartograms.
Cartograms showing population-attributable risk (**A**) and HIV-attributable disability-adjusted life-years per 100 000 persons (**B**) for HIV-associated cardiovascular disease. Each color category represents a septile.

especially in the low- and middle-income nations, and is likely to be a product of both temporal increases in the prevalence of HIV and the morbidity and mortality from cardiovascular disease. The prevalence of HIV varies by region with the greatest proportions seen in sub-Saharan Africa and the Asia Pacific region. Cardiovascular disease now accounts for >10% of all morbidity and mortality in sub-Saharan Africa with rates that are comparable to high-income regions. Consequently, the sub-Saharan region accounted for half of all DALYs from cardiovascular disease attributable to HIV. The population-attributable fraction of HIV-associated cardiovascular disease in the UNAIDS high-priority countries was up to 25% and similar to traditional lifestyle, metabolic, and environmental risk factors.[23,24]

The combined burden of HIV and cardiovascular disease in the UNAIDS high-priority countries is of growing concern and has important implications with respect to regional health policies, guidelines, and resource allocation. Risk stratification and identification of patients at intermediate or high risk of future cardiovascular disease are already challenging in resource-limited nations.[55] Furthermore, traditional risk scores perform poorly because they consistently underestimate risk in HIV-infected populations.[35,56,57] Whether patients living with HIV should be considered high risk and started on primary prevention, such as statin therapy, remains unclear. A recent randomized controlled trial of rosuvastatin in patients with HIV demonstrated a reduction in carotid artery intima-media thickness despite these individuals having low low-density lipoprotein cholesterol concentrations at baseline.[58] Although the latest international guidelines have expanded the use of lipid-lowering therapy

in the general population, over two-thirds of people living with HIV with evidence of high-risk morphology coronary atherosclerotic plaque would not have been recommended for statin therapy.[59] The REPRIEVE study (Randomised Trial to Prevent Vascular Events in HIV) is now underway to evaluate the efficacy of statin therapy in people living with HIV who are deemed low-risk based on traditional risk scores.[60,61]

CONCLUSIONS

This analysis evaluates the association between HIV and cardiovascular disease, and estimates the global burden of HIV-associated cardiovascular disease. We report that the risk of cardiovascular disease was 2-fold higher in people living with HIV. Moreover, the global burden of HIV-associated cardiovascular disease has tripled over the past 2 decades and is now responsible for 2.6 million DALYs per annum, with the majority in sub-Saharan Africa and the Asia Pacific regions. Our estimates have important policy implications for implementing appropriate cardiovascular risk stratification and treatment strategies across healthcare systems, especially in those countries with the greatest burden where resources remain limited.

ARTICLE INFORMATION

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Disclosures

None.

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