Factors Associated With Excess Myocardial Infarction Risk in HIV-Infected Adults: A Systematic Review and Meta-analysis

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Objectives: To estimate the pooled relative risk (RR) of incident acute myocardial infarction (AMI) among HIV-infected adults compared with HIV-uninfected controls and explore the contribution of traditional and HIV-related risk factors.

Background: Understanding AMI risk and associated risk factors in HIV-infected populations has the potential to inform clinical management and prevention strategies.

Methods: We systematically identified cohort studies of HIV-infected or HIV-infected and matched uninfected adults reporting AMI incidence rates published up to January 1, 2017. Random-effects meta-analysis models were used to estimate the aggregate RR of AMI by HIV status. Subgroup analysis and meta-regression were used to explore factors affecting risk.

Results: Sixteen studies (N = 1,619,690, median age 38.5 years, 78.9% male, mean follow-up of 6.5 years) were included. In pooled analyses of HIV-infected and matched uninfected cohorts (n = 5), HIV-infected individuals had higher AMI incidence rates (absolute risk difference = 2.2 cases per 1000 persons per year) and twice the risk of AMI [RR = 1.96 (1.5–2.6)] compared with matched HIV-uninfected controls. In a multivariate meta-regression, each additional percentage point in the proportion of male participants [odds ratio (OR) = 1.20 (1.14–1.27)] and each additional percentage point in the prevalence of hypertension [OR = 1.19 (1.12–1.27)], dyslipidemia [OR = 1.09 (1.07–1.11)], and smoking [OR = 1.09 (1.05–1.13)] were independently associated with increased AMI risk in HIV-infected adults.

Conclusions and Relevance: Chronic HIV infection is associated with a 2-fold higher AMI risk. Traditional risk factors such as hypertension, dyslipidemia, and smoking are significant contributors to AMI risk among HIV-infected adults and should be aggressively targeted in routine HIV care.

Key Words: cardiovascular disease, myocardial infarction, HIV

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INTRODUCTION

The advent and widespread rollout of antiretroviral therapy (ART) over the past several decades has resulted in dramatic reductions in AIDS-related deaths and a rise in life expectancy.[1–8] In this setting, cardiovascular disease (CVD) has emerged as a leading comorbidity and cause of death among HIV-infected adults around the world.[9] CVD also poses a greater burden on HIV-infected than HIV-uninfected populations, with the HIV population facing higher prevalence of CVD risk factors and in turn higher mortality associated with acute myocardial infarction (AMI).[4,10] This excess in AMI risk has been linked to the double burden of highly prevalent traditional (eg, smoking, hypertension, and diabetes) and HIV-specific risk factors (eg, inflammation, immune suppression, and viremia) the HIV population faces.[1,6,11,12] Gains in life expectancy in the HIV population may be threatened if CVD risk is not optimally managed.[13]

The existence of several cohort studies exploring CVD risk in HIV-infected populations has made possible the conduction of meta-analyses, which are helpful evidence summaries to inform clinical practice. For instance, meta-analyses have estimated the HIV population has about a 2-fold greater CVD risk than their uninfected counterparts.[14,15] Meta-analyses have also shown that both HIV-specific risk factors (such as immunosuppression and viral load) and vascular risk

factors contribute to increased CVD risk in the HIV population.[14–16] However, no previous meta-analysis has explored the relative contribution of traditional and HIV-specific risk factors, limiting practitioners' ability to design cost-effective preventive interventions for the HIV population.

To address this gap, we conducted a comprehensive systematic review and meta-analysis of longitudinal cohort studies and estimated the pooled incidence rates and relative risk (RR) of AMI in HIV-infected compared with HIV-uninfected populations. We also examined the contribution of traditional and HIV-related risk factors to AMI risk. Understanding the presence of and contributors to AMI risk in HIV-infected populations is important to inform clinical CVD management.

METHODS

Search Strategy and Study Selection

We systematically searched the PubMed and Embase databases for articles published in English prior to January 1, 2017, and containing one or more MeSH terms or keywords for HIV infection ("hiv infections," "AIDS," "HIV/AIDS," "anti-retroviral agents") and cardiovascular outcomes of interest ("myocardial ischemia," "myocardial infarction," "cardiovascular disease," "cardiovascular events," "stroke," "cardiovascular mortality," or "cardiovascular death"). We followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines in the conduction and reporting of this meta-analysis.[17]

To be included, studies had to use a longitudinal study design, include HIV-infected adults over 18 years of age with or without an uninfected comparator group, and report incidence rates of AMI. Where multiple publications from a single cohort were available, the most current publication that met the inclusion criteria and provided data on relevant risk factors was selected. Articles including only individuals with comorbid infection by hepatitis B virus, hepatitis C virus, tuberculosis, or Chagas disease were excluded as these conditions independently confer elevated cardiac risk. Populations for whom only nonatherosclerotic cardiac outcomes were reported (including heart failure, dilated cardiomyopathy, and infectious cardiomyopathy) were excluded because this was outside the scope of our current study. Titles and abstracts were independently screened for inclusion by 2 authors (S.G.R. and H.C.G.), and disagreements were resolved by a third author (M.K.A.).

Data Extraction and Outcomes

Baseline and outcome data, along with relevant study- and participant-level characteristics were extracted and entered into a standardized data extraction form. The outcome of interest was incidence of AMI, defined and adjudicated by each study, with most performing chart review and/or endpoint adjudication by external reviewers. HIV infection was defined in most cohorts as receiving HIV care or chart diagnosis of HIV infection.

Outcome data were extracted for crude AMI event rates and total person-years of follow-up with associated confidence intervals (CIs). Data on the prevalence of traditional cardiovascular risk factors at baseline (smoking, dyslipidemia, hypertension, and diabetes) and HIV-related risk factors (exposure to antiretroviral therapy and previous AIDS diagnosis) were extracted where these were reported.

Study Quality Assessment

The Newcastle–Ottawa Scale[18] for cohort studies was used to assess the quality of included studies. The scale consists of 3 domains (participant selection, comparability of cohorts, and outcome assessment) evaluated through 8 questions. For the selection domain, we assessed whether the exposed cohort was representative of the study intended population (1 star) or not representative (0 stars); whether HIV infection was ascertained through medical records (1 star), structured interviews (1 star), written self-report (0 stars), or not described (0 stars); and whether studies demonstrated AMI was not present at study start (yes = 1 star, no = 0 stars). Selection of the nonexposed cohort (ie, HIV-uninfected) was not used as studies with only HIV-infected persons were also included. For the same reason, we adapted the comparability of cohorts item to assess whether age (yes = 1 star, no = 0 stars) and other AMI risk factors (yes = 1 star, no = 0 stars) were controlled for in the design/analyses. For outcome assessment, we examined how AMI was determined (clinical tests/medical records = 1 star, no description = 0 stars), the length of follow-up ($\geq$3 years = 1 star, $<$3 years = 0 stars), and the proportion of participants lost at follow-up (0%–30% = 1 star, $>$30% or not reported = 0 stars). Each study was given a maximum of one star for each question within the selection and outcome domains; a maximum of 2 stars were given for comparability. We summed the number of stars earned by each study and categorized them as high (5–8 stars) or low quality (1–4 stars).

Data Synthesis and Statistical Analysis

Among studies with HIV-infected and matched HIV-uninfected cohorts, we pooled AMI incidence rates and estimated the absolute risk difference between HIV-infected and uninfected individuals. To account for heterogeneity between studies, a random-effects meta-analysis model was used to estimate the pooled RR for an AMI event and the corresponding 95% CIs, with HIV-uninfected individuals as reference. A RR with an associated 95% CI that did not contain 1 star was considered statistically significant.

Using data from all cohort studies, we grouped HIV-infected participant groups and HIV-uninfected participant groups together and conducted a random-effects meta-analysis to estimate the odds of having an AMI event, using HIV-uninfected participants as reference. We then performed subgroup analyses to examine the likelihood of having an AMI event according to participant demographic characteristics (age, sex, and race), AMI risk factor prevalence (hypertension, smoking, dyslipidemia, and diabetes), and HIV-related risk factor prevalence (percentage of participants on any ART and AIDS prevalence). Our definitions of subgroups were based on the distributions reported in the included articles; for instance, based on reported diabetes prevalence (mean 10.8%, median 9%, range 3%–25%),

a 10% prevalence cutoff was selected for subgroup analysis. Finally, multivariate meta-regressions were used to explore the contribution of different risk factors to AMI risk heterogeneity in HIV-infected adults.

Between-study heterogeneity was assessed by computing I^2, where I^2 >75% indicated significant heterogeneity. Publication bias was assessed using the Egger test and by visually exploring funnel plots. Finally, we conducted sensitivity analyses among high-quality studies and obtained a pooled estimate for this group of studies. We used the random-effects meta-analysis package[19] in R programming language (version 3.2.1) to fit the models described.

RESULTS

From the 2117 titles screened, 108 were selected for full text review and 16 were included in the meta-analysis (Fig. 1). Five studies included HIV-infected and matched uninfected cohorts,[6,10,20–22] whereas 11 studies reported only on HIV-infected cohorts.[3,23–32] Duration of study follow-up ranged from 1.8 years to 6.3 years. About half of the studies were conducted in North America (44%) and a third in Europe (31%). Characteristics of included studies are presented in Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B292.

The 16 studies included 248,145 HIV-infected participants (median age 40 years, 81% male, 47% white) and 1,371,545 HIV-uninfected participants (median age 42 years, 77% male, 50% white). Risk factor baseline prevalence and AMI incidence rates reported in each study by HIV status are presented in Table 1. The average prevalence of hypertension in HIV-infected and uninfected individuals (19% vs. 15%, respectively), smoking (46% vs. 49%, respectively), dyslipidemia (22% vs. 18%, respectively), and diabetes (6% vs. 7%, respectively) did not significantly differ ($P > 0.05$). The average prevalence of AIDS reported across studies was 27%, whereas the average proportion of HIV-infected participants with exposure to ART was 67%.

In HIV-infected and matched uninfected cohorts (n = 5), the average AMI incidence rate was 5.0 cases per 1000 person-years (95% CI = 4.3 to 5.8) in HIV-infected individuals and 2.8 cases per 1000 person-years (95% CI = 2.6 to 3.0) in HIV-uninfected individuals (absolute risk difference = 2.2 per 1000 person-years). The random-effects meta-analysis (Fig. 2) showed HIV-infected participants have a 2-fold higher risk of AMI compared with HIV-uninfected participants [RR = 1.96 (1.48–2.57), I^2 = 92.7%].

We grouped HIV-infected participants across the 16 studies included and compared AMI risk against that of HIV-uninfected participants included in 5 matched cohorts. HIV-infected participants had 87% greater odds of having an AMI event [odds ratio (OR) = 1.87 (1.42–2.47)] than HIV-uninfected participants. In unadjusted subgroup analyses exploring AMI risk in HIV-infected compared with uninfected individuals (Table 2), significantly greater odds for having an AMI event were observed in studies where >50% participants were exposed to any ART [OR = 2.66 (2.25–3.13)] compared with studies where <50% of participants were exposed [OR = 1.46 (1.32–1.61)]. Concerning traditional risk factors, significantly greater odds for having an AMI event were observed in studies with <80% male participants [OR = 2.44 (1.99–2.97)], than in studies with ≥80% male participants [OR = 1.38 (1.11–1.71)].

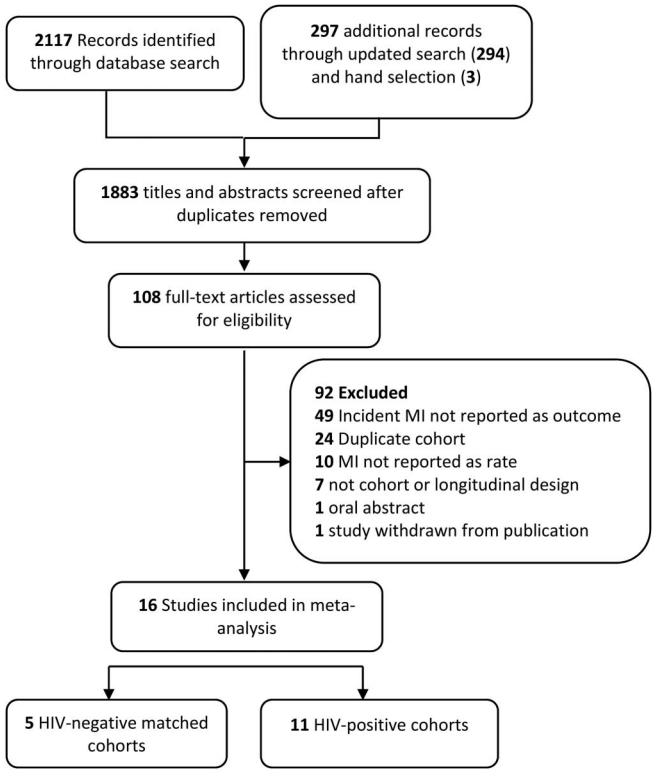

FIGURE 1. Study selection flow diagram.

In a multivariate meta-regression (n = 7), participant median age, percentage of male participants, and prevalence of smoking, hypertension, diabetes, and dyslipidemia were associated with increased AMI risk. Each additional percentage point in the proportion of male participants [OR = 1.20 (1.14–1.27)] and each additional percentage point in the prevalence of hypertension [OR = 1.19 (1.12–1.27)], dyslipidemia [OR = 1.09 (1.07–1.11)], and smoking [OR = 1.09 (1.05–1.13)] were associated with 9%–20% greater AMI risk. Conversely, each additional year in median age [OR = 0.60 (0.50–0.72)] and diabetes prevalence percentage point [OR = 0.78 (0.73–0.83)] associated with 40% and 22% lower AMI risk, respectively.

Regarding quality assessment, 9 studies were classified as high quality and 7 studies as low quality (see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/B292). A sensitivity analysis including only high-quality studies showed HIV-infected participants had 91% higher odds than HIV-uninfected participants of having an AMI event [OR = 1.91 (1.44, 2.52)], which is similar to that observed when all studies are included. Low-quality studies did not show a significant increased risk [OR = 1.01 (0.45–2.29)].

The Egger test suggested publication bias was present ($z = -3.6$, $P < 0{\cdot}0001$) in HIV-infected and HIV-uninfected matched cohort studies (n = 5). A visual examination of funnel plots among all studies confirmed that smaller studies with null

TABLE 1. Baseline Risk Factor Prevalence and AMI Incidence Rates by HIV Status Among Included Cohort Studies (n = 16)

Author	Smoker (%)	Dyslipidemia (%)	Hypertension (%)	Diabetes (%)	AIDS (%)	ART (%)	IR per 1000 PY (95% CI)
HIV-infected arms							
Althoff et al[20]	68.0	34.0	22.0	14.0	25.0	45.0	2.0 (1.8 to 2.3)
Bedimo et al[23]	29.0	26.0	38.0	13.0		75.0	3.7 (2.3 to 4.2)
Durand et al[21]		38.1	23.9	6.6	31.1	76.2	3.9 (3.3 to 4.6)
Hasse et al[3]	23.8	12.7	56.3	4.1	23.2	85.0	2.4 (1.9 to 3.2)
Holmberg et al[24]	56.5	27.9	11	4.5			1.19 (0.8 to 1.8)
Rasmussen et al[22]	65.7		3.5	2.9	21.7	77.2	5.2 (4.3 to 6.4)
Sabin et al[25]	54.8	38.4	9.2	2.9	23.2		3.2 (3.0 to 3.4)
Silverberg et al[6]	43.3	5.0	7.3	2.9	39.4	46.2	2.8 (2.5 to 3.2)
Triant et al[10]		23.3	21.2	11.5			11.1 (9.6 to 12.7)
Escaut et al[26]	36.1					85.5	5.2 (3.0 to 8.4)
Rickerts et al[27]					40	25.7	1.8 (1.2 to 2.5)
Lang et al[28]							1.2 (1.1 to 1.4)
Kwong et al[29]	40.3		2.01	1.08		100	1.2 (1.0 to 1.5)
Brothers et al[30]							2.1 (0.8 to 5.7)
Brouwer et al[31]							5.9 (4.3 to 8.2)
Ribaudo et al[32]	38.0	12.0	18.0	4.0	19.0		2.1 (1.5 to 2.8)
HIV-uninfected arms							
Althoff et al[20]	65.0	38.0	32.0	21.0			1.3 (1.2 to 1.4)
Durand et al[21]		12.3	15.1	4.7	0.0	0.0	2.2 (1.9 to 2.5)
Rasmussen et al[22]	53.9		3.0	1.3	0.0	0.0	2.0 (1.7 to 2.4)
Triant et al[10]		17.6	15.9	6.6	0.0	0.0	7.0 (6.9 to 7.1)

PY, person-years.

associations were less likely to be published than studies with positive higher-magnitude associations (see Figure 1, Supplemental Digital Content, http://links.lww.com/QAI/B292).

DISCUSSION

In this comprehensive systematic review and meta-analysis, we examined AMI risk in HIV-infected compared with HIV-uninfected populations and assessed the contribution of traditional and HIV-specific risk factors to excess AMI risk. We found HIV-infected adults have a 2-fold higher AMI risk compared with matched HIV-uninfected controls, with an absolute risk difference of 2.2 cases per 1000 persons per year. AMI risk was higher in HIV-infected individuals in every cohort included, despite differences in location, year of publication, and demographic variations between cohorts.

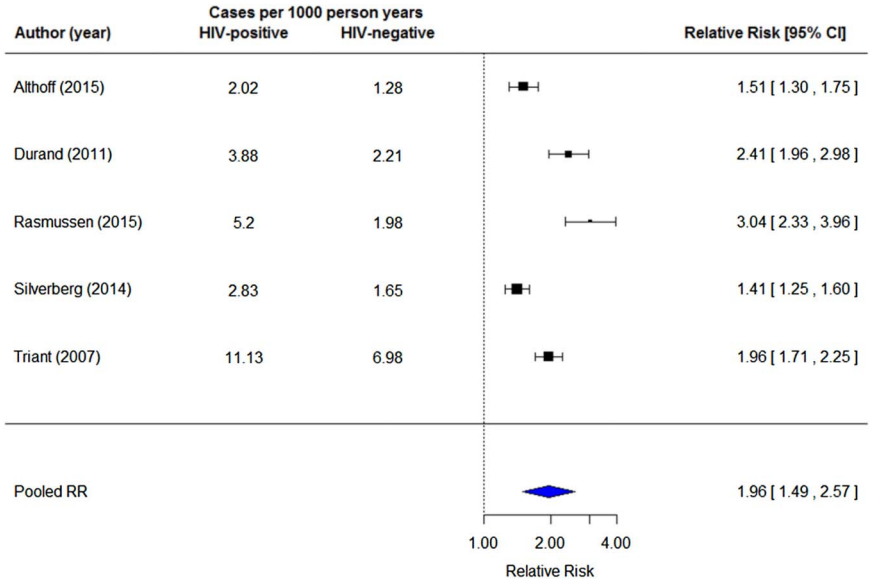

FIGURE 2. Random-effects meta-analysis showing AMI incidence rates and RR in HIV-infected individuals compared with matched HIV-uninfected individuals (n = 5). Square markers indicate risk ratios for AMI comparing HIV-infected and HIV-uninfected adults with error bars demonstrating 95% CIs.

TABLE 2. Subgroup Analysis Comparing AMI Risk Between HIV-Infected and HIV-Uninfected (Reference) Participants by Demographic Characteristics and Risk Factor Prevalence

Variable	N	AMI, OR (95% CI)
Age		
<38	4	1.32 (0.65 to 2.69)
≥38	9	1.92 (1.19 to 3.10)
Sex		
<80% male	6	2.44 (1.99 to 2.97)
≥80% male	9	1.38 (1.11 to 1.71)
Race		
<50% white	3	1.55 (1.06 to 2.28)
≥50% white	5	1.67 (1.27 to 2.19)
Hypertension		
<20%	6	1.75 (1.10 to 2.79)
≥20%	5	1.96 (1.32 to 2.92)
Smoking		
<50%	6	1.51 (0.87 to 2.61)
≥50%	4	2.11 (1.34 to 3.33)
Dyslipidemia		
<20%	4	0.92 (0.42 to 2.01)
≥20%	5	2.27 (1.22 to 4.23)
Diabetes		
<10%	3	1.86 (1.26 to 2.77)
≥10%	8	1.90 (1.18 to 3.06)
AIDS		
<30%	5	2.07 (1.23 to 3.49)
≥30%	3	1.81 (1.05 to 3.11)
ART*		
<50%	3	1.46 (1.32 to 1.61)
≥50%	6	2.66 (2.25 to 3.13)
Overall	16	1.87 (1.42 to 2.47)

N = studies included in the subgroup. OR with HIV-uninfected participants as reference.

*Proportion of participants on ART.

Traditional risk factors, namely hypertension, smoking, and dyslipidemia, emerged as significant contributors to AMI risk in HIV-infected individuals. Overall, our findings confirm and expand the evidence base showing HIV infection confers increased CVD risk and add to calls to integrate aggressive CVD risk management in routine HIV care.

Our results align with evidence from other meta-analyses. For instance, a meta-analysis exploring CVD risk in HIV-infected adults found a 61% increased risk of composite CVD outcomes compared with HIV-uninfected adults, whereas a 2-fold increased risk was observed among those exposed to ART.[14] Similarly, another meta-analysis reports a 60% greater AMI risk among HIV-infected compared with uninfected controls, and that ART use contributes to increased CVD risk.[15] We found a 2-fold increase in AMI risk among HIV-infected groups compared with matched uninfected groups; this allows us to speculate that excess risk cannot be solely explained by differences in demographic characteristics and risk factor prevalence but may be linked to HIV-related factors and amplified by traditional risk factors.

Regarding risk factors for AMI, we found increases in the prevalence of hypertension associated with a 20% increased AMI risk, while increases in the prevalence of hyperlipidemia and smoking associated with a 9% increased risk each. These findings align with those from the VACS cohort study showing that traditional risk factors contribute to increased AMI risk.[1] Furthermore, data from 7 cohorts contributing to the NA-ACCORD study showed that eliminating smoking and hypertension in HIV-infected adults would avert 38% and 41% of AMI, respectively.[33] Because HIV-infected adults have been found to have higher rates of smoking, dyslipidemia, diabetes, and hypertension than the general population,[10,34] aggressive management of these risk factors is needed to reduce AMI risk in the HIV population. Studies are needed to determine what specific treatment targets would be most beneficial for the HIV population.

We also found higher age and higher diabetes prevalence associated with lower AMI risk among HIV-infected participants. Although this may be driven by the younger age of most HIV-infected cohorts, other potential explanations include lower competing risks, health care use, and smoking rates in the uninfected group that were not accounted for in our analysis.[35] This finding may also be a reflection of the more rapid progression to clinically significant disease in the setting of HIV. The inverse association between diabetes prevalence and AMI risk could indicate that HIV-infected individuals with diabetes are benefiting from diabetes treatment and potentially from other CVD prevention strategies they receive. Overall, these findings suggest that aggressive CVD prevention efforts should be integrated in routine HIV care.

Subgroup analyses showed greater AMI risk in studies where ≥50% of participants had been exposed to any form of ART. Although this suggests ART has an impact on AMI risk, we were not able to parse out this association. We could not explore the link between specific ART classes and AMI risk because of incomplete reporting in included studies, whereeas other meta-analyses have implicated protease inhibitors and abacavir use in AMI risk.[16] For the same reason, we could not explore the effect of older and newer drugs, an important aspect to explore given the change in therapies used in the early and current ART eras.[36] Indeed some therapies used in the included studies are no longer first-line HIV therapies used in HIV care. It is therefore difficult to make valid conclusions about the link between ART use and AMI risk in the present analysis.

This meta-analysis has limitations. CVD risk factor data were reported in half of the included studies and only at study entry: thus, the time varying nature of risk factors was not accounted for and MI risk may have been underestimated or overestimated in our analyses. HIV-related variables, including mean CD4 cell counts, viral loads, exposure to specific ART classes, and duration of HIV infection were inconsistently reported and could not be included in our analysis. For the same reason, we were not able to explore the effects of specific ART classes on MI risk or the effects of old vs. new drugs in our analyses. Although we were unable to differentiate between type 1 and 2 AMI, most included studies used a strong adjudication protocol (with chart diagnoses, EKG

testing, and biomarker confirmation) that likely included mostly type 1 AMI. Finally, we noted a high level of clinical heterogeneity in our study attributable to substantial variability in demographics of participants followed in the included cohorts; this was partially accounted for in subgroup analyses.

Firmly establishing—and quantifying—an association between HIV infection and CVD events contributes to epidemiological research that may help clarify the mechanism of this association. Future studies should examine the association of AMI with individual markers of HIV infection, including CD4 cell count and viral load, as well as known mediators of risk. Therapeutic goals for the management of hyperlipidemia, hypertension, and diabetes in the HIV-infected population have not been studied, although ongoing research into the role of statin therapy in preventing CVD events has potential to inform clinical management in this arena. Because the receipt of CVD risk factor treatment among HIV-infected adults is often inadequate,[37] opportunities for actionable change in HIV care are numerous.

Clinical Perspectives

As HIV-infected individuals are living longer because of effective ART, they now face an increased risk of morbidity and death caused by CVD. It is increasingly clear that appropriate HIV care requires not only chronic viral suppression, but also early recognition and management of cardiovascular risk factors. We found HIV-infected adults have 2 times the risk of AMI compared with HIV-uninfected individuals, and that traditional risk factors play a pivotal role in this increased risk. Our findings underscore the importance of introducing aggressive management of traditional CVD risk factors such as hypertension, hyperlipidemia, diabetes, and smoking early in the care of HIV-infected individuals. Unless CVD risk is effectively managed in the HIV population, the gains in life expectancy conferred by antiretroviral therapies may be lost.

REFERENCES

1. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med.* 2013;173:614–622.
2. Friis-Moller N, Thiebaut R, Reiss P, et al. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. *Eur J Cardiovasc Prev Rehabil.* 2010;17:491–501.
3. Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis.* 2011;53:1130–1139.
4. Paisible AL, Chang CC, So-Armah KA, et al. HIV infection, cardiovascular disease risk factor profile, and risk for acute myocardial infarction. *J Acquir Immune Defic Syndr.* 2015;68:209–216.
5. Reekie J, Kowalska JD, Karpov I, et al. Regional differences in AIDS and non-AIDS related mortality in HIV-positive individuals across Europe and Argentina: the EuroSIDA study. *PLoS One.* 2012;7:e41673.
6. Silverberg MJ, Leyden WA, Xu L, et al. Immunodeficiency and risk of myocardial infarction among HIV-positive individuals with access to care. *J Acquir Immune Defic Syndr.* 2014;65:160–166.
7. Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet.* 2014;384:241–248.
8. Triant VA. HIV infection and coronary heart disease: an intersection of epidemics. *J Infect Dis.* 2012;205(suppl 3):S355–S361.
9. Feinstein MJ, Bahiru E, Achenbach C, et al. Patterns of cardiovascular mortality for HIV-infected adults in the United States: 1999 to 2013. *Am J Cardiol.* 2016;117:214–220.
10. Triant VA, Lee H, Hadigan C, et al. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab.* 2007;92:2506–2512.
11. Lichtenstein KA, Armon C, Buchacz K, et al. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. *Clin Infect Dis.* 2010;51:435–447.
12. Triant VA, Regan S, Lee H, et al. Association of immunologic and virologic factors with myocardial infarction rates in a US healthcare system. *J Acquir Immune Defic Syndr.* 2010;55:615–619.
13. Colasanti J, Galaviz KI, Christina Mehta C, et al. Room for improvement: the HIV-diabetes care continuum over 15 years in the women's interagency HIV study. *Open Forum Infect Dis.* 2018;5:ofy121.
14. Islam FM, Wu J, Jansson J, et al. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. *HIV Med.* 2012;13:453–468.
15. Gutierrez J, Albuquerque ALA, Falzon L. HIV infection as vascular risk: a systematic review of the literature and meta-analysis. *PLoS One.* 2017;12:e0176686.
16. Bavinger C, Bendavid E, Niehaus K, et al. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. *PLoS One.* 2013;8:e59551.
17. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA.* 2000;283:2008–2012.
18. Wells GA, Shea B, O'Connell D, et al. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*. Ottawa, ON: Ottawa Hospital Research Institute; 2011. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed February 22, 2017.
19. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw.* 2010;36:1–48.
20. Althoff KN, McGinnis KA, Wyatt CM, et al. Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer in HIV-infected versus uninfected adults. *Clin Infect Dis.* 2015;60:627–638.
21. Durand M, Sheehy O, Baril JG, et al. Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Quebec's public health insurance database. *J Acquir Immune Defic Syndr.* 2011;57:245–253.
22. Rasmussen LD, Helleberg M, May MT, et al. Myocardial infarction among Danish HIV-infected individuals: population-attributable fractions associated with smoking. *Clin Infect Dis.* 2015;60:1415–1423.
23. Bedimo RJ, Westfall AO, Drechsler H, et al. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. *Clin Infect Dis.* 2011;53:84–91.
24. Holmberg SD, Moorman AC, Williamson JM, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet.* 2002;360:1747–1748.
25. Sabin CA, Ryom L, De Wit S, et al. Associations between immune depression and cardiovascular events in HIV infection. *AIDS.* 2013;27:2735–2748.
26. Escaut L, Monsuez JJ, Chironi G, et al. Coronary artery disease in HIV infected patients. *Intensive Care Med.* 2003;29:969–973.
27. Rickerts V, Brodt H, Staszewski S, et al. Incidence of myocardial infarctions in HIV-infected patients between 1983 and 1998: the Frankfurt HIV-cohort study. *Eur J Med Res.* 2000;5:329–333.
28. Lang S, Mary-Krause M, Cotte L, et al. Increased risk of myocardial infarction in HIV-infected patients in France, relative to the general population. *AIDS.* 2010;24:1228–1230.
29. Kwong GP, Ghani AC, Rode RA, et al. Comparison of the risks of atherosclerotic events versus death from other causes associated with antiretroviral use. *AIDS.* 2006;20:1941–1950.
30. Brothers CH, Hernandez JE, Cutrell AG, et al. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr.* 2009;51:20–28.
31. Brouwer ES, Napravnik S, Eron JJ Jr, et al. Effects of combination antiretroviral therapies on the risk of myocardial infarction among HIV patients. *Epidemiology.* 2014;25:406–417.

32. Ribaudo HJ, Benson CA, Zheng Y, et al. No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT. *Clin Infect Dis.* 2011;52:929–940.
33. Althoff KN, Palella FJ, Gebo K, et al. Impact of smoking, hypertension and cholesterol on myocardial infarction in HIV+ adults. Conference on Retroviruses and Opportunistic Infections (CROI); February 13–16; Seattle, Washington. 2017.
34. Vachiat A, McCutcheon K, Tsabedze N, et al. HIV and ischemic heart disease. *J Am Coll Cardiol.* 2017;69:73–82.
35. Althoff KN, Gange SJ. A critical epidemiological review of cardiovascular disease risk in HIV-infected adults: the importance of the HIV-uninfected comparison group, confounding, and competing risks. *HIV Med.* 2013;14:191–192.
36. Freiberg Matthew S, So-Armah K. HIV and cardiovascular disease: we need a mechanism, and we need a plan. *J Am Heart Assoc.* 2016;5: e003411.
37. [GeSIDA/National AIDS Plan: consensus document on antiretroviral therapy in adults infected by the human immunodeficiency virus (Updated January 2014)]. *Enferm Infecc Microbiol Clin.* 2014;32:446.e1–42.