

Increased Risk of Myocardial Infarction in HIV-Infected Individuals in North America Compared to the General Population

Daniel R. Drozd, MD, MSc¹; Mari M. Kitahata, MD, MPH¹; Keri N. Althoff, PhD²; Jinbing Zhang, MS²; Stephen J. Gange, PhD²; Sonia Napravnik, PhD³; Greer A. Burkholder, MD⁴; William C. Mathews, MD⁵; Michael J. Silverberg, MPH, PhD⁶; Timothy R. Sterling, MD⁷; Susan R. Heckbert, MD, MPH, PhD⁸; Matthew J. Budoff, MD⁹; Stephen Van Rompaey, PhD¹; Joseph A.C. Delaney, PhD, MSc⁸; Cherise Wong²; Weiqun Tong²; Frank J. Palella, MD¹⁰; Richard A. Elion, MD^{11,12}; Jeffrey N. Martin, MD, MPH¹³; John T. Brooks, MD¹⁴; Lisa P. Jacobson, ScD²; Joseph J. Eron, MD³; Amy C. Justice, MD, PhD¹⁵; Matthew S. Freiberg, MD, MSc⁷; Daniel B. Klein, MD¹⁶; Wendy S. Post, MD¹⁷; Michael S. Saag, MD⁴; Richard D. Moore, MD¹⁷; Heidi M. Crane, MD, MPH¹

¹Department of Medicine, University of Washington School of Medicine, Seattle, WA

²Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

³Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

⁴Department of Medicine, University of Alabama School of Medicine, Birmingham, AL

⁵Department of Medicine, University of California San Diego, San Diego, CA

⁶Kaiser Permanente Division of Research, Oakland, CA

⁷Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN

⁸Department of Epidemiology, University of Washington School of Public Health, Seattle, WA

⁹Department of Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA

¹⁰Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

¹¹Department of Medicine, George Washington University School of Medicine, Washington, District of Columbia

¹²Department of Clinical Investigations, Whitman Walker Health, Washington, District of Columbia

¹³Department of Epidemiology & Biostatistics, University of California San Francisco, San Francisco, CA

¹⁴Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA

¹⁵Department of Medicine, Yale School of Public Health, New Haven, CT

¹⁶Department of Infectious Diseases, San Leandro Medical Center, CA

¹⁷Department of Medicine, Johns Hopkins University, Baltimore, MD

Author for Correspondence and Reprint Requests:

Daniel R. Drozd, MD MSc

University of Washington, Division of Allergy & Infectious Diseases

Box 359931

325 9th Avenue

Seattle, WA 98104

Phone: 206.685.7791

Facsimile: 206.744.3694

Email: ddrozd@uw.edu

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Abstract

Background

Previous studies of cardiovascular disease (CVD) among HIV-infected individuals were limited by the inability to validate and differentiate atherosclerotic type 1 myocardial infarctions (T1MIs) from other events. We sought to define the incidence of T1MIs and risk attributable to traditional and HIV-specific factors among participants in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), and compare adjusted incidence rates to the general population Atherosclerosis Risk in Communities (ARIC) cohort.

Methods

We ascertained and adjudicated incident MIs among individuals enrolled in seven NA-ACCORD cohorts between 1995-2014. We calculated incidence rates (IR), adjusted incidence rate ratios (aIRRs), and 95% confidence intervals ([,]) of risk factors for T1MI using Poisson regression. We compared aIRRs of T1MIs in NA-ACCORD with those from ARIC.

Results

Among 29,169 HIV-infected individuals, the IR for T1MIs was 2.57[2.30-2.86] per 1000 person-years, and the aIRR was significantly higher compared with participants in ARIC (1.30[1.09-1.56]). In multivariable analysis restricted to HIV-infected individuals, traditional CVD risk factors were independent predictors of T1MI, the rate of T1MI increased with decreasing CD4 count (≥ 500 cells/ μL : ref; 350-499 cells/ μL : aIRR=1.32[0.98-1.77]; 200-349 cells/ μL : aIRR=1.37[1.01-1.86]; 100-199 cells/ μL : aIRR=1.60[1.09-2.34]; <100 cells/ μL : aIRR=2.19[1.44-3.33]) and was higher among those with detectable HIV RNA (<400 copies/mL: ref; ≥ 400 copies/mL: aIRR=1.36[1.06-1.75]).

Conclusions

The higher incidence of T1MI in HIV-infected individuals and increased risk associated with lower CD4 count and detectable HIV RNA suggest that early suppressive antiretroviral treatment and aggressive management of modifiable traditional CVD risk factors are necessary to maximally reduce MI risk.

Keywords: HIV, cardiovascular disease, myocardial infarction, MI, CVD

Introduction

The introduction of effective combination antiretroviral therapy (ART) transformed HIV infection from a rapidly progressive fatal illness into a chronic manageable disease. However, HIV-infected individuals remain at increased risk for comorbid conditions that are associated with inflammation and aging in the general population, including cardiovascular disease (CVD)^{1,2}. Although traditional CVD risk factors such as smoking are prevalent among HIV-infected individuals³, cumulative exposure to chronic inflammation and immune activation that persists in persons with treated HIV infection⁴⁻⁶ may also contribute to the development of atherosclerotic CVD (ASCVD)⁷⁻⁹.

Increases in subclinical atherosclerosis¹⁰⁻¹⁶, endothelial dysfunction^{17,18} and levels of inflammatory biomarkers^{19,20} that are associated with myocardial infarction (MI) in the general population occur in HIV-infected individuals. HIV infection has also been associated with risk for clinical CVD outcomes²¹⁻²⁵. However, previous studies have relied on unvalidated MI events^{21,23-25} and not classified MIs by pathophysiologic mechanism as defined by the Universal Definition of MI (UDMI), a standard endorsed by international cardiology societies²⁶, in order to focus on atherosclerotic type 1 MIs (T1MIs) and exclude type 2 MIs (T2MIs). Distinguishing between types is important because T2MIs result from an imbalance of myocardial oxygen supply and demand caused by a diverse set of clinical conditions, including sepsis and cocaine-induced vasospasm²⁷, whereas T1MIs are due to spontaneous atherosclerotic plaque rupture²⁶. We have shown²⁸ that T2MIs may account for a greater proportion of MIs among HIV-infected individuals as compared with what is seen in the general population due in part to the high prevalence of illicit drug use²⁹ and concurrent infections among HIV-infected individuals.

Unvalidated or poorly defined outcomes in studies of the association of HIV infection with CVD^{22,23,30-32} may have contributed to inconsistent findings, and studies of MI incidence in HIV-infected individuals conducted in single healthcare systems^{22-24,33} may not have broad generalizability. To account for these limitations, we implemented a state-of-the-art centralized MI ascertainment, adjudication and classification protocol in the largest and most diverse cohort of HIV-infected individuals in North America. Classification of MI type enabled us to define the incidence and predictors of validated T1MI, while excluding those events that were secondary to conditions other than atherosclerosis. A primary aim of this study was to determine the risk of MI associated with HIV disease severity measured by current CD4 count and effective antiretroviral treatment measured by undetectable HIV RNA. In addition, we sought to compare adjusted MI incidence rates in HIV-infected individuals to those in the general population.

Methods

HIV-Infected Study Population: NA-ACCORD

The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is the largest consortium of HIV cohorts in North America as previously described³⁴. Briefly, NA-ACCORD consists of single and multi-site clinical and interval cohorts that prospectively collect data on >150,000 HIV-infected adults (≥ 18 years old) from more than 200 sites in the US and Canada. Each cohort has standardized methods of data collection and submits data on enrolled participant characteristics, diagnoses, laboratory measures, prescribed medications and vital status to the Data Management Core (University of Washington, Seattle WA) where they undergo quality control and are harmonized across cohorts. Data are then transmitted to the Epidemiology/Biostatistics Core (Johns Hopkins University, Baltimore, MD), which conducted the analyses presented here. For the present study, seven US clinical cohorts within NA-ACCORD

with complete access to both inpatient and outpatient electronic medical record (EMR) data contributed information about 29,169 individuals enrolled [on or after January 1, 1995](#) and followed [up to](#) March 31, 2014. NA-ACCORD has been approved by the local institutional review boards (IRB) of all participating cohorts.

General Population CVD Study Cohort: ARIC

We examined data collected on individuals aged ≥ 40 from a large, multi-center prospective, observational cohort study designed to assess CVD risk, the Atherosclerosis Risk in Communities (ARIC)³⁵. ARIC contributed 14,308 individuals aged 45-64 at baseline who enrolled between 1987-1989 and were followed through 2010. De-identified data were obtained through the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). While ARIC does not determine the HIV status of participants, the prevalence of HIV infection should be similar to that of the general population. NA-ACCORD IRB approval was provided prior to receipt of the BioLINCC data.

Primary Outcome: Type 1 MI

The protocol for ascertainment, validation and classification of MIs within NA-ACCORD has been previously published³⁶. Potential MI events were centrally ascertained within the NA-ACCORD data repository using a standard protocol based on the presence of an MI diagnosis or elevated cardiac biomarkers. We have shown among HIV-infected adults that screening based on cardiac biomarkers in addition to diagnoses increases the sensitivity of identifying confirmed T1MIs compared with relying on diagnosis codes alone³⁶. Comprehensive medical records pertaining to each potential event including clinician progress notes, electrocardiograms, laboratory measures, echocardiography results, and coronary catheterization and operative reports were abstracted from EMRs

at the contributing site, de-identified and uploaded to the NA-ACCORD data repository. Information regarding antiretroviral (ARV) drugs used was redacted to avoid potential reviewer bias during adjudication. Sites attempted to obtain complete clinical data from potential events that occurred outside of their hospital system. Each potential event was adjudicated by at least two physician reviewers who have extensive experience adjudicating MIs in other CVD cohorts^{37,38}. A third review was conducted if the adjudications of the first two reviewers differed. Potential events were classified as atherosclerotic T1MI or as T2MI according to the UDMI²⁶. Reviewers also identified individuals who screened positive by diagnosis or cardiac biomarkers and underwent a cardiac intervention consistent with treatment of severe underlying coronary artery disease (coronary artery bypass graft or percutaneous coronary intervention with stent placement) but did not meet MI criteria. We excluded participants with prevalent MIs and those who had a T2MI in order to focus the analysis on atherosclerotic T1MIs rather than MIs that occur via other mechanisms. The primary outcome was an incident T1MI or invasive cardiac intervention.

ARIC has an established protocol for MI validation that incorporates clinical data³⁵. Individuals with prevalent CVD events were excluded from ARIC in order to focus on incident MIs. While ARIC does not classify MIs by type, it is designed to evaluate the natural history of atherosclerotic disease leading to T1MIs, and incident MIs that are T2MIs occur infrequently in the general population^{27,36}.

Covariates

For analyses of HIV-infected individuals in NA-ACCORD, we assessed the association of demographic and clinical variables with T1MI defined as follows. Race/ethnicity was self-reported and categorized as black, white, Hispanic, and other/unknown. An

individual was classified as having ever or never smoked cigarettes based on clinician-recorded diagnoses and patient-reported responses to validated questionnaire items. Hypertension requiring pharmacologic treatment was defined as a clinical diagnosis of hypertension and prescription of antihypertensive medication. Diabetes mellitus was defined as a diagnosis of diabetes and prescription of a diabetes-related medication, or prescription of a diabetes-specific medication, or a [glycated](#) hemoglobin $\geq 6.5\%$.

Dyslipidemia was defined based on serum lipid values prior to lipid-lowering treatment if applicable; elevated total cholesterol was defined as ≥ 240 mg/dL and low high-density lipoprotein (HDL) cholesterol was defined as ≤ 40 mg/dL for men and ≤ 50 mg/dL for women. Statin-treated dyslipidemia was defined as prescription of an HMG-CoA reductase inhibitor. We calculated estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease (CKD) Epidemiology Collaboration equation³⁹ and required two measurements separated by 90 days, and dichotomized eGFR to represent CKD severity (eGFR < 30 mL/min or ≥ 30 mL/min). Hepatitis C virus (HCV) coinfection was defined as ever having a positive HCV RNA, antibody or documented HCV genotype. History of an AIDS-defining illness was based on clinical diagnoses defined according to the 1993 CDC case definition⁴⁰. CD4 counts were categorized using clinically meaningful cut points (< 100 , 100-199, 200-349, 350-499, and ≥ 500 cells/ μ L). Virologic suppression was defined as HIV RNA < 400 copies/mL. ART was defined as three ARV agents from at least two classes or a triple nucleoside/nucleotide reverse transcriptase inhibitor regimen containing abacavir or tenofovir disoproxil fumarate.

For the analysis comparing HIV-infected adults in NA-ACCORD to participants in ARIC, age (40-49, 50-59, ≥ 60 years), sex, race, hypertension, diabetes mellitus, elevated total cholesterol (≥ 240 mg/dL) and cigarette smoking were assessed at study entry. In ARIC, self-reported race was categorized as black vs. non-black. Hypertension was defined as

diastolic blood pressure >95mmHg, systolic blood pressure >160mmHg or self-report of current antihypertensive medication use. Diabetes was defined as random glucose ≥ 200 mg/dL, fasting glucose ≥ 140 mg/dL, or self-report of diabetes diagnosis or current diabetes medication use. An individual was classified as having ever or never smoked cigarettes based on responses to questionnaire items.

Statistical Analysis

In NA-ACCORD, person-time accrued for individuals from study entry defined as the latter of enrollment in the cohort or the date a cohort began full capture of inpatient and outpatient laboratory and diagnosis data (MI observation start date) until study exit defined as incident T1MI, death, cohort MI observation end date, one year after last CD4 count or HIV RNA measurement which was considered to be the time an individual was lost to follow-up or administrative censoring in 2014. Individuals who had a T2MI were excluded from the primary analysis, but were included in a sensitivity analysis and censored at the time of T2MI. In ARIC, person-time was accrued from enrollment (which initiated in 1987) until date of MI, death, lost to follow-up or censoring in 2010.

Age-specific crude incidence rates per 1,000 person years (IRs) and 95% confidence intervals (95% CI or [,]) were estimated for NA-ACCORD and ARIC. In analyses restricted to NA-ACCORD participants, adjusted incidence rate ratios (aIRR) and 95% CIs for T1MIs were estimated for the following time-fixed covariates: sex, race/ethnicity, HIV transmission risk, year of enrollment, cigarette smoking, HCV coinfection, and cohort. Time-updated covariates in the multivariable models included: age, hypertension, statin-treated dyslipidemia, diabetes mellitus, CKD, total and HDL cholesterol, CD4 count, detectable HIV RNA, AIDS-defining illness, and ART. HCV was omitted from the final model to avoid collinearity with injection drug use as a risk factor for HIV

transmission, as was ART in order to evaluate the impact of effective ART use measured by undetectable HIV RNA. Because of the interrelationship between HIV RNA and CD4 count, we also examined the direct effect of HIV RNA without CD4 in sensitivity analysis. Nearly a third of the study population was on ART at study entry inhibiting our ability to examine measures of cumulative HIV RNA. Finally, we examined IRs by calendar year in order to determine if the rate of T1MIs varied over calendar time.

We estimated aIRR and 95% CIs for MIs comparing HIV-infected participants in NA-ACCORD to participants in ARIC using Poisson regression to account for key baseline risk factors including age, sex, race, hypertension, diabetes, elevated total cholesterol, and cigarette smoking. All analyses were performed using SAS version 9.3 (SAS Institute) and a p-value <0.05 guided statistical interpretations.

Results

NA-ACCORD Incidence Rates

Among the 29,169 HIV-infected individuals in NA-ACCORD, 335 had an incident T1MI during 131,534 person-years of follow-up. Excluded from the analysis were 257 individuals who had a T2MI, nearly half of which were caused by sepsis and drug-induced vasospasm (e.g. cocaine). Median follow-up was 3.2 [IQR 1.3, 5.9] years among individuals with a T1MI and 3.6 [IQR 1.5, 7.0] years among those without a T1MI. The crude IR [95% CI] for T1MIs was 2.57 [2.30-2.86] per 1,000 person-years and increased significantly with each decade of age. Incidence rates for T1MIs did not vary significantly across calendar periods (data not shown). At study entry, NA-ACCORD participants who went on to have a T1MI were more likely to have been older, male, white, to have enrolled in the cohort in the early ART era (1995-2000), and to have had a history of cigarette smoking, hypertension, diabetes mellitus, statin-treated dyslipidemia,

elevated total cholesterol, low HDL cholesterol, eGFR <30 mL/min, prior ARV use and an AIDS-defining illness (Table 1). A sensitivity analysis that included individuals with T2MI and censored them at the time of T2MI did not substantively change our results.

Risk Factors for Atherosclerotic Type 1 MIs in NA-ACCORD

In multivariable analysis examining factors associated with risk of atherosclerotic T1MI among HIV-infected individuals in NA-ACCORD, traditional CVD risk factors (aIRR [95% CI]) including time-updated age, hypertension, diabetes, statin-treated dyslipidemia, and eGFR <30 mL/min were independent predictors of incident T1MI (Table 2). In addition to CVD risk factors, we found an increased risk of T1MI with lower time-updated CD4 count across strata. Time-updated detectable HIV RNA was significantly associated with increased risk of T1MI (1.36 [1.06-1.75]) in the analysis omitting CD4 count suggesting that ART-mediated viral suppression may decrease MI risk.

Comparing MI incidence in NA-ACCORD to ARIC

ARIC participants contributed 1,448 MI events and 281,284 person-years of follow-up. HIV-infected individuals in NA-ACCORD were younger and more likely to be male and of black race than participants in ARIC (Appendix Table 1), while ARIC participants had a greater prevalence of hypertension and diabetes. Age-specific MI IRs were higher in NA-ACCORD than ARIC (Fig 1). In multivariable analysis, HIV-infected individuals in NA-ACCORD had significantly higher adjusted rates of MIs compared with participants in ARIC (Table 3). As expected, increased age, male sex, race, hypertension, diabetes, elevated total cholesterol, and cigarette smoking were all significantly associated with risk of MI independent of HIV infection status. HIV infection was significantly associated with increased risk of MI (aIRR 1.21 [95% CI 1.02, 1.45]). A sensitivity analysis excluding individuals <40 years of age from NA-ACCORD showed similar results.

Discussion

This study is the first to define the incidence of adjudicated atherosclerotic T1MIs and associated clinical risk factors in HIV-infected individuals. Our analysis, from the largest cohort collaboration of HIV-infected persons in North America, found significantly higher adjusted rates of MIs than observed among the general population. The large number of well-characterized T1MIs observed in NA-ACCORD enabled us to examine multiple factors simultaneously, including known CVD risk factors, in order to define the independent association between HIV-specific factors and ASCVD.

After controlling for traditional CVD risk factors, we found that having lower CD4 counts was significantly associated with increased risk of T1MI, and that this relationship was dose-dependent by CD4 strata. There was over 2-fold higher risk of MI among individuals with a CD4 <100 cells/uL compared to those with a CD4 \geq 500 cells/uL, a magnitude similar to the risk associated with hypertension or cigarette smoking. Our findings suggest that individuals at successively lower CD4 count levels, indicative of increasing severity of poorly controlled HIV infection, are at greater risk of MI. Finally, undetectable HIV RNA, an accurate measure of effective ART use, was significantly associated with lower risk of T1MIs. Our results are thus consistent with the Strategies for Management of Antiretroviral Therapy (SMART) study that found significantly lower risk of major CVD events among persons randomized to continuous treatment with ART as opposed to delay or interruption of ART⁴¹. Similarly, our goal was to determine the impact of virally suppressive ART and so we did not examine individual ARV agents for which findings to date regarding CVD risk remain inconsistent^{21,42,43} therefore, while effective ART may reduce the risk of CVD, risk may vary by specific ARV agent. Our

findings provide further evidence of the benefit of HIV treatment to prevent not only AIDS-defining illnesses⁴⁴, but also important HIV-associated chronic conditions^{2,45,46} including ASCVD^{33,41} that can occur regardless of CD4 count, but are more common among individuals with lower CD4 counts⁴⁷.

Traditional CVD risk factors including metabolic derangements, such as diabetes and dyslipidemia, were also independent predictors of incident T1MI. Analysis of many modifiable CVD risk factors in HIV-infected individuals is complex given that both HIV infection itself^{48,49} and some older ARV drugs^{25,50} have been linked to metabolic changes that are associated with atherosclerosis in the general population. Our results demonstrate an independent beneficial effect of ART-mediated viral suppression on MI risk after accounting for the effect of traditional CVD risk factors, regardless of their etiology. While one study performed in a large HMO showed decreasing MI risk in HIV-infected individuals in recent years³³, we did not observe a similar trend, perhaps owing to greater demographic and socioeconomic diversity within our study population. For clinicians caring for HIV-infected persons, these findings highlight the importance of aggressive management of both modifiable HIV-specific and traditional CVD risk factors, including early suppressive ART and a renewed clinical focus on smoking cessation, as well as screening for and treatment of hypertension, dyslipidemia and diabetes mellitus to reduce the overall burden of ASCVD in HIV-infected individuals.

Our analysis has several strengths. We conducted this study in the largest, most diverse cohort of HIV-infected individuals in North America. In contrast to previous studies conducted in single healthcare systems, the diversity of our cohort with regard to geographic, demographic and clinical characteristics including the full spectrum of HIV disease severity and comorbidities make our findings more broadly applicable to HIV-

infected persons in settings where treatment with ART is readily available. To our knowledge, ours is the first study of MI rates in HIV-infected individuals to incorporate cardiac biomarker data as a means of screening for potential MIs that might have been missed had we relied on diagnoses alone. This allowed us to more completely capture the burden of ASCVD and define robust age-specific rates that demonstrate the absolute rate of T1MI in the aging HIV-infected population. Although contemporary troponin assays may also increase the sensitivity of detecting T2MIs⁵¹, we excluded these events in order to focus our analysis on ASCVD risk, which made our outcome more comparable to the general population cohort where the prevalence of T2MIs is substantially lower than in HIV-infected persons²⁷. An expert panel of physicians centrally reviewed detailed medical records for each potential MI event to adjudicate and classify confirmed MIs by type according to the UDMI. In contrast, most prior studies involving HIV-infected persons defined MI outcomes using diagnosis codes without undertaking MI event validation^{21,23-25} leading to potential misclassification and under or over estimation of true event rates⁵²⁻⁵⁴. The few studies conducted among HIV-infected persons that did validate outcomes may have also underestimated MI incidence by relying on diagnosis codes alone to ascertain events^{22,32} or review of case report forms completed by the local site personnel³² rather than centralized expert adjudication of the primary clinical data.

The importance of distinguishing T1MIs and T2MIs is increasingly recognized in the general population⁵¹, and essential in HIV-infected populations given the large proportion of T2MIs identified in our cohort that would have been misclassified as presumptive atherosclerotic outcomes in previous studies. Because prior studies in HIV-infected persons did not differentiate T1MIs from T2MIs, our estimates provide the most accurate assessment to date of the impact of HIV infection on atherosclerotic MIs in HIV-infected

individuals. The magnitude of excess risk seen when comparing NA-ACCORD to ARIC is somewhat smaller than that seen in prior studies that did not differentiate MIs by type, suggesting that some of the excess MI risk in HIV-infected individuals found in previous studies was the result of higher rates of T2MI in this population. Because the mechanisms and prevention of these types of events differ, clinicians will need distinct approaches to minimizing risk of T1MI and T2MI in HIV-infected persons.

Our study has important limitations. We examined known clinical and behavioral CVD risk factors, but diet and exercise were unmeasured and data regarding cigarette smoking may have been incomplete. Our analysis did not include silent MIs or sudden fatal MIs that may have occurred outside of the healthcare setting and could not have been captured by our protocol. By ascertaining potential events using both outpatient and inpatient MI diagnoses and collecting records from outside hospitals for independent review, we attempted to capture events that may have been managed outside of our sites' hospital systems. While the possibility remains that we may not have captured all events in NA-ACCORD, were this to be the case, we would have underestimated MI incidence and found an even greater difference in incidence rates between HIV-infected individuals and those seen in the general population. Although our comparison to ARIC was limited by potential differences in variable definitions, specifically that ARIC did not differentiate between T1MIs and T2MIs, had we included T2MIs in our analysis, the higher risk of MIs seen in HIV-infected individuals would have been even more pronounced. We adjusted for key traditional CVD risk factors, but other factors including potential socioeconomic differences between cohorts, may have impacted our results. However, our findings are consistent with estimates from comparisons between HIV-infected and uninfected individuals within a single health care system²²⁻²⁴.

In summary, by focusing our analysis on atherosclerotic T1MIs, and comparing incidence rates among HIV-infected individuals within a large and diverse cohort with rates from a well-characterized general population-based CVD study cohort, we have shown with greater generalizability that HIV infection is an independent risk factor for atherosclerosis and provided robust estimates of the risk conferred by HIV-specific factors compared with traditional CVD factors. To maximally reduce the risk of ASCVD in HIV-infected individuals, clinicians need to both modify traditional CVD risk factors, and suppress HIV viral replication and boost CD4 count by initiating early and continuous ART.

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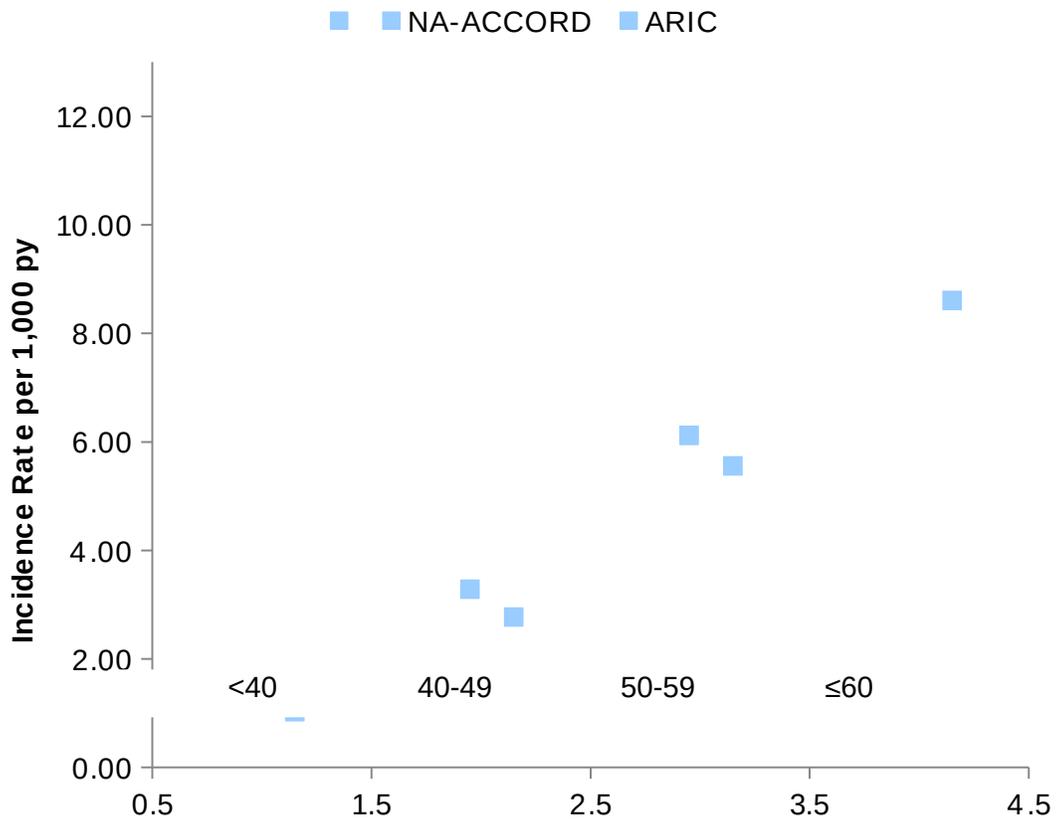
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Figures (

Figure 1. Incidence Rates of Myocardial Infarction by Age per 1,000 Person Years among HIV-infected individuals in NA-ACCORD and the general population in ARIC.



Tables (uploaded in separate file)