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

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Abstract

Background—Previous studies of cardiovascular disease (CVD) among HIV-infected individuals have been 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 and including traditional CVD risk factors, 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]). Risk associated with detectable HIV RNA (<400 copies/mL: ref; ≥400 copies/mL: aIRR=1.36 [1.06–1.75]) was significantly increased only when CD4 was excluded.

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 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 individuals[3], cumulative exposure to chronic inflammation and immune activation that persists in persons with treated HIV infection[4–6] may also contribute to the development of atherosclerotic CVD (ASCVD)[7–9].

Increases in subclinical atherosclerosis[10–16], 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 outcomes[21–25]. 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 societies[26], 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 vasospasm[27], whereas T1MIs are due to spontaneous atherosclerotic plaque rupture, erosion, or dissection with associated intraluminal thrombus[26]. We have shown[28] 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 use[29] 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 described[34]. 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 was chosen because it is relatively contemporaneous with NA-ACCORD, has well-defined clinical outcomes, and captures an ethnically and racially diverse patient population comparable to NA-ACCORD. 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 published[36]. 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 alone[36]. 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 UDMI[26]. 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 data[35]. However cardiac biomarkers are not used to screen for MI in ARIC, whereas they are part of the screening algorithm in NA-ACCORD. While this could lead to more potential MIs identified in NA-ACCORD compared with ARIC, we anticipated that a substantial portion of events identified by biomarkers alone would be T2MIs, which likely occur infrequently in ARIC by design since biomarkers are not used for ascertainment. Thus, by excluding T2MIs in NA-ACCORD from these analyses, we sought to maximize similarities between the two cohorts. Lastly, individuals with prevalent CVD events were excluded from ARIC in order to focus on incident MIs.

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 ≥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 equation[39] 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 definition[40]. CD4 counts were categorized using clinically

meaningful cut points (<100, 100–199, 200–349, 350–499, and ≥500 cells/μL). 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 ≥200mg/dL, fasting glucose ≥140mg/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. We hypothesized that the effect of HIV RNA on MI risk is at least partially mediated through CD4 count, so in a sensitivity analysis we analyzed HIV RNA without adjusting for CD4 count. 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 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. Detectable HIV RNA did not reach statistical significance (1.20 [0.92, 1.56] in the main model, whereas in sensitivity analysis excluding CD4 count, time-updated detectable HIV RNA was significantly associated with increased risk of T1MI (1.36 [1.06–1.75]).

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 (NA-ACCORD age <40: 43%, 40–49: 36%, 50–59: 16%, ≥60: 4%; ARIC age 40–49: 32%, 50–59: 45%, ≥60: 23%), more likely to be male (NA-ACCORD 80%; ARIC 45%) and of black race (NA-ACCORD 37%; ARIC 26%) than participants in ARIC (Appendix Table 1), while ARIC participants had a greater prevalence of hypertension (NA-ACCORD 16%; ARIC 28%) and diabetes (NA-ACCORD 5%; ARIC 10%). 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 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 adjusting 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 ≥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 and immune dysfunction, are at greater risk of MI. Combined, the results of our main model and sensitivity analysis are consistent with our hypothesis that both undetectable HIV RNA, an accurate measure of effective ART use, and increased CD4 count are associated with decreased risk of MI. Furthermore, as expected, the risk associated with HIV RNA is partially mediated by CD4 count. Our results are 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 ART[41]. 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]. Thus, 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 illnesses[44], 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 counts[47].

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 are consistent with an independent benefit 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 years[33], we did not observe a similar trend, likely owing to more inclusive event ascertainment in NA-ACCORD, adjudication of outcomes, and greater demographic and socioeconomic diversity within our study population. Furthermore, a newer study found

increasing CVD mortality among HIV-infected persons in recent years.[51] For clinicians caring for HIV-infected persons, these findings provide additional evidence to support 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 (as opposed to use in event validation) 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 T2MIs[52], 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 vast majority of MIs were likely T1MIs. 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 rates[53–55]. 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 local site personnel[32] rather than centralized expert adjudication of comprehensive primary clinical data, which is unique to our study.

The importance of distinguishing T1MIs and T2MIs is increasingly recognized in the general population[52], 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. Our comparison to ARIC was potentially limited by differences in variable definitions and event ascertainment, specifically that ARIC did not use cardiac biomarkers in screening or differentiate between T1MIs and T2MIs. However, excluding T2MIs from the NA-ACCORD analysis likely increased the comparability of outcomes since cardiac biomarkers would be expected to disproportionately identify T2MIs. Furthermore, 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 system[22–24].

In summary, by focusing our analysis on 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 cohort, we have shown with broad generalizability that HIV infection is independently associated with MI risk and provided robust estimates of the risk associated with HIV-specific factors compared with traditional CVD factors. Our results suggest that clinicians need to both modify traditional CVD risk factors, and suppress HIV viral replication and boost CD4 count by initiating early and continuous ART to maximally reduce the risk of ASCVD in HIV-infected individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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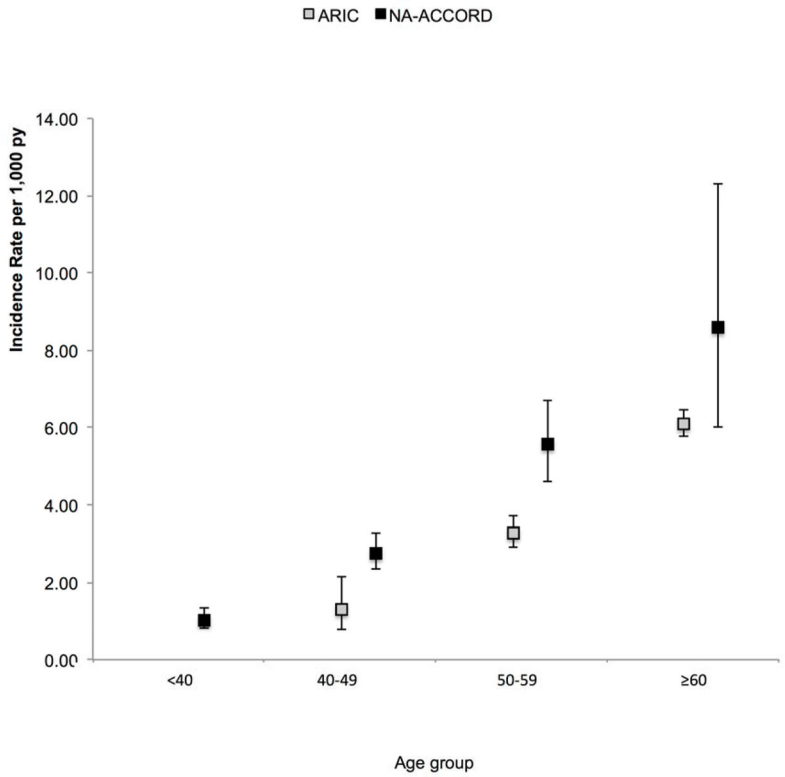

Figure 1.

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.

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Table 1

Characteristics of HIV-infected individuals in NA-ACCORD at study entry who experienced a Type 1 myocardial infarction (T1MI) and those who did not

Characteristic		T1MI n=335		No T1MI n=28,577	
		n	%	n	%
Age (years)	<40	60	18	12,560	44
	40–49	136	41	10,397	36
	50–59	109	33	4,591	16
	≥60	30	9	1,029	4
Sex	Male	287	86	22,997	80
	Female	48	14	5,580	20
Race/ethnicity	White	188	56	13,245	46
	Black	119	36	10,564	37
	Hispanic	18	5	2,997	10
	Other/unknown	10	3	1,771	6
HIV transmission risk	MSM	182	54	15,249	53
	IDU	52	16	3,439	12
	Heterosexual	75	22	7,382	26
	Other/unknown	26	8	2,507	9
Enrollment into cohort	1995–2000	188	56	9,708	34
	2001–2005	96	29	8,340	29
	2006–2014	51	15	10,529	37
Cigarette smoking *	Never	52	16	6,730	24
	Ever	283	84	21,847	76
Hypertension †	No	191	57	24,092	84
	Yes	144	43	4,485	16
Diabetes mellitus ‡	No	285	85	27,277	95

Characteristic		T1MI n=335		No T1MI n=28,577	
		n	%	n	%
	Yes	50	15	1,300	5
Elevated total cholesterol[§]	No	260	78	23,519	82
	Yes	72	21	2,638	9
	Unknown	3	1	2,420	8
Low HDL cholesterol[‖]	No	196	59	15,020	53
	Yes	126	38	8,311	29
	Unknown	13	4	5,246	18
Statin-treated dyslipidemia[¶]	No	295	88	27,401	96
	Yes	40	12	1,176	4
Chronic kidney disease[**]	eGFR ≥30	315	94	28,390	99
	eGFR <30	20	6	187	1
CD4 count (cells/mm^3)	<100	71	21	4,369	15
	100–199	49	15	3,175	11
	200–349	72	21	6,003	21
	350–499	51	15	5,809	20
	≥500	87	26	8,965	31
	Unknown	5	1	256	1
HIV viral load (copies/mL)	<400	98	29	8,676	30
	400–9,999	84	25	6,591	23
	10,000–99,999	87	26	7,691	27
	≥100,000	63	19	5,264	18
	Unknown	3	1	355	1
History of AIDS-defining illness[††]	No	230	69	22,475	79
	Yes	105	31	6,102	21
Prior ARV use[‡‡]	No	135	40	14,465	51
	Yes	200	60	14,112	49

Characteristic		T1MI n=335		No T1MI n=28,577	
		n	%	n	%
Hepatitis C infection[§§]	No	248	74	23,317	82
	Yes	87	26	5,260	18

NA-ACCORD: North American AIDS Cohort Collaboration on Research and Design

HDL: high-density lipoprotein

ARV: antiretroviral

[*] 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 mediation, or a glycated hemoglobin (HbA1c) ≥6.5%

[§] Elevated total cholesterol was defined as ≥240 mg/dL based on serum lipid values prior to lipid-lowering treatment if applicable

[‖] Low HDL cholesterol was defined as ≤40 mg/dL for men and ≤50 mg/dL for women based on serum lipid values prior to lipid-lowering treatment if applicable

[¶] Statin-treated dyslipidemia was defined as prescription of an HMG-CoA reductase inhibitor

[**] eGFR was calculated using the CKD-Epi equation (38) and required two measurements separated by 90 days

[††] History of an AIDS-defining illness was based on clinical diagnoses defined according to the 1993 CDC case definition

[‡‡] Prior use of any antiretroviral medication(s)

[§§] Hepatitis C infection was defined as ever having a positive HCV RNA, antibody, or a documented HCV genotype

Table 2

Multivariable analysis of time-updated traditional CVD and HIV-related factors* in association with risk of Type 1 myocardial infarction (T1MI) among HIV-infected individuals in NA-ACCORD

Characteristic		T1MI Risk	
		aIRR	95% CI
Age (years)	<40	1.00	
	40–49	**2.92**	**[1.88, 4.52]**
	50–59	**4.04**	**[2.57, 6.37]**
	60–69	**6.47**	**[3.91, 10.70]**
Sex	Male	1.00	
	Female	0.75	[0.52, 1.07]
Race/ethnicity	White	1.00	
	Black	**0.72**	**[0.54, 0.95]**
	Hispanic	0.65	[0.39, 1.07]
	Other/unknown	0.60	[0.32, 1.14]
HIV transmission risk	MSM	1.00	
	IDU	1.11	[0.78, 1.57]
	Heterosexual	0.87	[0.62, 1.22]
	Other/unknown	1.09	[0.71, 1.67]
Enrollment into cohort	1995–2000	1.00	
	2001–2005	**0.65**	**[0.50, 0.85]**
	2006–2014	**0.55**	**[0.39, 0.79]**
Cigarette smoking	Never	1.00	
	Ever	**1.47**	**[1.08, 2.00]**
Hypertension	No	1.00	
	Yes	**2.49**	**[1.93, 3.20]**
Diabetes mellitus	No	1.00	
	Yes	**1.40**	**[1.05, 1.86]**
Elevated total cholesterol	No	1.00	
	Yes	1.23	[0.96, 1.58]
Low HDL cholesterol	No	1.00	
	Yes	1.16	[0.89, 1.52]
Statin-treated dyslipidemia	No	1.00	
	Yes	**1.90**	**[1.46, 2.48]**
Chronic kidney disease	eGFR ≥30	1.00	
	eGFR <30	**6.03**	**[4.11, 8.85]**

Characteristic		T1MI Risk	
		aIRR	95% CI
CD4 count (cells/mm^3)	<100	**2.19**	**[1.44, 3.33]**
	100–199	**1.60**	**[1.09, 2.34]**
	200–349	**1.37**	**[1.01, 1.86]**
	350–499	1.32	[0.98, 1.77]
	≥500	1.00	
HIV viral load (copies/mL)	<400	1.00	
	≥400	1.20	[0.92, 1.56]

CVD: cardiovascular disease

NA-ACCORD: North American AIDS Cohort Collaboration on Research and Design

HDL: high-density lipoprotein

aIRR: adjusted incidence rate ratio

Bold signals statistical significance ($p<0.05$)

* NA-ACCORD variable definitions, see Table 1

Table 3

Adjusted risk of myocardial infarction among HIV-infected individuals (NA-ACCORD*) compared with the general population (ARIC†)

Characteristic		NA-ACCORD vs. ARIC	
		aIRR	95% CI
Cohort	General population (ARIC)	1.00	
	HIV-infected population (NA-ACCORD)	**1.21**	**[1.02, 1.45]**
Age (years)	40–49	1.00	
	50–59	**1.72**	**[1.39, 2.13]**
	≥60	**2.97**	**[2.38, 3.71]**
Sex	Male	1.00	
	Female	**0.60**	**[0.54, 0.66]**
Race	Non-black	1.00	
	Black	0.90	[0.81, 1.00]
Cigarette smoking	Never	1.00	
	Ever	**1.53**	**[1.38, 1.71]**
Hypertension	No	1.00	
	Yes	**1.80**	**[1.63, 1.99]**
Diabetes	No	1.00	
	Yes	**2.51**	**[2.22, 2.84]**
Elevated total cholesterol	No	1.00	
	Yes	**1.51**	**[1.36, 1.67]**

NA-ACCORD: North American AIDS Cohort Collaboration on Research and Design

ARIC: Atherosclerosis Risk in Communities

aIRR: adjusted incidence rate ratio

Bold signals statistical significance ($p<0.05$)

*NA-ACCORD variable definitions, see Table 1

†ARIC variable definitions: race was self-reported and categorized as black vs. non-black; an individual was classified as having ever or never smoked cigarettes based on patient-reported responses to validated questionnaire items; 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 ≥200mg/dL, fasting glucose ≤140mg/dL, self-report of diabetes diagnosis or self-report of current diabetes medication use; elevated total cholesterol was defined as ≥240 mg/dL