Title

HIV Infection, Cardiovascular Disease Risk Factor Profile, and Risk for Acute Myocardial Infarction

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Human immunodeficiency virus infection, cardiovascular risk factor profile and risk for acute myocardial infarction

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Article summary: The prevalence of optimal cardiac health is low in this cohort. Among those without major CVD risk factors (CVDRFs), HIV+ veterans have twice the AMI risk. Compared to HIV- with high CVDRF burden, AMI rates were higher in HIV+ veterans.

Conflicts of interest and sources of funding

None of the authors report a relevant conflict of interest except Dr. Matthew Budoff, Dr. Heidi Crane, Dr. Sheldon Brown, Dr. Amy Justice and Dr. Matthew Freiberg received funding from the National Institutes of Health related to this work, Dr. Adeel Butt has received Investigator Initiated Research Support from Merck and Pfizer and Dr. Roger Bedimo has received grants and research support awarded to the VA North Texas Healthcare System from Merck & Co, Inc, Janssen Therapeutics, and Bristol-Myers Squibb. Dr. Bedimo has also served as a scientific advisor for Janssen Therapeutics, ViiV Healthcare, and Bristol-Myers Squibb.

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1**Abstract**

Background: Traditional cardiovascular disease risk factors (CVDRFs) increase the risk of acute myocardial infarction (AMI) among HIV infected (HIV+) participants. We assessed the association between HIV and incident AMI within CVDRF strata.

Methods: Cohort - 81322 participants (33% HIV+) without prevalent CVD from the Veterans Aging Cohort Study-Virtual Cohort (prospective study of HIV+ and matched HIV- veterans). Veterans were followed from first clinical encounter on/after 4/1/2003 until AMI/death/last follow-up date (12/31/2009). Predictors**:** HIV, CVDRFs (total cholesterol, cholesterol-lowering agents, blood-pressure (BP), BP medication, smoking, diabetes) used to create 6 mutually exclusive profiles: all CVDRFs optimal, 1+ non-optimal CVDRFs, 1+ elevated CVDRFs, and 1, 2, 3+ major CVDRFs. Outcome**:** Incident AMI (defined using enzyme, EKG clinical data, 410 inpatient ICD-9 (Medicare), and/or death certificates). Statistics: Cox models adjusted for demographics, comorbidity, and substance use.

Results: 858 AMIs (42% HIV+) occurred over 5.9 years (median). Prevalence of optimal cardiac health was <2%. Optimal CVDRF profile was associated with the lowest adjusted AMI rates. Compared to HIV- veterans, AMI rates among HIV+ veterans with similar CVDRF profiles were higher. Compared to HIV- veterans without major CVDRFs, HIV+ veterans without major CVDRFs had a 2-fold increased risk of AMI (HR: 2.0 95%CI: 1.0-3.9, p=0.044).

Conclusion: The prevalence of optimal cardiac health is low in this cohort. Among those without major CVDRFs, HIV+ veterans have twice the AMI risk. Compared to HIV- veterans with high CVDRF burden, AMI rates were still higher in HIV+ veterans. Preventing/reducing CVDRF burden may reduce excess AMI risk among HIV+ people.

Introduction

With the advent of antiretroviral medications, persons with HIV are living long enough to face significant morbidity and mortality from chronic illness like cardiovascular disease (CVD). [1][2][3][4][5] Traditional CVD risk factors (e.g., diabetes, hypertension, dyslipidemia, smoking), HIV-related risk factors (e.g. renal disease) and other risk factors (e.g. antiretroviral therapy, substance abuse), contribute to increased risk of CVD in HIV infected patients.[6][7] While traditional CVD risk factors are often assessed individually, there is strong evidence that they occur in clusters[8][9], which can be categorized as CVD risk factor profiles[10]. Comparisons among infected and uninfected people with similar traditional CVD risk factor profiles are needed to more accurately estimate the independent effect of HIV on AMI risk. One way to assess the independent effects of HIV versus comorbidity on CVD risk is to compare people with low traditional CVD risk factor burden or even optimal cardiac health, a phenomenon whose prevalence is low among uninfected people but unknown among HIV infected people[11][12]. Our objectives were to compare the association of HIV status and incident acute myocardial infarction (AMI) within specific cardiac health profiles and to assess the prevalence of the optimal cardiac health profile by HIV status.

Methods

Subject selection

The Veterans Aging Cohort Study Virtual Cohort (VACS VC) is a prospective longitudinal cohort of HIV infected and age, gender, race/ethnicity, and clinical site matched uninfected participants

who were identified from United States Department of Veterans Affairs (VA) administrative data in the fiscal years 1998-2003 using a modified existing algorithm.[13]

This cohort has been described in detail elsewhere.[2][13] Briefly, this cohort consists of data from the immunology case registry; the VA HIV registry; the pharmacy benefits management database; the VA Decision Support System; the National Patient Care Database, and Health Factor data, which are data collected from physician clinical reminders within the VA electronic medical record system.

For this analysis, we considered all VACS VC participants alive and enrolled in VACS VC on or after 2003. The baseline was a participant's first clinical encounter on or after April 1, 2003. All participants were followed from their baseline date to an AMI event, death, or the last follow-up date. Participants were followed until December 31, 2009.

AMI event data were obtained from Medicare and the Ischemic Heart Disease Quality Enhancement Research Initiative (IHD-QUERI), an initiative designed to improve the quality of care and health outcomes of Veterans with IHD.[14] Subjects with prevalent CVD based on ICD-9 codes for AMI, unstable angina, cardiovascular revascularization, stroke or transient ischemic attack, peripheral vascular disease or heart failure (N=17,229)[15][16] were excluded from all analyses. Given the J-shaped mortality curve associated with blood pressure,[17] those with systolic/diastolic blood pressure less than 90/60 mmHg were also excluded to avoid misclassifying people with hypotension as having optimal cardiac health when their low blood pressure may be more reflective of poor overall health. After these exclusions, 81,322 Veterans (33% HIV+) were eligible for this study.

Independent Variable

Participants were categorized into mutually exclusive CVD risk profiles. Components of the risk profiles were diabetes, current smoking, total cholesterol, blood pressure, HMG-CoA reductase inhibitor use and antihypertensive medication use (Table 1). Diabetes was identified using outpatient and clinical laboratory data collected closest to the baseline date. Specifically, diabetes was diagnosed using glucose measurements, use of insulin or oral hypoglycemic agents, and/or ≥1 inpatient and/or 2 outpatient ICD-9 codes.[18] Smoking was measured from the VA Health Factors data.[19] Cholesterol measurements were obtained from the VA Decision Support System. Systolic and diastolic blood pressure was averaged across the three routine outpatient clinical blood pressure measurements performed closest to the baseline date. HMG-CoA reductase inhibitor and antihypertensive medication use were based on pharmacy data.

Cardiac health risk profiles were based on prior work[10] and categorized as optimal, non-optimal, elevated risk factors, and major risk factors (Table 1). Optimal cardiac health was defined as having no history of diabetes, not currently smoking, total cholesterol <180 mg/dL and blood pressure of 90-120/60-80 mmHg without anti-hypertensive medication. Non-optimal cardiac health was defined as having no history of diabetes, not currently smoking, total cholesterol of 180-199 mg/dL and untreated blood pressure of 120-139/80-89 mmHg. Elevated risk factor profile was defined as no history of diabetes, not currently smoking, total cholesterol of 200-239 mg/dL, and untreated blood pressure of 140-159/90-99 mmHg. Major risk factors were defined as having 1, 2, or 3 or more of the following: diagnosis of diabetes, current smoking, use of HMG-CoA reductase inhibitors or untreated total cholesterol ≥240 mg/dL, or

blood pressure ≥160/100 mmHg. Participants were placed in the highest risk category ascertainable. For example, someone with a blood pressure of 120/80 mmHg, total cholesterol of 190 mg/dL who smoked and had no other major risk factors was considered to have 1 major CVD risk factor.

Participants with missing cardiovascular disease risk factor data were categorized based only on non-missing data and were placed in the highest risk profile ascertainable. For example, a smoker with diabetes, no other major risk factors and missing cholesterol would be categorized as having 2 major risk factors though the missing cholesterol could be in the major risk factor range.

Dependent variable

The protocol for incident AMI determination has previously been described.[2] Briefly, we determined AMI incidence using adjudicated VA data, and Medicare and death certificate data. Documentation of AMI in the discharge summary along with a review of the VA physician notes and medical chart (including elevation of serum markers of myocardial damage and EKG findings) were required to confirm diagnosis of AMI. For participants with non-VA AMI events who were not transferred to the VA, we used ICD-9 code, 410, which had strong agreement with adjudicated AMI outcomes in the Cardiovascular Health Study (CHS).[15] Using CHS criteria, fatal AMI was designated as definite or possible fatal AMI as previously described.[2] Definite fatal AMI was defined as a death within four weeks of a clinically confirmed AMI and possible fatal AMI was determined by death certificate documenting AMI as the underlying cause (ICD-10 code I21.0-I21.9). The following were used to identify deaths: VA vital status file, the Social

Security Administration death master file, the Beneficiary Identification and Records Locator Subsystem, and the Veterans Health Administration medical Statistical Analysis Systems inpatient datasets. Causes of death were obtained from the National Death Index.

Covariates

Covariates included sociodemographic data (age, sex, and race/ethnicity). Body mass index (BMI) was measured from Health Factors data; renal disease and anemia were measured using outpatient and clinical laboratory data collected closest to the baseline date. Renal disease was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m^2 per National Kidney Foundation Kidney Disease Outcomes Quality Initiative thresholds for chronic kidney disease.[20] Hepatitis C (HCV) infection was defined as a positive HCV antibody test or ≥1 inpatient and/or ≥2 outpatient ICD-9 codes for this diagnosis.[21] History of cocaine and alcohol abuse or dependence was defined using ICD-9 codes.[22]

We obtained data on HIV-1 RNA, CD4+ T-lymphocyte counts (CD4+ cell counts), and current use of antiretroviral therapy (ART). CD4+ cell counts and HIV-1 RNA measurements were obtained as part of clinical care within 180 days of our baseline date. ART was categorized by regimens defined as protease inhibitors (PI) plus nucleoside reverse-transcriptase inhibitors (NRTI), non-nucleoside reverse-transcriptase inhibitors (NNRTI) plus NRTI, other, and no ART use (i.e., referent group). We included all ART medications that were on VA formulary during the study

period. A prior study using a nested sample demonstrated that 96% of HIV+ Veterans on ART obtain their medications from the VA.[13]

Statistical Analysis:

We compared baseline characteristics by CVD risk factor profile using χ^2 and Kruskal Wallis tests. We used similar tests to compare baseline characteristics by HIV status and CVD risk factor profile. We calculated average AMI rates across the study period and performed Cox proportional hazards regression to estimate the independent effect of CVD risk factor profile and HIV status on AMI risk. The referent group for the Cox analyses consisted of those with no major CVD risk factors (i.e., those with an optimal, 1+ non-optimal and 1+ elevated CVD risk factor profile). These analyses were adjusted for age, race/ethnicity, hepatitis C infection, BMI, estimated glomerular filtration rate, history of cocaine abuse/dependence, and alcohol abuse /dependence. Models restricted to HIV-infected people were additionally adjusted for CD4+ cell count, HIV-1 RNA and ART regimen at baseline.

Results

Over a median follow-up of 5.9 (mean [SD]: 4.9 [2.0]) years, 858 AMI events occurred (42% were among HIV infected Veterans). Less than 2% of the cohort had optimal cardiac health (58% in optimal group were HIV infected). Twelve percent of the cohort had no major CVD risk factors, 46% had one major CVD risk factor, 20% had 2 major CVD risk factors and 7% had 3 major CVD risk factors. HIV infected Veterans had a higher prevalence of having a single major CVD risk factor; uninfected Veterans had a higher prevalence of multiple major CVD risk factors (Table 2).

In this cohort, compared to those with optimal CVD risk profiles, those with 1 or more major CVD risk factors were older, more likely to be black, obese (Table 2) and have LDL-cholesterol ≥160 mg/dL (0.4% vs. 12.6%), triglycerides ≥150 mg/dL (25.0% and 43.5%), renal disease (eGFR<60; 3.9% vs. 5.9%) and a history of cocaine (4.9% vs. 10.5%) or alcohol abuse (7.1% vs. 16.4%), respectively. Among HIV-infected Veterans, immune depletion (CD4+ cell count <200 cells/mm^3) and unsuppressed viremia (HIV-1 RNA≥500 copies/mL) were more common among those in the optimal cardiac health group compared to other groups (Table 2). Veterans with only 1 major CVD risk factor risk were likely to have smoking as their one major risk factor. Those with 2 major risk factors were often diabetic smokers while those with 3 major risk factors were typically diabetic smokers taking HMG-CoA reductase inhibitors (Table 2).

An optimal CVD risk profile was associated with low AMI rates (6.0/10,000py [95% CI: 1.9-18.8]; age/race-ethnicity adjusted). Veterans with one, two or three or more major CVD risk factors had significantly higher AMI rates (18.5/10,000py [95% CI: 15.7-21.8]; 34.5/10,000py [29.2-40.9]; 42.5 95% CI [34.4-52.6] respectively] compared to those with optimal CVD risk factors. Compared to uninfected people with the same CVD risk factor profile, HIV infected Veterans had higher AMI rates (age/race-ethnicity adjusted), particularly among those with at least one major CVD risk factor present (Figure 1). The CVD risk factor categorization was based on prior work and only considered current smoking (and not past smoking) as a major CVD risk factor. A sensitivity analysis excluding past smokers showed very similar absolute AMI rates overall and by HIV status (Supplementary Digital Content Figure 1).

Compared to those without major CVD risk factors, both HIV infected and uninfected Veterans showed a step-wise increase in AMI risk with increasing number of major CVD risk factors (Table 3). Compared to uninfected people with no major CVD risk factors, HIV infected people with no major CVD risk factors had a 2-fold increased risk of AMI (HR: 2.1 95%CI: 1.1-4.0; Table 4). This association was slightly attenuated after covariate adjustment (HR: 2.0 95% CI: 1.0-3.9, p-value 0.044; Table 4).

Sensitivity analyses limiting the sample to those without missing cholesterol, smoking or blood pressure data still showed increased AMI risk among HIV infected compared to uninfected people with similar CVD risk factors (Supplementary Digital Content Table 1).

Discussion

Among Veterans without major CVD risk factors, HIV infected Veterans had a twofold increased risk of AMI compared to uninfected Veterans. The prevalence of optimal cardiac health was low in this population of Veterans, regardless of their HIV status. The presence of any major CVD risk factors was associated with a 2-7 fold increased risk of AMI regardless of HIV status.

Our results support prior observations in the general population showing lowest CVD risk among those with optimal cardiac health and increased risk among those with major CVD risk factors present.[10][11][23] Prior studies have described increased risk for AMI and other cardiovascular diseases among HIV infected compared to uninfected people.[2][24][25][26] These analyses typically adjusted for CVD risk factors individually. Risk factor clustering has been

11

of increasing importance in CVD research in the general population.[27][28][29] The present study supports these findings and extends them by specifically comparing HIV infected to uninfected people with similar levels of global cardiovascular risk. Our findings suggest that the rates of AMI with increasing burden of CVD risk factors are significantly higher among HIV infected with at least one major CVD risk factor compared to uninfected people with at least one major CVD risk factor. For example, HIV infected Veterans with three or more major CVD risk factors had absolute AMI rates that were 30 events per 10000 person years higher than those for uninfected Veterans with the same CVD risk factor profile compared to 20 and 7 events per 10000 person years for those with 2 or 1 major CVD risk factors respectively (Figure 1).

While optimal health was associated with lower AMI risk overall, among HIV infected Veterans, it was not associated with an optimal HIV biomarker profile. As compared to HIV infected Veterans with a higher burden of CVD risk factors, those with an optimal profile were more likely to have HIV-1 RNA ≥500 copies/mL or CD4+ count <200 cells/mm.^{3} Although the reason for this finding is not clear, HIV seroconversion without initiation of or with poor adherence to ART is associated with decreases in LDL and total cholesterol and weight loss.[30][31][32] Those with poor HIV control may have had more extreme decreases in these lipids and weight loss making them appear healthier from a traditional CVD risk factor perspective. However, their risk is likely higher than that of uninfected veterans due to independent effect of an unsuppressed HIV viremia on AMI risk.[2]

12

Our findings have important clinical implications for reducing AMI risk in the HIV population. First, optimal cardiac health is rare yet associated with a very low rate of AMI. These results suggest that interventions focusing on primary prevention of CVD risk factors in this population are needed. Second, the majority of HIV infected Veterans have CVD risk factors and increasing risk factor burden substantially increases AMI risk. These results suggest that future studies comparing various strategies for the implementation of CVD risk factor management in the HIV population are also needed. For example, comparing whether managing all CVD risk factors equally and simultaneously is more effective in reducing CVD risk among HIV infected people than a personalized and prioritized approach is an important area of research. The latter approach has been suggested as a means of improving outcomes in a health care environment where clinicians rarely have time to fully evaluate and implement all recommended clinical guidelines.[33] Further, in this healthcare environment, polypharmacy among those with multi-morbidity is common and associated with decreased medication adherence, serious adverse drug events, organ system injury, hospitalization, and mortality.[34]

This study has limitations that warrant discussion. Missing data on CVD risk factors may have led to some misclassification in assigning CVD risk factor profiles. However, it is unlikely that these Veterans with missing data had optimal cardiac health because the rates and risk of AMI in the missing risk factor group were more consistent with those for Veterans who had one major CVD risk factor. Further, sensitivity analyses excluding participants with missing cholesterol, smoking and blood pressure data did not change our conclusions. Our analyses do not consider changes in AMI risk factor management, development of new AMI risk factors over time, duration of risk

13

factor prevalence, or treatment heterogeneity within risk factor categories. As the number of women in the VACS VC is small, our findings may not be generalizable to women.

Conclusion

In conclusion, less than two percent of HIV infected and uninfected Veterans have an optimal cardiac profile while almost 75% have at least one or more major CVD risk factors. Compared to HIV- veterans, AMI rates among HIV+ veterans with the same CVD risk factor profile were higher and increased faster with each additional major CVD risk factor. Preventing or reducing AMI risk factor burden may result in a substantial reduction in AMI risk among HIV infected people. Future studies therefore should focus on new strategies and or compare current implementation strategies designed to prevent and manage existing CVD risk factors in this high-risk population.

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14

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238

Tables and Figure

Table 1. Definition of CVD risk factor profiles

Table 2. Baseline characteristics by CVD risk factor profile stratified by HIV status

Figure 1. Age/race-ethnicity adjusted rates of acute myocardial infarction (AMI) by cardiovascular disease risk factor profile (CVDRF) stratified by HIV status (see attached)

Table 3. AMI risk by cardiovascular disease risk factor (CVDRF) profile stratified by HIV status (separate referent groups for HIV- and HIV+)

Table 4. Rates and risk of AMI by cardiovascular disease risk factor (CVDRF) and HIV status (common referent group)

Supplementary digital content Figure 1: Age/race-ethnicity adjusted rates of acute myocardial infarction (AMI) by cardiovascular disease risk factor profile (CVDRF) stratified by HIV status with past smokers excluded (see attached)

Supplementary digital content Table 1: Risk of AMI in whole sample versus sample restricted to participants without missing cholesterol, blood pressure or smoking data

Table 1. Mutually exclusive risk factor categories

Risk Factor	Optimal	Not optimal	Elevated	Major
Diabetes	No	No	No	Yes
Current smoking	No	No	No	Yes

18

Total cholesterol (mg/dL)	<180	180-199	200-239	≥240 or cholesterol medication
Blood pressure (BP) (mm Hg)	<120/80	120-139/80-89	140-159/ 90-99	≥160/100 or BP medication

Definitions of risk factor categories derived from reference[11]. Participants are placed in the highest risk category ascertainable.

19

239Table 2. Baseline characteristics by CVD risk factor profile stratified by HIV status

Data represent % of column unless otherwise specified	**All CVDRFs optimal**		**1+ CVDRFs non-optimal**		**1+ CVDRFs elevated**		**1 major CVDRF**		**2 major CVDRFs**		**3+ major CVDRFs**		**Missing CVDRFs**	
	HIV-	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**	**HIV-**	**HIV+**
N [% of HIV group]	458 [0.8]	634 [2.4]	2565 [4.7]	1895 [7.1]	2932 [5.4]	1446 [5.4]	23865 [43.8]	13600 [50.7]	11289 [20.7]	4731 [17.6]	4298 [7.9]	1185 [4.4]	9084 [11.2]	3340 [4.1]
Median Framingham risk score (%)	1	1	2	2	4	4	5	5	7	7	9	9	3	3
Median (p25, p75) followup time, years	5.3 3.0 6.5	5.1 2.7 6.6	5.5 3.2 6.5	6.0 3.4 6.6	5.9 3.8 6.5	6.2 3.8 6.6	5.9 3.8 6.5	5.8 3.3 6.6	6.2 4.2 6.6	6.0 3.2 6.6	6.4 4.9 6.7	6.4 3.8 6.7	5.1 2.6 6.3	4.9 2.0 6.5
Mean age [SD], years	47 [10]	45 [11]	47 [10]	46 [11]	49 [10]	47 [10]	48 [9]	47 [9]	51 [8]	51 [8]	52 [8]	53 [8]	46 [10]	47 [11]
Race/ethnicity														
White	41	33	39	42	41	44	38	38	36	36	34	34	38	38
Black	38	46	41	41	41	39	49	49	52	52	55	56	42	45
Hispanic	12	12	12	8	10	8	7	7	7	7	7	7	8	7
Other	8	9	8	9	8	8	6	6	4	5	3	4	12	11

Data represent % of column unless otherwise specified	All CVDRFs optimal		1+ CVDRFs non-optimal		1+ CVDRFs elevated		1 major CVDRF		2 major CVDRFs		3+ major CVDRFs		Missing CVDRFs	
	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+
Female	8	4	5	2	4	3	2	3	2	2	2	3	4	3
BMI (kg/m^2)														
Median,	26	24	28	26	29	26	28	24	29	26	31	27	28	25
mean	26	24	29	26	30	27	28	25	30	26	32	28	29	25
[SD]	[5]	[4]	[5]	[4]	[5]	[4]	[6]	[4]	[6]	[5]	[6]	[5]	[5]	[4]
≥ 30	21	8	39	14	44	18	34	13	46	20	58	29	44	19
Diabetes	0	0	0	0	0	0	10	7	46	39	85	84	0	0
SBP mean, SD, mmHg	112 6	112 6	127 8	127 8	133 12	135 13	132 14	128 14	138 16	137 17	142 16	140 17	130 12	128 12
DBP mean, SD, mmHg	70 5	69 5	77 6	77 7	80 8	80 9	79 9	78 9	82 10	82 10	83 10	83 10	78 8	77 8
BP meds	0	0	0	0	0	0	12	8	47	47	77	79	0	0

Data represent % of column unless otherwise specified	All CVDRFs optimal		1+ CVDRFs non-optimal		1+ CVDRFs elevated		1 major CVDRF		2 major CVDRFs		3+ major CVDRFs		Missing CVDRFs	
	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+
Cholesterol median mean, SD, mg/dL	159	150	178	167	210	206	189	175	196	188	203	201	189	169
	155.1	146	172	163	205	197	191	179	202	196	209	211	186	170
	18.4	22	21	26	25	31	39	43	50	56	55	67	29	35
HMG-CoA reductase inhibitor use within 6 months of enrollment	0	0	0	0	0	0	4	4	19	16	50	39	0	0
Smoking status														
Never	69	67	67	70	65	70	18	13	18	13	12	9	46	44
Current	0	0	0	0	0	0	67	77	69	78	79	83	0	0
Past	31	33	33	30	35	30	11	7	11	7	8	7	21	20
Missing smoking status	0	0	0	0	0	0	4	3	2	2	1	2	33	36
HIV-1 RNA, copies/mL														

Data represent % of column unless otherwise specified	All CVDRFs optimal		1+ CVDRFs non-optimal		1+ CVDRFs elevated		1 major CVDRF		2 major CVDRFs		3+ major CVDRFs		Missing CVDRFs	
	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+
Median		11.5		1.4		0.4		1.9		0.4		0.4		3.5
(mean		112		73		37		60		42		31		74
*[SD]) *10^3*		[202]		[167]		[106]		[191]		[117]		[96]		[234]
≥500		67		56		47		58		49		43		60
CD4 count, cells/mm^3														
Median		295		356		403		348		386		418		327
mean		331		392		439		392		439		480		363
[SD]		[275]		[289]		[307]		[295]		[318]		[335]		[288]
<200		38		27		21		29		24		20		34
ART regimen														
PI + NRTI		18		20		23		20		23		22		17

Data represent % of column unless otherwise specified	All CVDRFs optimal		1+ CVDRFs non-optimal		1+ CVDRFs elevated		1 major CVDRF		2 major CVDRFs		3+ major CVDRFs		Missing CVDRFs	
	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+
NNRTI+ NRTI		22		22		26		21		25		28		17
Other		9		7		7		6		7		8		7
No ART use		51		50		44		52		45		42		59

240Unless otherwise stated, data are (% non-missing) of column

241Abbreviations: BMI-body mass index; BP-blood pressure; EGFR-estimated glomerular filtration rate; HAART-highly active antiretroviral therapy;

242HCV-hepatitis C virus; HDL-high density lipoprotein; HIV-human immunodeficiency virus; HIV(-)-HIV uninfected; HIV(+)-HIV infected; HMG CoA-3-

243hydroxy-3-methylglutaryl-coenzyme A; LDL-low density lipoprotein; RNA-ribonucleic acid; PI-proteaase inhibitor; NRTI-nucleoside reverse-

244transcriptase inhibitor; NNRTI-non-nucleoside reverse-transcriptase inhibitor; SD-standard deviation.

245All variables had complete data except smoking (HIV-: 4182, HIV+: 1784 missing), total cholesterol (HIV-: 23512, HIV+: 8692), blood pressure

246(HIV-: 1141, HIV+: 288) CD4+ T-lymphocyte count (5401 missing), and HIV-1 RNA (4593 missing).

247

248**Figure 1. Age/race-ethnicity adjusted rates of acute myocardial infarction (AMI) by cardiovascular disease risk factor profile (CVDRF) stratified by HIV status**

249Table 3. AMI risk by cardiovascular disease risk factor (CVDRF) profile stratified by HIV status (separate referent groups for HIV- and

250HIV+)

	HIV-				HIV+				
	N	**No. of AMI events**	**HR (95% CI) (Age/race-ethnicity adjusted)**	**HR (95% CI) (all covariates)**	**N**	**No. of AMI events**	**HR(95% CI) (Age/race-ethnicity adjusted)**	**HR (95% CI) (all covariates)**	**HR (95% CI) (all covariates plus HIV specific biomarkers**
All CVDRFs optimal	458	1	1 (REF)	1 (REF)	634	2	1 (REF)	1 (REF)	1 (REF)
1+ CVDRFs non-optimal	2565	6			1895	10			
1+ CVDRFs elevated	2932	9			1446	11			
1 major CVDRF	23865	188	3.0 (1.8-5.0)	2.9 (1.7-4.9)	13600	152	2.0 (1.3-3.0)	2.0 (1.2-3.1)	1.9 (1.2-3.2)
2 major CVDRFs	11289	170	4.8 (2.9-8.0)	4.3 (2.5-7.4)	4731	112	3.5 (2.2-5.5)	3.0 (1.9-4.9)	3.1 (1.9-5.2)
3+ major CVDRFs	4298	85	5.7 (3.3-9.7)	4.9 (2.8-8.7)	1185	40	4.4 (2.6-7.4)	3.6 (2.0-6.2)	4.0 (2.2-7.1)
Missing CVDRFs*	9084	42	2.2 (1.2-3.9)	2.1 (1.1-3.9)	3340	30	1.8 (1.0-3.1)	1.8 (1.0-3.3)	1.7 (0.9-3.4)

*Missing Risk factor category: Veterans were placed in this category if a participant was missing data on enough risk factors (i.e., diabetes, smoking total cholesterol level, or blood pressure) to prevent categorization

Adjustment covariates: age, sex, race, hepatitis C status, estimated glomerular filtration rate, body mass index, cocaine and alcohol abuse/dependence, hemoglobin, HIV-1 RNA, CD4 count, and ART regimen.

HIV specific biomarkers: baseline HIV-1 RNA, CD4 cell count, antiretroviral therapy regimen, HR= Hazard Ratio

Table 4. Rates and risk of AMI by cardiovascular disease risk factor (CVDRF) and HIV status (common referent group)

	HIV status	AMI rate per 10,000py	HR (95% CI)		
			Model 1 (unadjusted)	Model 2 (age/race-	Model 3 (fully adjusted)
No major CVDRF	HIV uninfected	5.3 (3.2-8.8)	1 (REF)	1 (REF)	1 (REF)
	HIV infected	11.5 (7.5-17.7)	2.1 (1.1-4.0)	2.4 (1.3-4.5)	2.0 (1.0-3.9)**
1 major CVDRF	HIV uninfected	15.8 (13.1-19.1)	2.8 (1.7-4.7)	3.0 (1.8-5)	2.9 (1.7-4.9)
	HIV infected	23.2 (19.0-28.4)	4.2 (2.5-7.0)	4.6 (2.8-7.8)	3.9 (2.3-6.7)
2 major CVDRF	HIV uninfected	29.2 (24.1-35.4)	5.1 (3.0-8.5)	4.8 (2.9-8.0)	4.4 (2.6-7.5)
	HIV infected	49.6 (39.8-62)	8.7 (5.2-14.7)	8.1 (4.8-13.8)	6.0 (3.4-10.3)
3+ major CVDRF	HIV uninfected	36.5 (28.7-46.6)	6.3 (3.7-10.8)	5.7 (3.3-9.7)	5.0 (2.9-8.7)
	HIV infected	68.3 (49.1-95)	11.8 (6.6-21.0)	10.2 (5.7-18.2)	7.0 (3.8-12.9)
Missing CVDRFs	HIV uninfected	10.5 (7.5-14.7)	1.9 (1.1-3.5)	2.2 (1.2-3.8)	2.1 (1.1-3.9)
	HIV infected	22.1 (15.1-32.4)	3.9 (2.1-7.2)	4.3 (2.3-7.9)	3.6 (1.9-7.0)

Adjustment covariates for fully adjusted models were: age, sex, race, hepatitis C status, estimated glomerular filtration rate, body mass index, cocaine and alcohol abuse/dependence, hemoglobin. HR= Hazard Ratio

**p-value for this hazard ratio was 0.044