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Baseline, Time-updated, and Cumulative HIV Care Metrics for Predicting Acute Myocardial Infarction and All-Cause Mortality

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Six HIV care metrics (baseline and time-updated HIV-1 RNA, viremia copy-years, time-updated CD4, time-updated VACS Index, and VACS Index score-years) predicted AMI and mortality among HIV infected individuals. Time-updated VACS Index provided the best prediction for both AMI and mortality.

ABSTRACT

Background: After adjustment for cardiovascular risk factors and despite higher mortality, those with HIV (HIV+) have a greater risk of acute myocardial infarction (AMI) than uninfected individuals. We modeled the association of baseline, time-updated, and cumulative measures of HIV-1 RNA, CD4 count, and the VACS Index on AMI incidence and mortality.

Methods: We included HIV+ starting combination antiretroviral therapy (cART) in the Veterans Aging Cohort Study (VACS) from 1996–2012. We fitted multivariable proportional hazards models for baseline, time-updated and cumulative measures of HIV-1 RNA, CD4 counts, and the VACS Index. We used the trapezoidal rule to build cumulative measures: viremia copy-years, CD4-years, and VACS Index score-years, captured 180 days after cART initiation until AMI, death, last clinic visit or 9/30/2012. The primary outcomes were incident AMI (Medicaid, Medicare and Veterans Affairs ICD-9 codes) and death.

Results: 8,168 HIV+ (53,861 person-years) were analyzed with 196 incident AMIs and 1,710 deaths. Controlling for known cardiovascular risk factors, six of the nine metrics predicted AMI and all metrics predicted mortality. Time-updated VACS Index had the lowest Akaike information criterion among all models for both outcomes. A time-updated VACS Index score of 55+ was associated with a HR of 3.31 (95% CI: 2.11-5.20) for AMI and a HR of 31.77 (95% CI: 26.17-38.57) for mortality.

Conclusion: Time-updated VACS Index provided better AMI and mortality prediction than CD4 count and HIV-1 RNA suggesting that current health determines risk more than prior history and that risk assessment can be improved by biomarkers of organ injury.

INTRODUCTION

Once those with HIV infection (HIV+) achieve viral suppression on combination antiretroviral therapy (cART), their life expectancy is dramatically extended [1] and morbidity and mortality due to non-AIDS-related events including cardiovascular disease become the predominant concern [2]. Accounting for established risk factors, HIV+ have 50-75% greater risk of acute myocardial infarction (AMI) than demographically similar uninfected individuals [3, 4]. Suggested underlying causes include a greater burden of chronic inflammation, immune suppression and dysfunction, anemia, renal disease, liver disease, and hepatitis C co-infection among those with HIV compared with uninfected individuals [4-6].

While many of these factors have been studied in a cross-sectional or time-updated manner, few have considered the association of cumulative HIV viral load (HIV-1 RNA), CD4 count, or organ injury measures with incident AMI among HIV+. Viremia copy-years, a measure of the amount of HIV-1 RNA exposure over time, has been used to predict mortality but not incident AMI[7]. Although chronic immunosuppression has also been postulated as a risk factor for the development of non-AIDS events [4], it has not been extensively studied in a cumulative fashion [8]. Notably, the Veterans Aging Cohort Study (VACS) Index, incorporates HIV specific measures (HIV-1 RNA and CD4 count), hepatitis C infection, and measures of organ system injury (anemia, renal disease, and liver disease) and has been shown to predict AIDS and non-AIDS morbidity and mortality in multiple settings [9-16] but has not been evaluated as a cumulative measure. Further, when studying associations between biomarkers and clinical events, mortality can act as a competing risk in which those with advanced disease die before they experience the clinical event of interest. To compare our findings with previous work and to determine whether competing risk of death might explain a lack of association for some measures, we felt it important to consider AMI and mortality in parallel analyses. We compare the association of baseline, time-updated, and cumulative measures of HIV-1 RNA, CD4 counts and VACS Index scores with incident AMI and mortality in a cohort of HIIV+ individuals.

METHODS

The VACS study has been well described [17, 18]. This analysis included all HIV+ who initiated cART with at least 3 unique antiretrovirals in VACS between 1 July 1996 and 30 September 2012 and excluded: patients with previous mono or dual ART history defined as having used at least one antiretroviral drug, those with HIV-1 RNA <500 copies/mL at the time of cART initiation, those without baseline and with less than two HIV-1 RNA, CD4, or VACS Index values during the study period, and patients with known coronary heart disease prior to cART initiation using International Classification of Diseases-9 (ICD-9) codes 410.xx-414.xx from Medicaid, Medicare, and Veterans Affairs (VA) data.

We began follow-up 180 days after cART initiation to allow sufficient time for virologic suppression and for ICD-9 codes to be updated after qualifying events [7]. Patients were followed through incident AMI, last known follow-up or censor date (September 30, 2012). An inpatient ICD-9 code of 410.xx was used to determine the presence of an AMI (supplementary table 1). When ICD-9 based outcomes were compared with a smaller validated VACS dataset of AMI outcomes, the ICD-9 classification had a sensitivity of 86%; specificity of 100%; positive predictive value of 82%; and negative predictive value of 100% (supplementary table 2). We built baseline, time-updated, and cumulative time-updated measures for HIV-1 RNA (in copies/mL), CD4 values (in cells/mm^3), and VACS Index scores (totaling nine measures). The VACS Index score is calculated using age, gender, race, HIV-1 RNA, CD4 count, aspartate and alanine transaminases, hemoglobin, platelet count, creatinine and known hepatitis C infection (supplementary table 3). Baseline laboratory values were the closest to cART initiation date within a range of 180 days prior to and 7 days after cART initiation date. The time-updated measures were calculated daily using the date that new laboratory data were available. The cumulative measures – viremia copy-years (in copy-years/mL), CD4-years (in cells-years/ mm^3), and VACS Index score-years – were created using the trapezoidal method [7]. To be consistent with current viremia copy-years literature, all extreme HIV-1 RNA values (>1,000,000 copies/mL) were set at 1,000,000 copies/mL [19]. Additionally, since there had been varying levels of HIV-1 RNA assay sensitivity over time, all undetectable viral load values were set to 200 copies/mL(half of the highest limit of detection during the study period). Our proposed cumulative measures (viremia copy-years, CD4-years, and VACS Index score-years) have not been previously assessed for AMI incidence prediction. Of them, viremia copy-years has been previously used to predict mortality and we validated our method by assessing its predictive value in mortality incidence.

We created age-adjusted and fully adjusted Cox proportional hazards models for risk of AMI and mortality using baseline, time-updated, and cumulative time-updated versions for each of the exposures of interest (HIV-1 RNA, CD4, and the VACS Index score). The cut-points used for categorizing each measure were derived by distributing the number of incident AMIs equally over the categories and then by rounding to the nearest clinically relevant threshold. The fully adjusted models controlled for age, diabetes, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), smoking, and hypertension at baseline, as well as time-updated calendar year. Models investigating HIV-1 RNA as the predictor were adjusted for baseline CD4 count. Conversely, models investigating CD4 as the predictor were adjusted for HIV-1 RNA. We examined interactions between each exposure of interest and calendar year in the fully adjusted models.

The Akaike information criterion (AIC) has been used as a means of model selection and lower AICs represent better model fit [20]. In this analysis, we used the AIC in conjunction with the magnitude and precision of the main effect estimates to determine which exposure best predicted incident AMI.

VACS has been approved by the Institutional Review Boards of the VA Connecticut Healthcare System and Yale University School of Medicine, granted a waiver of informed consent, and deemed HIPAA compliant. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

During the time period of interest, 47,805 HIV+ patients were in VACS and 35,300 (74%) initiated cART. Of the 35,300 initiators, 13,924 (39%) were exposed to mono or dual therapy prior to more effective three or more antiretroviral cART, 7.379 (21%) had a baseline HIV-1 RNA <500 copies/mL, 6,303 (18%) did not have the required labs, 3,523 (10%) had coronary heart disease prior to baseline, and 1,736 (5%) had less than six months of follow-up time after cART. After applying exclusions, 8,168 (23%) patients remained eligible for this study.

We analyzed data on 8,168 individuals (53,861 person years) from VACS who initiated cART for the first time during the time period and experienced 196 AMIs and 1,710 deaths (Table 1). The median age was 46 years [interquartile range = 40–53 years], most were male (96.9%) and African-American (54.8%). Those who experienced AMIs were older, more likely to be White, and more likely to have hypertension and metabolic disease (all p<0.002). They did not differ substantially at baseline by CD4 count (p=0.08) or HIV-1 RNA (p=0.74). Similarly, hemoglobin and FIB-4 were not significantly different (p=0.27, and p=0.06, respectively), but those experiencing AMI were less likely to have an elevated eGFR (p<0.0001), and more likely to have hepatitis C co-infection (p=0.04). Further, their VACS Index scores were more likely to be high (55+) (43% vs. 31%, p=0.0005).

Six of nine metrics were significantly associated with risk of AMI. In the fully adjusted HIV-1 RNA models (Table 2 and Figure 1), individuals with baseline HIV-1 RNA ≥100,000 copies/mL had 41% higher risk of AMI in age adjusted and fully adjusted models (hazard ratio

(HR): 1.41; 95% confidence interval (95% CI): 1.05–1.91) compared to those with HIV-1 RNA <100,000 copied/mL. At any time during the study period (time-updated HIV-1 RNA), patients with HIV-1 RNA = 201–999 copies/mL had a 71% increased risk of AMI than those who had a HIV-1 RNA ≤200 copies/mL (HR: 1.71; 95% CI: 1.06–2.74). However, time-updated HIV-1 RNA was not predictive of AMI at higher levels of viremia: HIV-1 RNA = 1,000–9,999 copies/mL (HR: 1.11; 95% CI: 0.64–1.93), or HIV-1 RNA ≥10,000 copies/mL (HR: 1.30; 95% CI: 0.85–1.99). The cumulative measure, viremia copy-years, demonstrated a significant association with AMI at all levels: viremia copy-years = 1,000–14,999 (HR: 1.61; 95% CI: 1.06–2.44), 15,000–99,999 (HR: 1.67; 95% CI: 1.07–2.61), and ≥100,000 (HR: 2.02; 95% CI: 1.30–3.14) all compared with <1000 copy-years/mL.

In the fully adjusted CD4 models, there was no evidence of increased risk of AMI among HIV+ with a baseline CD4 <200 cells/mm^3 (HR: 1.11, 95% CI: 0.82–1.49) compared with those with a baseline CD4 ≥200 cells/mm^3. The time-updated CD4 model demonstrated an association with AMI incidence only at the lowest CD4 levels: CD4 <200 cells/mm^3 (HR: 1.58, 95% CI: 1.06–2.35) compared with CD4 >500 cells/mm^3. The cumulative immunosuppression measure (CD4-years) was not significantly associated with AMI risk in any of the studied categories (p>0.05).

In the fully adjusted VACS Index models, baseline VACS Index scores ≥50 were not associated with AMI incidence when compared to those with scores <50 (HR: 1.23; 95% CI: 0.91–1.66), but time-updated VACS Index scores ≥55 were associated with incident AMI (HR: 3.31; 95% CI: 2.11–5.20) when compared to those with VACS Index scores <20. Values of cumulative VACS Index score-years significantly predicted AMI incidence at all levels: VACS Index score-years = 85–149 (HR: 1.99; 95% CI: 1.26–3.14), VACS Index score-years 150-264 (HR: 1.85; 95% CI: 1.11–3.09), and VACS Index score-years ≥265 (HR: 2.71; 95% CI: 1.51–4.87) when compared to VACS Index score-years <85. Finally, there was no evidence that time modified the relationship between any exposure of interest and incident AMI (all p>0.05).

All 9 metrics were associated with mortality in the age-adjusted and fully adjusted models (Table 2 and Figure 2). Strongest associations were seen for time-updated HIV-1 RNA and viremia copy-years demonstrating a four-fold higher risk of mortality when comparing the highest HIV-1 RNA levels to the lowest for each respective measure, time-updated CD4 count <200 cells/mm^3 demonstrating a nearly seven-fold higher risk of mortality compared with >500 cells/mm^3 (HR 6.92, 95% CI 6.03, 7.96) and time-updated VACS Index of >55 compared to <20 demonstrating a 32-fold increased risk of mortality (HR 31.8, 95% CI 26.2, 38.6).

Based on AIC measures (Table 3) of fully adjusted models, among HIV-1 RNA models, viremia copy-years provided more information regarding the risk of AMI while time-updated viremia provided more information regarding mortality among the HIV-1 RNA models. Time-updated CD4 provided the most information among the CD4 models for both AMI and mortality. Among VACS Index models, time-updated VACS Index provided more information regarding risk of AMI and mortality. Based on AICs, the fully adjusted time-updated VACS Index model was preferred over any HIV-1 RNA or CD4 count models for both AMI and mortality.

DISCUSSION

Ongoing HIV viral replication and inflammation, immunosuppression, anemia, renal disease, and liver disease have been postulated in the pathogenesis of coronary heart disease in HIV+ [4]. After adjusting for traditional AMI risk factors, we present a comparison of the ability to predict AMI and mortality using baseline, time-updated, and cumulative measures of three HIV care parameters (HIV-1 RNA, CD4 count, and the VACS Index). The VACS Index provided substantially more information than either HIV-1 RNA or CD4 counts alone. Specifically, time-updated VACS Index best predicted both AMI incidence and all-cause mortality; a score of 55+ was associated with a HR of 3.31 (95% CI: 2.11-5.20) for AMI and a HR of 31.8 (95% CI: 26.2-38.6) for mortality.

Most of the previous work has focused on time-updated and cumulative measures of

HIV-1 RNA and CD4 count. Some of these demonstrate an association of uncontrolled viremia with mortality [2] and acute myocardial infarctions [21]. Cumulative HIV viremia is more predictive of mortality over single cross-sectional measures of HIV viremia [7, 22]. Our findings show that baseline HIV-1 RNA and cumulative viremia copy-years were associated with AMI while time-updated viremia was not. SMART [23] also found "no clear evidence that… time-updated viral load is…associated with CVD risk." Similarly, there is no clear consensus regarding the association of immunosuppression with AMI. Studies have shown conflicting results for CD4 measures at baseline, nadir, last value, duration of immunosuppression, or time-updated values [2, 23]. A recent study [24] showed a protective effect of higher CD4 values: individuals with recent or nadir CD4 ≥ 500 cells/mm^3 had risk of AMI comparable to that of an HIV uninfected population. Another study assessing immunosuppression and cardiovascular outcomes found a small association of immunosuppression with strokes but not with AMI [25]. Our findings did not support an advantage of measuring cumulative CD4 counts but there did appear to be a trend towards protection for individuals with time-updated CD4 counts ≥ 500 cells/mm^3.

We found stronger associations between more extreme values of time updated HIV-1 RNA and CD4 count and mortality than with AMI. It is tempting to attribute the weaker association with AMI to competing risk from mortality. If this were true, we would have expected the VACS Index to have an even weaker association with AMI since its association with mortality was stronger than that for HIV-1 RNA or CD4 count. Instead we found that the time updated VACS Index was a better predictor of both outcomes.

The VACS Index is a validated score capable of predicting all-cause mortality [26], cardiovascular mortality [27], and an array of morbidity measures [10, 28]. It can be constructed with basic clinical information available in most settings. An online calculator is available (http://vacs.med.yale.edu/IC/). Both time-updated and cumulative measures of VACS Index were more strongly associated with incident AMI than CD4 or HIV-1 RNA measures alone. This may not be surprising since, in addition to HIV-RNA and CD4 counts, the VACS Index also accounts for anemia, chronic kidney diseases, liver disease, and hepatitis C co-infection, giving a more comprehensive overview of the non-traditional factors associated with cardiovascular disease. Of note, all components of the VACS Index are correlated with measures of chronic inflammation including IL-6, soluble CD4, and D-dimer [29], which may explain the strength of this association. The time-updated VACS Index may be complementary to traditional risk factors in AMI risk assessment.

Our finding that time-updated VACS Index provides superior prediction of risk of AMI and mortality compared with all cumulative measures considered is clinically convenient since past measures may not always be obtained. Additionally, cumulative measures are highly dependent upon the period of observation making them less generalizable. Further, it suggests that a patient's current status is much more important than how they got there or the duration of time they have spent in a particular state. Future studies are required to assess how the VACS Index might enhance AMI risk estimation beyond currently proposed indices such as DAD [30] and/or Framingham [31, 32]. Further, because mortality can act as a competing risk in which those with advanced disease die before they experience the clinical event of interest, our findings are more conclusive. Had one measure been superior for mortality and another for AMI, we might have been concerned about competing risk. Fortunately, time updated VACS Index was the best predictor for both events, thus we can be confident that competing risk of death did not distort our comparison.

Our study has limitations. Findings may not generalize to women since only a small proportion of our sample was female. An indepth analysis of cART regimen was beyond the scope of this paper. Some reports have suggested that protease inhibitors as a class and abacavir as a specific agent may be associated with risk of AMI [33, 34]. We see no reason why the relative prognostic importance of the biomarkers and index we report should depend upon regimen. We used administrative data (ICD-9 coding), which may limit the accuracy of the outcome. To address this issue, we validated the use of ICD-9 coding with data from chart review with an acceptable positive predictive value. Additionally, the use of ICD-9 codes to identify AMI precludes our ability to further differentiate AMI into Type 1 and Type 2 classifications. Our study measured and compared nine clinical metrics but we were unable to compare them with established risk estimators such as the Framingham risk score calculator or the ASVCD Risk Estimator [31, 32]. We did, however, adjust at baseline for important components of the Framingham calculator including diabetes, hypertension, cholesterol levels, and smoking. Given the observational nature of our study, we can only postulate associations, not causality. Despite these limitations, we were able to compare the predictive ability of novel cumulative measures for AMI incidence and mortality using one of the largest cohorts of aging HIV+ in the United States.

In conclusion, we determined that the time-updated VACS Index was the best predictor of AMI incidence and all-cause mortality compared to eight other HIV care metrics included in this study of US Veterans. Future studies seeking to refine cardiovascular risk in HIV+ should consider the time-updated VACS Index as it has the potential for improving currently available cardiovascular risk assessment strategies.

Notes

Author contributions. All authors contributed to study design. A.C.J., J.L.S., C.R. and J.T. contributed to data collection; J.L.S, C.R., V.C.M., J.T., A.C.J and D.R. contributed to data quality and analysis; all authors contributed to manuscript development and have critically reviewed the manuscript and approved the final version.

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Figures

Figure 1. Crude and adjusted hazard ratios and 95% CI for the risk of acute myocardial infarction

Notes: hazard ratio (HR) and 95% confidence intervals (CI) are presented on a $\log_2$ scale, grey diamonds denote crude measures, black squares denote adjusted measures

Adjusting factors: *all models* age, diabetes, cholesterol, low- and high-density lipoprotein, smoking, hypertension; *HIV viral load models* additionally adjusted for CD4; *CD4 models* additionally adjusted for HIV viral load

Figure 2. Crude and adjusted hazard ratios and 95% CI for the risk of all-cause mortality

Notes: hazard ratio (HR) and 95% confidence intervals (CI) are presented on a $\log_2$ scale, grey diamonds denote crude measures, black squares denote adjusted measures.

Adjusting factors: *all models* age, diabetes, cholesterol, low- and high-density lipoprotein, smoking, hypertension; *HIV viral load models* additionally adjusted for CD4; *CD4 models* additionally adjusted for HIV viral load

Table 1. Baseline characteristics of 8,168 HIV-infected veterans

Characteristic	**No AMI** (n=7,972)	**AMI** (n=196)	***p***[a]
Age, years	46 (40-52)	51 (46-57)	<0.0001
Male sex	7,726 (96.9)	192 (98.0)	0.4014
Race/ethnicity			
Black/African-American	4,388 (55.0)	90 (45.9)	0.0008
White	2,651 (33.3)	89 (45.4)	
Hispanic	573 (7.2)	15 (7.7)	
Other	360 (4.5)	2 (1.0)	
Diabetes	532 (6.7)	28 (14.3)	<0.0001
Hypertension	1,386 (17.4)	51 (26.0)	0.0017
Composite LDL and TC			
LDL<130 or TC<200	5,141 (64.5)	93 (47.5)	<0.0001
LDL 130-160 or TC 200-240	634 (8.0)	19 (9.7)	
LDL>160 or TC>240	209 (2.6)	8 (4.1)	
Other or missing	1,988 (24.9)	76 (38.8)	
HDL			
HDL<40	3,184 (39.9)	65 (33.2)	0.1442
HDL>=60	417 (5.2)	10 (5.1)	
Other or missing	4,371 (54.8)	121 (61.7)	
Smoking			
Current	4,873 (61.1)	128 (65.3)	0.0098
Former	980 (12.3)	33 (16.8)	

Never	2,119 (26.6)	35 (17.9)	
eGFR, mL/min/1.73m^2			
≥60	6,054 (75.9)	119 (60.7)	<0.0001
30-59	284 (3.6)	13 (6.6)	
<30	86 (1.1)	5 (2.6)	
Missing	1,548 (19.4)	59 (30.1)	
VACS Index			
<20	1,297 (16.3)	20 (10.2)	0.0005
20-34	2,016 (25.3)	35 (17.9)	
35-54	2,173 (27.3)	56 (28.6)	
55+	2,486 (31.2)	85 (43.4)	
CD4 count, cells/mm^3			
≥500	703 (8.8)	20 (10.2)	0.0804
350-499	1,194 (15.0)	29 (14.8)	
200-349	2,403 (30.1)	43 (21.9)	
<200	3,672 (46.1)	104 (53.1)	
HIV-1 RNA, copies/mL			
501-999	216 (2.7)	7 (3.6)	0.7352
1,000-9,999	1,173 (14.7)	30 (15.3)	
10,000+	6,583 (82.6)	159 (81.1)	
Hemoglobin, g/dL			
≥14	3,049 (38.3)	66 (33.7)	0.2700
12-13.9	3,020 (37.9)	73 (37.2)	
10-11.9	1,383 (17.4)	44 (22.5)	

<10	520 (6.5)	13 (6.6)	
FIB-4			
<1.45	4,508 (56.6)	98 (50.0)	0.0612
1.45-3.25	2,683 (33.7)	70 (35.7)	
>3.25	781 (9.8)	28 (14.3)	
Hepatitis C co-infection	1,742 (21.9)	55 (28.1)	0.0381
AIDS[b]	662 (8.3)	18 (9.2)	0.6597

Abbreviations: AMI - acute myocardial infarction; LDL - low-density lipoprotein; TC - total cholesterol; HDL - high-density lipoprotein; eGFR - estimated glomerular filtration rate; CD4 - cluster of differentiation 4; HIV-1 RNA - human immunodeficiency virus viral load; FIB-4 - fibrosis-4; AIDS - acquired immune deficiency syndrome

Note: statistics given in median (interquartile range) or n (%)

[a]Tested for significance with two-sided Wilcoxon rank-sum and chi-square ($\chi 2$) tests

[b]Includes diagnosis of Kaposi's sarcoma or Pneumocystis pneumonia

Table 2. Crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) by exposure of interest and outcome, n=8,168

	AMI models				Mortality models			
	PY	Events	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)	PY	Events	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)
HIV-1 RNA measures[a]								
Baseline HIV-1 RNA (copies/mL)								
<100,000	32253	99	1	1	32587	930	1	1
100,000+	21608	97	1.44 (1.09, 1.91)	1.41 (1.05, 1.91)	21881	780	1.24 (1.13, 1.37)	1.17 (1.06, 1.30)
Time-updated HIV-1 RNA (copies/mL)								
<=200	42258	135	1	1	42769	842	1	1
201-999	2660	20	1.74 (1.09, 2.79)	1.71 (1.06, 2.74)	2617	108	1.44 (1.18, 1.76)	1.40 (1.15, 1.72)
1,000-9,999	2710	14	1.15 (0.66, 2.01)	1.11 (0.64, 1.93)	2737	159	1.98 (1.67, 2.35)	1.88 (1.58, 2.23)
10,000+	6233	27	1.34 (0.88, 2.04)	1.30 (0.85, 1.99)	6345	601	4.32 (3.88, 4.81)	4.00 (3.59, 4.47)
Cumulative time-updated viremia (VCY) (copy-years/mL)								
<1,000	10914	49	1	1	10895	360	1	1
1,000-14,999	15657	56	1.63 (1.08, 2.45)	1.61 (1.06, 2.44)	15855	303	1.39 (1.18, 1.63)	1.36 (1.16, 1.59)
15,000-99,999	10205	39	1.68 (1.09, 2.61)	1.67 (1.07, 2.61)	10341	305	1.97 (1.68, 2.31)	1.89 (1.61, 2.21)
100,000+	17085	52	2.08 (1.37, 3.18)	2.02 (1.30, 3.14)	17377	742	4.38 (3.82, 5.03)	4.09 (3.55, 4.70)

Note: All undetectable HIV-1 RNA values were set to 200 copies/mL, which is half of the largest lower detection limit; [a]adjusted factors include age,

CD4, diabetes, cholesterol, LDL, HDL, smoking, hypertension, and calendar year								
CD4 measures[b]								
Baseline CD4 (cells/mm^3)								
<200	25192	104	1.20 (0.91, 1.59)	1.11 (0.82, 1.49)	25461	962	1.40 (1.27, 1.54)	1.34 (1.21, 1.49)
200+	28669	92	1	1	29007	748	1	1
Time-updated CD4 (cells/mm^3)								
<200	9356	43	1.68 (1.14, 2.49)	1.58 (1.06, 2.35)	9522	881	7.63 (6.65, 8.75)	6.92 (6.03, 7.96)
200-349	9483	46	1.37 (0.93, 2.01)	1.31 (0.89, 1.93)	9540	336	2.31 (1.97, 2.72)	2.21 (1.88, 2.60)
350-499	10053	46	1.39 (0.95, 2.04)	1.39 (0.95, 2.04)	10137	223	1.54 (1.29, 1.84)	1.55 (1.30, 1.85)
500+	24968	61	1	1	25269	270	1	1
Cumulative time-updated CD4-years (CD4Y) (cell-years/mm^3)								
<815	4106	42	1.34 (0.81, 2.23)	1.22 (0.73, 2.03)	4067	665	5.44 (4.62, 6.41)	4.66 (3.94, 5.50)
815-1,499	5635	40	1.21 (0.76, 1.93)	1.16 (0.73, 1.85)	5640	329	2.50 (2.11, 2.96)	2.32 (1.96, 2.74)
1,500-2,699	10714	48	1.11 (0.74, 1.67)	1.10 (0.73, 1.65)	10744	343	1.76 (1.51, 2.06)	1.71 (1.46, 2.00)
2,700+	33406	66	1	1	34018	373	1	1
[b]adjusted factors include age, HIV viral load, diabetes, cholesterol, LDL, HDL, smoking, hypertension, and calendar year								
VACS Index measures[c,d]								
Baseline VACS Index score								

<50	34319	97	1	1	34678	729	1	1
50+	19542	99	1.22 (0.90, 1.64)	1.23 (0.91, 1.66)	19790	981	1.98 (1.79, 2.19)	1.91 (1.73, 2.12)
Time-updated VACS Index score								
<20	18082	38	1	1	18120	125	1	1
20-34	15272	56	1.40 (0.91, 2.14)	1.33 (0.87, 2.04)	15408	198	2.24 (1.79, 2.81)	2.14 (1.71, 2.69)
35-54	10281	38	1.23 (0.76, 2.00)	1.18 (0.72, 1.92)	10509	306	5.56 (4.49, 6.89)	5.28 (4.26, 6.55)
55+	10226	64	3.62 (2.32, 5.65)	3.31 (2.11, 5.20)	10432	1081	34.19 (28.22, 41.43)	31.77 (26.17, 38.57)
Cumulative time-updated VACS Index score-years (VISY)								
<85	10405	37	1	1	10354	246	1	1
85-149	8197	51	2.05 (1.30, 3.23)	1.99 (1.26, 3.14)	8153	315	4.17 (3.48, 5.00)	3.92 (3.27, 4.70)
150-264	13994	50	1.95 (1.18, 3.24)	1.85 (1.11, 3.09)	14092	496	10.74 (8.87, 13.00)	9.82 (8.10, 11.91)
265+	21265	58	2.90 (1.63, 5.17)	2.71 (1.51, 4.87)	21868	653	30.10 (24.37, 37.18)	26.95 (21.75, 33.39)

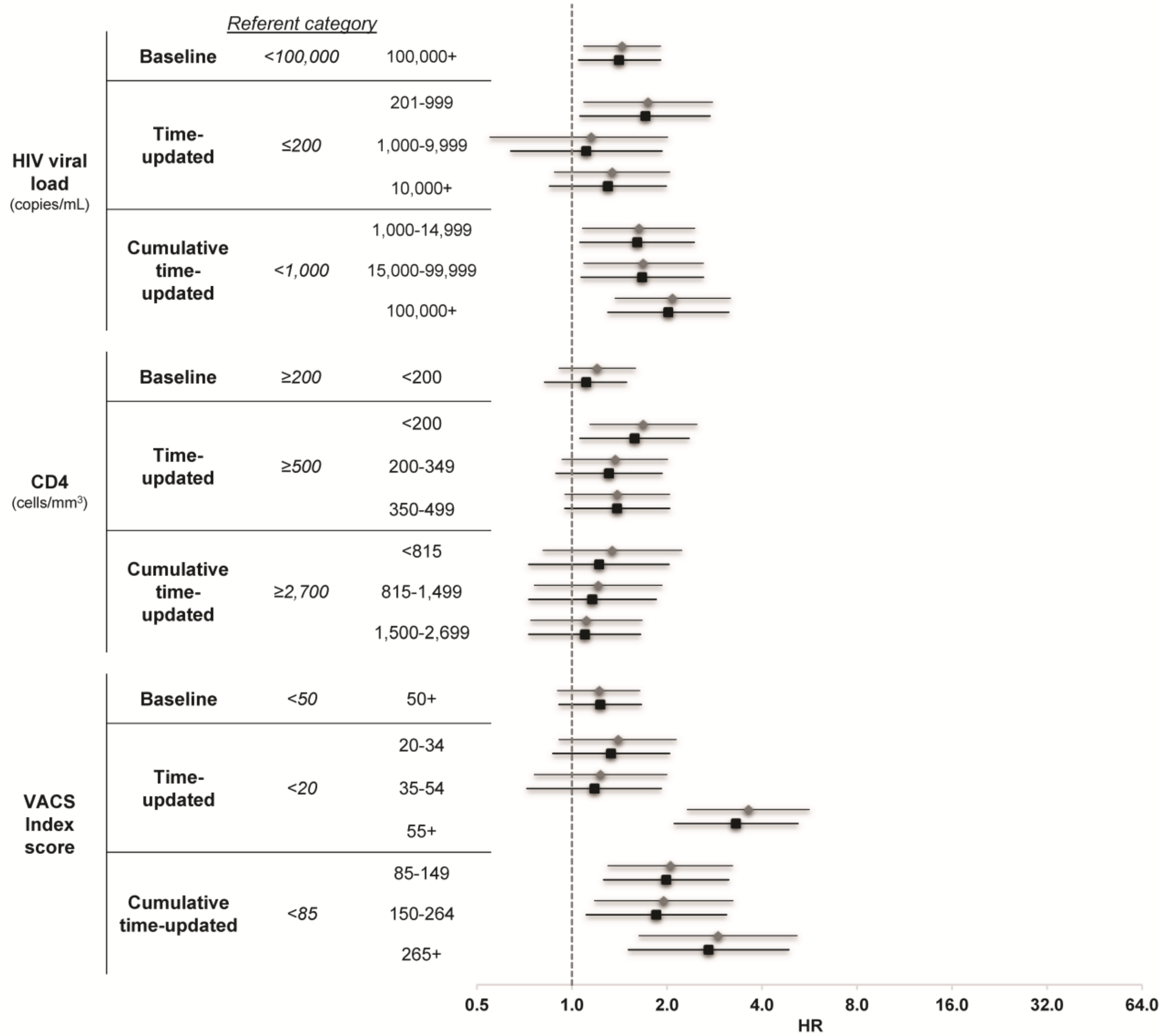
[c]VACS Index scores included age, indicators of HIV disease, and indicators of organ system injury; [d]adjusted factors included age, diabetes, cholesterol, LDL, HDL, smoking, hypertension, and calendar year

Table 3. Akaike Information Criterion (AIC) values for crude and adjusted Cox regression models by exposure of interest and outcome, n = 8,168

	AMI models		Mortality models	
	Age-adjusted	Fully adjusted	Age-adjusted	Fully adjusted
HIV-1 RNA measures				
Baseline HIV-1 RNA (copies/mL)	3154	3141	28339	28007
Time-updated HIV-1 RNA (copies/mL)	3158	3145	27728	27466
Cumulative time-updated viremia (copy-years/mL)	3152	3139	27820	27552
CD4 measures				
Baseline CD4 (cells/mm^3)	3159	3140	28312	27953
Time-updated CD4 (cells/mm^3)	3157	3139	27222	26987
Cumulative time-updated CD4-years (cell-years/mm^3)	3163	3144	27939	27650
VACS Index measures				
Baseline VACS Index score	3158	3145	28178	27905
Time-updated VACS Index score	3122	3114	25608	25507
Cumulative time-updated VACS Index score-years	3149	3138	27189	27004

Abbreviations: HIV-1 RNA - human immunodeficiency virus viral load; VACS - Veterans Aging Cohort Study

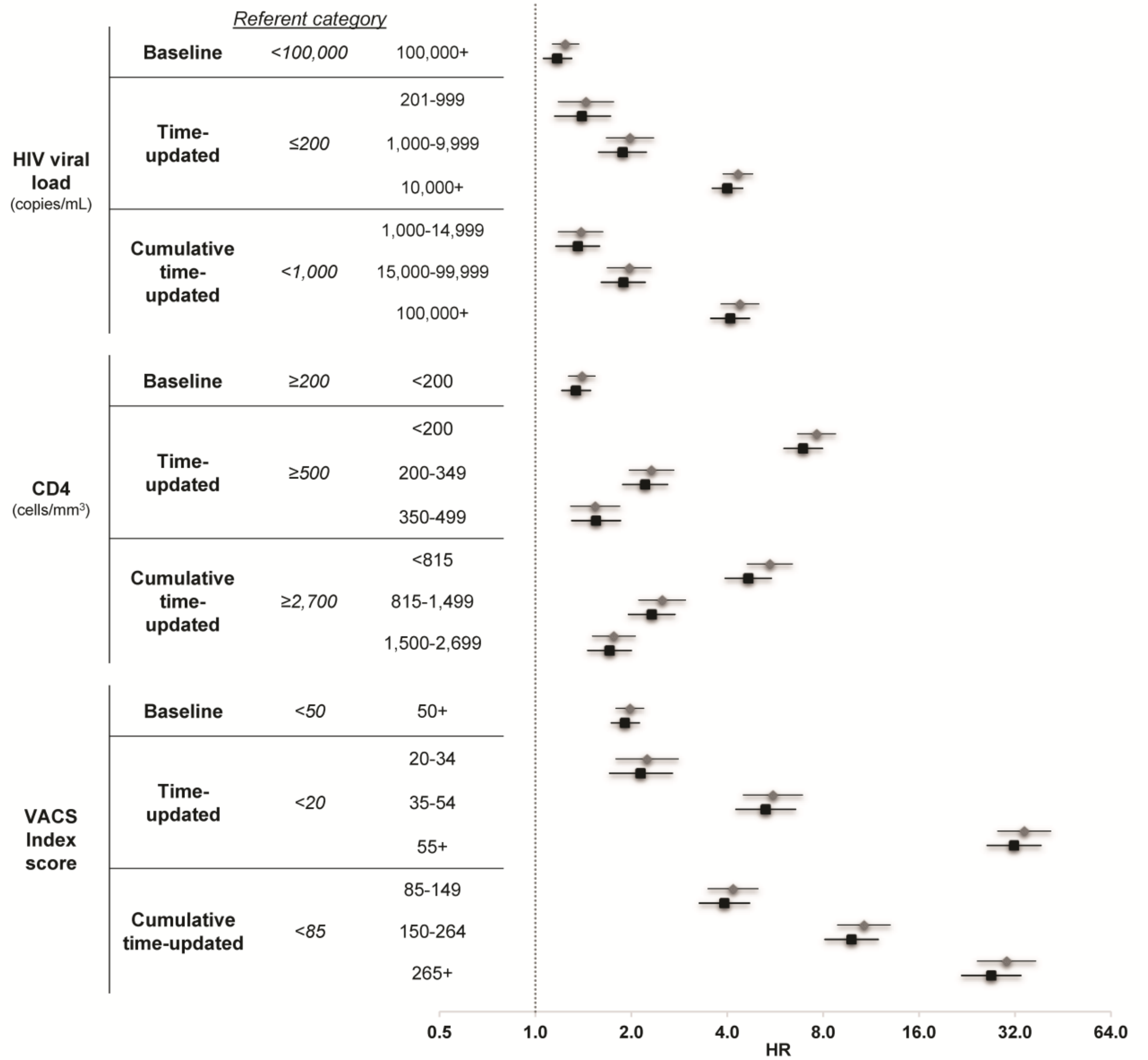
Figure 1. Crude and adjusted hazard ratios and 95% CI for the risk of acute myocardial infarction



Notes: hazard ratios (HR) and 95% confidence intervals (CI) are presented on a $\log_2$ scale, grey diamonds denote crude measures, black squares denote adjusted measures

Adjusting factors: *all models* age, diabetes, cholesterol, low- and high-density lipoprotein, smoking, hypertension; *HIV viral load models* additionally adjusted for CD4; *CD4 models* additionally adjusted for HIV viral load

Figure 2. Crude and adjusted hazard ratios and 95% CI for the risk of all-cause mortality



Notes: hazard ratios (HR) and 95% confidence intervals (CI) are presented on a $\log_2$ scale, grey diamonds denote crude measures, black squares denote adjusted measures
Adjusting factors: *all models* age, diabetes, cholesterol, low- and high-density lipoprotein, smoking, hypertension; *HIV viral load models* additionally adjusted for CD4; *CD4 models* additionally adjusted for HIV viral load