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VACS Index is superior to nadir CD4 count for predicting AMI and mortality

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Background

- The Veterans Aging Cohort Study (VACS) Index is a composite measure of physiologic injury incorporating:
  - age
  - CD4 count
  - HIV-1 RNA
  - hemoglobin
  - a marker of liver fibrosis (FIB-4)
  - estimated glomerular filtration rate (eGFR)
  - hepatitis C sero-status
- Time-updated VACS Index is superior to CD4 count or HIV-1 RNA (as baseline, time-updated, or cumulative measures) in predicting acute myocardial infarction (AMI) and mortality among HIV-infected (HIV+) patients[1]
- Nadir CD4 count has also been shown to be independently associated with AMI[2]

[1]Salinas et al. CID 2016; 63(11): 1423-30; [2]Silverberg et al. JAIDS 2014; 65: 160-166

Specific Aims

- **Aim 1**: Compare model fit between time-updated VACS Index and nadir CD4 count on incident AMI and all-cause mortality
  - Hypothesis: Time-updated VACS Index provides better model fit than nadir CD4 count
- **Aim 2:** Compare associations between time-updated VACS Index and nadir CD4 count with incident AMI and all-cause mortality
  - Hypothesis: Time-updated VACS Index will be associated with a higher risk of both outcomes

Study Design

- **Design**: Open cohort study using Veterans Aging Cohort Study (VACS)
- **Data Sources**: Electronic health record (EHR) data from Veterans Health Administration (VA), Medicaid, and Medicare
- **Study Patients:**
  - HIV+ patients who initiated combination antiretroviral therapy (cART) between 1996 and 2012
  - HIV-1 RNA ≥ 500 copies/mL at baseline
  - No prevalent coronary artery disease (ICD-9 410-414)
- **Study Period:** cART initiation to outcome (AMI using first inpatient diagnosis of ICD-9 410.xx, or death), last clinic visit, or 9/30/2012

Methods

- Akaike information criterion (AIC) assessed model fit (lower AIC = better model fit)
- For each outcome, two separate Cox models and one combined Cox model to estimate hazard ratios by:
  - nadir CD4 (≥500, 350-499, 200-349, 50-199, <50)
    - between 6 months pre-cART and end of study
  - time-updated VACS Index (<20, 20-34, 35-54, 55+)
- Each model was adjusted for baseline measures of age, diabetes, cholesterol, smoking, hypertension, CD4 count, HIV-1 RNA, and time-updated calendar year

Results

Table 1. Baseline characteristics

Characteristic	AMI (n=196)	No AMI (n=7,972)	p
Age, *median (IQR)*	51 (46-57)	46 (40-52)	<0.0001
Male sex	192 (98)	7,726 (97)	0.4014
Race/ethnicity			
Black/African-American	90 (46)	4,388 (55)	0.0008
White	89 (45)	2,651 (33)	
Hispanic	15 (8)	573 (7)	
Other	2 (1)	360 (5)	
Diabetes	28 (14)	532 (7)	<0.0001
Hypertension	51 (26)	1,386 (17)	0.0017
Composite LDL and TC			
LDL<130 or TC<200	93 (48)	5,141 (65)	<0.0001
LDL 130-160 or TC 200-240	19 (10)	634 (8)	
LDL>160 or TC>240	8 (4)	209 (3)	
Other or missing	76 (39)	1,988 (25)	
HDL			
HDL<40	65 (33)	3,184 (40)	0.1442
HDL>=60	10 (5)	417 (5)	
Other or missing	121 (62)	4,371 (55)	
Smoking			
Current	128 (65)	4,873 (61)	0.0098
Former	33 (17)	980 (12)	
Never	35 (18)	2,119 (27)	
HIV-1 RNA, copies/mL			
501-999	7 (4)	216 (3)	0.7352
1,000-9,999	30 (15)	1,173 (15)	
10,000+	159 (81)	6,583 (83)	
CD4 count, cells/mm^3			
≥500	20 (10)	703 (9)	0.0804
350-499	29 (15)	1,194 (15)	
200-349	43 (22)	2,403 (30)	
<200	104 (53)	3,672 (46)	
Nadir CD4 count, cells/mm^3			
≥500	7 (4)	244 (3)	0.0935
350-499	21 (11)	755 (10)	
200-349	37 (19)	2,119 (27)	
50-199	79 (40)	2,633 (33)	
<50	52 (27)	2,221 (28)	
VACS Index *(higher is worse)*			
<20	20 (10)	1,297 (16)	0.0005
20-34	35 (18)	2,016 (25)	
35-54	56 (29)	2,173 (27)	
55+	85 (43)	2,486 (31)	

Reported as n(%) unless otherwise stated; LDL - low-density lipoprotein; TC - total cholesterol; HDL - high-density lipoprotein; eGFR - estimated glomerular filtration rate

Results

- **8,168 HIV+ patients (55,263 person-years) had 196 AMIs (2.4%) and 1,711 deaths (21%)**
  - Patients who had an AMI were older; more likely to be white; more likely to have diabetes, hypertension, lower LDL and/or total cholesterol; and more likely to be a former or current smoker than patients who did not have an AMI (Table 1)

Table 2. Akaike information criterion (AIC) values

	AMI	Mortality
Separate models		
Nadir CD4	3150	27981
Time-updated VACS Index	3124	25602
Combined model		
Nadir CD4 + time-updated VACS Index	3120	25597

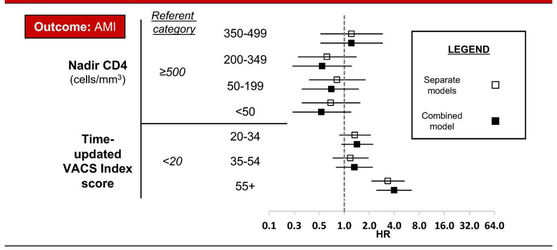
Key Points

Time-updated VACS Index models had much lower AIC values than nadir CD4 models for both outcomes

Adding nadir CD4 to the time-updated VACS Index model did not substantively improve model fit

- **AMI models**
  - Nadir CD4 count was not predictive of AMI (HR 0.69; 95% CI: 0.31-1.54 for nadir CD4<50)
  - Time-updated VACS Index score of 55+ was predictive of AMI (HR 3.36; 95% CI: 2.14-5.28)

Figure 1. Adjusted hazard ratios for the risk of AMI



Notes: hazard ratios (HR) and 95% confidence intervals (CI) are presented on a $\log_2$ scale

Key Points

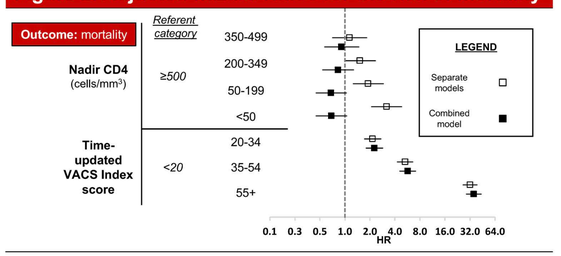
Time-updated VACS Index predicted incident AMI, while nadir CD4 demonstrated no predictive value

Adding nadir CD4 to the time-updated VACS Index model did not change these relationships

Results

- **Mortality models**
  - Nadir CD4 count <50 was predictive of mortality (HR 3.17; 95% CI: 2.09-4.81)
  - Time-updated VACS Index score of 55+ was also predictive of mortality (HR 32.0; 95% CI: 26.4-38.9)

Figure 2. Adjusted hazard ratios for the risk of mortality



Notes: hazard ratios (HR) and 95% confidence intervals (CI) are presented on a $\log_2$ scale

Key Points

Both time-updated VACS Index and nadir CD4 predicted mortality

In the combined model, only time-updated VACS Index remained independently associated with mortality

Conclusions

- Time-updated VACS Index provided better model fit than nadir CD4 alone or in a combined model with nadir CD4
- When both measures were entered in a combined model, nadir CD4 count was no longer predictive of either event
- Current health status, as determined by time-updated VACS Index, determined risk more than prior history, which was improved by biomarkers of organ injury

Clinical Implications

- Healthcare providers should consider using the VACS Index calculator (https://vacs.med.yale.edu/Calculator/) to assess the health status of their HIV+ patients

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