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Improved discrimination of mortality with Veterans Aging Cohort Study (VACS) Index 2.0 in HIV-positive individuals

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Running head: Improved risk index for people with HIV infection

ABSTRACT

Objective: Despite viral suppression and immune response on antiretroviral therapy (ART), people with HIV infection experience excess mortality compared to uninfected individuals. The Veterans Aging Cohort Study (VACS) Index incorporates clinical biomarkers of general health with age, CD4 count, and HIV-1 RNA to discriminate mortality risk in a variety of HIV positive populations. We asked whether additional biomarkers further enhance discrimination.

Design and Methods: Using patients from VACS for development and from the Antiretroviral Therapy Cohort Collaboration (ART-CC) for validation, we obtained laboratory values from a randomly selected visit from 2000-2014, at least one year after ART initiation. Patients were followed for 5-year, all-cause mortality through September 2016. We fitted Cox models with established predictors and added new predictors based on model fit and Harrell's c-statistic. We converted all variables to continuous functional forms and selected the best model (VACS Index 2.0) for validation in ART-CC patients. We compared discrimination using c-statistics and Kaplan-Meier plots.

Results: Among 28,390 VACS patients and 12,109 ART-CC patients, 7,293 and 722 died respectively. Nadir CD4, CD8, and CD4:CD8 ratio did not improve discrimination. Addition of albumin, white blood count (WBC), and body mass index (BMI), improved c-statistics in VACS from 0.776 to 0.805 and in ART-CC from 0.800 to 0.831. Results were robust in all 9 ART-CC cohorts, all lengths of follow-up and all subgroups .

Conclusion VACS Index 2.0, adding albumin, WBC, and BMI to version 1.0 and using continuous variables, provides improved discrimination and is highly transportable to external settings.

Key words: albumin, BMI, cohort study, comorbidity, mortality, prognostic index, validation

Introduction

With antiretroviral treatment (ART), people with HIV infection (PWH) typically achieve and maintain viral suppression, leading to increases in CD4 count. However their health remains compromised compared with demographically similar individuals without HIV [1-4]. Therefore, the traditional HIV biomarkers (CD4 count and HIV-1 RNA level) are necessary but not sufficient metrics of health status for clinical management and research. The Veterans Aging Cohort Study (VACS) Index, a validated, generalizable risk index [5], employs routine clinical data to provide a summary metric of overall disease burden. Higher scores indicate increasing risk of all-cause mortality as well as hospitalization [6], medical intensive care admission [6], cardiovascular disease [7], fragility fractures [8] and cognitive compromise [9, 10]. The original VACS Index (version 1.0) includes age, CD4, HIV-1 RNA and general health biomarkers (hemoglobin, alanine and aspartate transaminases, platelets, creatinine and hepatitis C virus [HCV] sero-status). Adding these general health biomarkers to an index restricted to age, CD4 and HIV-1 RNA substantially improved discrimination (c-statistic: 0.78 vs 0.72) [5]. The VACS Index is widely used in research for risk adjustment and as a clinical outcome. It is increasingly used in decision support tools available by website or app (https://vacs.med.yale.edu, https://www.mdcalc.com/veterans-aging-cohort-study-vacs-index), and in electronic health records.

As currently constructed, VACS Index 1.0 has limitations. First, it categorizes predictors to simplify calculation and interpretation, limiting its ability to detect small changes, which commonly occur in longitudinal observation of an individual patient. Second, while discrimination (how well those who die are distinguished from those who do not die) is better than other risk indices in common use [11-14] addition of new predictors might further improve discrimination. While we have demonstrated that blood pressure, cholesterol and smoking do not improve discrimination of mortality in VACS Index 1.0 [15], our clinical team suggested other variables

that have been shown to be associated with poor outcomes. These include: nadir CD4, CD8, CD4:CD8 ratio [16, 17], albumin [18-21], white blood count (WBC) or absolute neutrophil count (ANC) [22, 23], and body mass index (BMI) [24, 25].

We aimed to 1) develop an improved VACS Index (2.0) using data from United States (US) military veterans with HIV infection, 2) externally validate it using data from European and North American cohorts participating in the Antiretroviral Therapy Cohort Collaboration (ART-CC), and 3) evaluate its generalizability among important subgroups.

Methods

Development of VACS Index 2.0

We developed VACS Index 2.0 using patients from VACS, a cohort of all HIV-infected US military veterans in Veterans Health Administration (VA) care [26]. For this analysis, eligible patients were at least 18 years old, initiated ART between 1996 and 2014, and had a visit between 2000 and 2014. We excluded 2,782 individuals who had negative HCV RNA (at any time during the study period) after previously having detectable HCV RNA, because they may have received treatment for HCV infection or spontaneously cleared the virus. Few patients were treated prior to availability of direct acting antivirals (DAA) starting in 2014 and there is not yet long-term follow-up for those treated with DAAs. We obtained all laboratory values and BMI for a given individual for each visit date, at least one year after ART initiation. Values obtained prior to the visit date were allowed to carry forward for up to 180 days, resulting in complete information for 75% of visits. In sensitivity analysis, allowing values to carry forward for one year, 87% of visits had complete data. We randomly selected a visit date from among those with complete data to represent a typical patient in care. In addition to outpatient data, laboratory results obtained during hospitalization were included to provide a wider range of values. We only included one random day per hospitalization in the visit pool to avoid over-representation in

the sampled visit days. Patients were followed up to five years for, all-cause mortality until September 30, 2016. Ascertainment of deaths of VA patients is excellent [27, 28].

We first replicated the previously published VACS Index (1.0) by fitting a Cox model in the newly derived dataset using categorical predictors (age, CD4 count, HIV-1 RNA and laboratory measurements of hemoglobin, aspartate and alanine transaminases (AST, ALT), platelets, creatinine, and HCV status). Composite markers of liver and renal injury (FIB-4 and estimated glomerular filtration rate [eGFR] based on the CKDEPI equation) were calculated. FIB-4 (years of age×AST)/(platelets in 100/L×sqrt of ALT) is a validated indicator of liver fibrosis [29]. eGFR ($141\times\min(S_{Cr}/\kappa, 1)^{\alpha}\times\max(S_{Cr}/\kappa, 1)^{-1.209}\times0.993^{Age}\times1.018$ [if female]×1.159 [if black]; where κ=0.7 (females) or 0.9 (males); α=-0.329 (females) or -0.411 (males)); is a validated indicator of impaired renal function [30]. HCV infection status was based on detectable plasma HCV-RNA (85%) positive antibody test (10%) or documented diagnosis (5%). Once testing HCV positive, patients were assumed to remain positive (since we excluded treated patients). For comparison, we also modeled VACS Index 1.0 predictors as continuous vriables, as described below.

We then evaluated candidate variables for addition to the VACS Index 1.0 model, one at a time and in combination using Akaike's information criterion (AIC, lower is better) for model fit and Harrell's c-statistic (range 0.5 to 1.0, higher is better) for discrimination. This was done using categorical variables with 10-level categories for each predictor with equal number of deaths in each category. We fitted a Cox model and plotted coefficients of categorized variables by median of each category. Categories were refined to adequately assess shape of the curve, maintaining at least 100 deaths per level. Then we determined an appropriate continuous functional form for each variable including quadratic, cubic, and natural log terms to account for U-shaped or J-shaped associations. Extreme values were replaced with the 1st or 99th

percentile to avoid undue influence; most variables were centered at the median. Splines were used if a suitable polynomial form was not found. Once a candidate final model was developed, we left out one variable at a time and compared model fit and discrimination to see if any predictor could be dropped without affecting model fit and discrimination.

To create VACS Index scores, we used regression coefficients, estimated in this sample, for VACS Index 1.0 (original index, categorical variables) and VACS Index 2.0 (additional predictors, continuous variables). We applied regression equations to each patient using their individual lab values and the model coefficients to create linear predictors for each index, which were then scaled to create scores of approximately 0 to 100. To illustrate in a more clinically meaningful way, we calculated scores using a range of plausible values (between lowest and highest included in the model) for each predictor, while setting all others to the median. The magnitude of the ranges of scores showed which predictors had the largest association.

Validation of VACS Index 2.0

We validated VACS Index 2.0 using data from ART-CC (described in detail elsewhere [31]), an international collaboration that combines data on PWH from European and North American cohorts. Eligible cohorts contributed data on the laboratory values of interest and reported at least 40 deaths in such patients. These were the AIDS Therapy Evaluation Project Netherlands (ATHENA), Austrian HIV Cohort Study (AHIVCOS), Italian Cohort of Antiretroviral-Naive Patients (ICONA), Aquitaine Cohort (France), Swiss HIV Cohort Study (SHCS), VACH (Spain), South Alberta Clinical Cohort (Canada), Tennessee Center for AIDS Research Cohort (US), and the University of Washington HIV Cohort (US). The nine included cohorts were randomly assigned a letter from A through I for anonymity. Patients and laboratory values were selected using the same approach as described above for VACS patients, but without any limitation of values obtained during hospitalization (as hospitalization dates were not available at the time of this analysis). The proportion of visit dates with complete information varied between 5% and

82% by cohort. Those with linkage to an electronic health record (EHR) had the highest proportion with complete data. In sensitivity analysis we compared discrimination between cohorts with at least 50% completeness to those with less than 50% completeness.

Using VACS Index scores as predictors we compared performance in VACS and ART-CC (overall and by cohort). We evaluated discrimination using c-statistics, hazard ratios per 5-unit increase in VACS Index 2.0 score in Cox models, and Kaplan-Meier (KM) plots by decile of risk (customized for VACS and ART-CC so as to have equal number of deaths per decile). We evaluated discrimination at varying lengths of follow-up (30 days, 90 days, 6 months, 1, 2, 3, 4 and 5 years) using fixed weights from 5-year outcome models developed in VACS.

Performance across subgroups

Finally, development and validation datasets were combined to evaluate index performance in important patient subgroups [women; those with HIV-1 RNA<500 copies/mL; HCV co-infected patients; and low-risk patients defined according to conventional HIV indicators (age <50 years, CD4 ≥200 cells/mm^3 and HIV-1 RNA ≤500 copies/mL)]. Those not meeting criteria for low-risk were categorized as high-risk. We calculated c-statistics and calculated mortality rates in patients defined as low-risk and high-risk as a function of VACS Index 2.0 score.

We used SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) for all analyses, except that calculation of Harrell's c-statistic used Stata version 14 (Stata Corp., College Station, Texas, USA). Institutional review boards from each cohort approved analysis of routinely collected data.

Results

Half the randomly selected visit dates were in 2010 and later (Table 1). Among 28,390 VACS patients there were 7,293 deaths (7.2 per 100 person-years (PY)); 39% occurred in the first year of follow-up. Median time on ART as of the random visit date was 4.2 years; subsequent median follow-up was 4.1 years. Among 12,109 ART-CC patients there were 722 deaths (2.0 per 100 PY, ranging 1.2 to 4.5 by cohort); 44% occurred in the first year. Median time on ART was 4.2 years, median follow-up was 3.2 years. Compared to ART-CC, VACS patients were older (median 53 vs 43 years), more likely to be male (98% vs 74%) and more likely to have initiated ART before 1999 (Table 1). VACS patients were less likely than ART-CC patients to be virally suppressed (76% vs 88%) and be defined as low-risk (24% vs 60%).

In VACS (development) data, model fit and discrimination improved with addition of CD4:CD8 ratio, BMI, albumin and WBC, individually and in combination, compared to VACS Index 1.0 (Appendix Figure 1). However, removal of CD4:CD8 ratio from the candidate final model did not decrease performance so it was dropped. Prediction was not improved with addition of nadir CD4 or CD8 count. WBC and ANC were highly correlated (r = 0.87) and performed equally well, but WBC was more widely available. The final VACS Index 2.0, using all continuous variables, included all original variables (age, CD4 count, HIV-1 RNA, hemoglobin, FIB-4, eGFR, and HCV status) plus albumin, WBC, and BMI. Suitable polynomial forms were found for all variables except eGFR which was modeled using splines (Appendix Table 1). Extending last value carried forward time to one year provided <3% additional visit dates or deaths, and all estimates were similar to those obtained using 180 days in the main analysis.

When we calculated scores using a plausible range of values: age and albumin had the greatest influence. To illustrate, age 30 corresponds to 32 points and age 75 corresponds to 59 points, for a range of 27 points. An albumin value of 2.0 g/dl corresponds to 65 points and 5.0 g/dl corresponds to 39 points, for a range of 26 points (Appendix Table 2). CD4 count (10-900 cells/ul, 23 points), HIV-1 RNA (1.3-5.0 $\log_{10}$ copies/mL, 18 points), FIB4 (0.5-7.5, 20 points), BMI (15-35 kg/m^2, 20 points), hemoglobin (9-16 g/dl, 16 points), and eGFR (0-180 ml/min, 16

points) were also quite influential on total score. In contrast HCV (yes or no, 6 points) was the least influential, as in VACS Index 1.0.

VACS Index 2.0 scores were 10 points higher in VACS (median 51, interquartile range 39-66) than in ART-CC (41, 33-52), with little variation by cohort except for Cohort C (35, 27-46). Scores were approximately normally distributed, but slightly right skewed (means: 54 in VACS, 44 in ART-CC). With these risk scores as the sole predictor in Cox models, mortality hazard ratios associated with a 5-point increment of score were 1.31 (95% confidence interval [CI], 1.30-1.31) in VACS and 1.37 (1.35-1.39) in ART-CC with little variation by cohort (range 1.34 to 1.41) (Appendix Table 3). In VACS (development) data, the c-statistic increased from 0.779 (95% CI 0.774, 0.784) for VACS Index 1.0 to 0.786 (0.781, 0.791) using continuous predictor variables limited to VACS Index 1.0 predictors. The c-statistic further increased to 0.805 (0.800, 0.810) after addition of albumin, WBC, and BMI (VACS Index 2.0). Corresponding c-statistics in the ART-CC (validation) data were 0.800 (0.782, 0.818) for VACS Index 1.0; 0.808 (0.790, 0.825) for continuous VACS 1.0 predictors and 0.831 (0.814, 0.847) for VACS Index 2.0. C-statistics improved in all 9 ART-CC cohorts (Figure 1a). In cohorts with at least 50% completeness in the visit pool and in those with less than 50% completeness, the c-statistic was greater with VACS Index 2.0, with no separation in the confidence intervals comparing completeness. At all follow-up intervals VACS Index 2.0 had greater discrimination than VACS Index 1.0 (Figure 1b and 1c). As expected, c-statistics were greater for shorter follow-up times. Additionally, improvement from VACS Index 1.0 to 2.0 was greatest for shorter follow-up times.

Kaplan-Meier plots by decile of risk (Figure 2 and Appendix Table 4) for VACS showed better separation with VACS Index 2.0 compared to 1.0, especially in earlier years of follow-up. With VACS Index 1.0 deciles 6 and 7 overlapped until 1 year. With VACS Index 2.0 all deciles were distinct at about 6 months of follow-up. The range of 5-year survival for extreme deciles expanded from 13-92% with VACS Index 1.0 to 8-93% with VACS Index 2.0. More than 100 people were still under follow-up at five years for VACS Index 2.0 deciles 1-8. In the 9th decile

729/888 people had died by 5 years and 95 remained. In the 10th decile 399/811 people had died by 6 months, and 730 by 5 years, with 41 remaining.

In ART-CC, with only one-tenth as many deaths, the curves were less distinct, but still showed improvement with VACS Index 2.0 (Figure 2 and Appendix Table 4). The range of 5-year survival expanded from 35-97% with VACS Index 1.0 to 25-98% with VACS Index 2.0. Similar patterns were seen with 1-year survival. . More than 100 people were still under follow-up at five years in deciles 1-5. In the 9th decile 71/151 people had died by 5 years and 15 remained. In the 10th decile 44/114 people had died by 6 months, and 73 by 5 years, with 15 remaining. In both VACS and ART-CC median survival was less than a year for those in the highest VACS Index 2.0 decile. Based on the above findings we combined VACS and ART-CC data to look at subgroups.

In combined data, we found higher c-statistics for VACS Index 2.0 than VACS Index 1.0 for all subgroups (Figure 3): age <50(0.85, 0.83), age 50+ (0.79, 0.75), men (0.82, 0.79), women (0.84, 0.80), suppressed virus (0.82, 0.78), unsuppressed virus (0.77, 0.75), HIV mono-infected (0.82, 0.79) and HCV co-infected (0.75, 0.72) and patients defined as low-risk (0.79, 0.73) and high-risk (0.79, 0.76).

Mortality rates in both low-risk and high-risk patients had strong and similar associations with VACS Index 2.0 score (Figure 4).

Discussion

Compared with VACS Index 1.0, VACS Index 2.0 had better discrimination in development (VACS) and external validation (ART-CC) data. This was achieved by study design; treating all predictors as continuous; and adding albumin, WBC, and BMI. Improved discrimination was evident across a variety of clinically defined subgroups, varying length of follow-up and across ART-CC cohorts. Improved discrimination was evident beyond c-statistics. Compared to VACS

Index 1.0, Kaplan-Meier plots comparing deciles of VACS Index 2.0 showed better separation of mortality risk during the first 6-12 months of follow-up that persisted across the 5-year follow up. In both low-risk and high-risk patients there was a strong and consistent gradient of higher mortality with increasing score. Importantly, improved discrimination of VACS Index 2.0 is generalizable across clinically important subgroups and among individual cohorts and transportable to other settings [32].

Thus, VACS Index 2.0 can be used as a measure of disease burden for risk adjustment and/or as an outcome for clinical research. With automated calculation and risk interpretation by way of smartphone apps, online calculators, or decision support modules in EHRs, it can also be incorporated in medical decision making.

Generalizability of VACS Index 2.0 was likely enhanced by the design of the current study. Because we started follow-up from a randomly selected date, the index was designed around a typical patient in care, rather than optimizing for patients at some fixed point after initiating ART. We did not restrict to patients who were ART naïve at study entry. Including laboratory values obtained during hospitalization increased the range of severity of illness represented in the model development dataset.

Importantly, VACS Index 2.0 predictors are continuous, offering important advantages over the thresholds in VACS Index 1.0. For example, on the day a patient turns 50 the VACS Index 1.0 score increases by 12 points, translating to roughly 40% increased risk of mortality. While this increased risk is accurate in aggregate for those aged 50-64 years, it is not realistic for an individual to have such an abrupt change in risk. VACS Index 2.0 models this change in risk smoothly across ages. Thresholds used in VACS Index 1.0 limited investigator's ability to use the index as an outcome to detect change from baseline to end of observation. With the higher resolution provided by continuous variables more subtle changes in risk can be detected, enhancing suitability for longitudinal patient monitoring.

Addition of albumin, WBC, and BMI both enhanced discrimination of the VACS Index as a metric of mortality risk, and provided interesting insights. After age, albumin has become the single most important marker of general health in the model. Low serum albumin levels may be associated with multiple conditions that are related to HIV (e.g. poor nutritional status, inflammation, nephropathy, and liver disease). We suspect that albumin is particularly important as an added indication of liver disease, which is increasingly common among those aging with HIV. In VACS Index 1.0 liver injury was only ascertained with FIB-4 and an indicator for HCV infection. Albumin measures liver synthetic function thus enhancing detection of significant liver injury. We chose not to include hospitalization as a predictor in the index for several reasons. We want to use the VACS Index to predict future hospitalization. Second, hospitalization can be considered a downstream effect in the causal pathway between VACS Index components and subsequent death. As such, inclusion would obfuscate associations with the validated predictors. Finally, varying causes of hospitalization would have differential associations with mortality risk.

VACS Index 2.0 is a stronger predictor than the original. Despite having similar range of scores, the hazard ratio for 5-year, all-cause mortality increased from 1.221 (1.216-1.227) per 5 points with VACS Index 1.0, to 1.307 (1.300-1.314) per 5 points with VACS Index 2.0. VACS Index 2.0 is better able to identify very high-risk patients with as little as 6 months of follow-up, a time frame of concern to both clinicians and patients. In the 10th decile on the Kaplan-Meier plots, estimated 6-month survival in VACS patients decreased from 61% with VACS Index 1.0 to 51% with VACS Index 2.0. In ART-CC this change was 74% to 59%.

Interestingly, VACS Index 2.0 had higher discrimination in validation (ART-CC) than in development (VACS). This was also observed in our original validation of VACS Index 1.0 in ART-CC [5]. There are several possible explanations for this. First, the follow up time in ART-CC is shorter and, all else being equal, more proximal deaths are easier to predict than more distant deaths. Second, ART-CC subjects are younger and discrimination is slightly better

among those under 50 years of age. Finally, the index is not designed to detect risk of unnatural deaths, such as suicide, accident, or overdose. These deaths are more common in the military veteran population [33, 34].

A common problem in prognostic modelling is that some subgroups may be underrepresented in a development sample, such as women in VACS. Therefore, it is important to demonstrate that the index can discriminate well within these underrepresented but clinically important subgroups. We found superior discrimination with VACS Index 2.0 in all subgroups (including women) and among each of the nine participating cohorts in ART-CC. These observations offer strong evidence that improved discrimination of VACS Index 2.0 will generalize to new populations. It also suggests that the strong associations previously demonstrated with VACS Index 1.0 and biomarkers of inflammation [16, 35-37], hospitalization and medical intensive care unit admission [38], myocardial infarction [7], neurocognitive performance [9, 10], and fragility fractures [8, 39] will hold for VACS Index 2.0.

Improvement in discrimination was particularly large in cohort F, increasing from 0.790 (95% CI 0.744, 0.835) with VACS Index 1.0 to 0.873 (0.841, 0.906) with VACS Index 2.0. This cohort had one of the highest proportions of death in the first year of follow-up and did not supply race data, possibly resulting in under-estimation of eGFR. With addition of albumin to VACS Index 2.0, eGFR became a weaker predictor so the potential impact of this misclassification would have decreased. Furthermore only 5% of Cohort F patient visits had complete data, so only a small fraction of the entire cohort is included. The proportion with hemoglobin <12 is 23%, highest of all cohorts. Albumin, the least available lab, was only present for 12% of patients. Per the cohort principal investigator, “selecting people with both hemoglobin and albumin present will give a selection of people who are sicker than the rest of the cohort.” This assessment is supported by the finding that 40% of the deaths occurred in the first 6 months, 10% higher (absolute) than any other cohort, consistent with differentially sick

patients. As noted in Figure 1c, the increase from VACS Index 1.0 to 2.0 was greater for shorter follow-up times.

The original VACS Index has been increasingly used in a variety of research, public health, and clinical settings. As of August 1, 2018 the VACS Index Risk Calculator (link above) has been accessed >80,000 times since March of 2013 and most of these represent repeated use. The VACS Index has been used as a risk adjuster in observational studies [25, 40]. It is also useful in randomized clinical trials. Two NIH funded, alcohol intervention trials are underway which include the VACS Index as an outcome. The AIDS Clinical Trials Group has begun to use the VACS Index in randomized trials [41]. Independent groups are now using the VACS Index as a measure of frailty or severity of illness [10, 36, 37, 42-50]. In addition, the VACS Index is being used in public health surveillance. The Public Health-Seattle & King County, HIV/STD Program and the Washington State Department of Health use the VACS Index to monitor risk of mortality and burden of disease among PWH. Several health systems have incorporated the index as a patient management tool within their EHR. These include: Fenway Healthcare System in Boston; San Francisco General Hospital HIV Clinic and University of California, San Diego Owen Clinics. In Italy, the VACS Index is calculated on every patient seen at the University of Modena Metabolic Clinic. Providers use these data to target care to the sickest patients and in overall patient management. The modifications in VACS Index 2.0 will enhance its utility for all these applications.

An important limitation of VACS Index 2.0 is that we have not incorporated the prognostic implications of HCV cure. For this analysis, we excluded those who were treated for HCV from the development sample. In the validation sample most of the follow-up is before widespread availability of DAAs. But treatment of HCV may still have influenced our findings. In future work we hope to address this limitation once adequate mortality data are available among PWH successfully treated for HCV co-infection. Another limitation is that we could only consider

nadir CD4 as observed within the VA EHR and we cannot be sure it is truly the lowest CD4 cell count prior to ART initiation. However, this is likely more a limitation of the metric since lack of prior history can be a common problem when patients present to a new clinic for care. Missing data may also be a concern. We only randomly selected visit dates when patients had complete data within the prior 180 days. Nonetheless we found consistent results across all cohorts regardless of the proportion of visits with complete data. Finally, we have yet to conduct analyses determining the calibration of VACS Index 2.0. As with the original index, we plan to conduct this analysis in an even broader array of cohorts in the coming months.

In conclusion, VACS Index 2.0 is highly predictive of risk of all-cause mortality among those on treatment for HIV infection. With use of continuous variables it is now better suited to application for individual patients. With addition of parameters readily obtained during routine clinical practice it is more discriminating than the original VACS Index. Its superior discrimination is robust across development and validation sets, among important clinical subgroups, and among individual cohorts.

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J.P.T. performed the analysis and wrote the first draft.
A.C.J. and J.A.C.S. made major revisions.
All member of the writing group contributed to editing the manuscript and reviewed and approved the submission.

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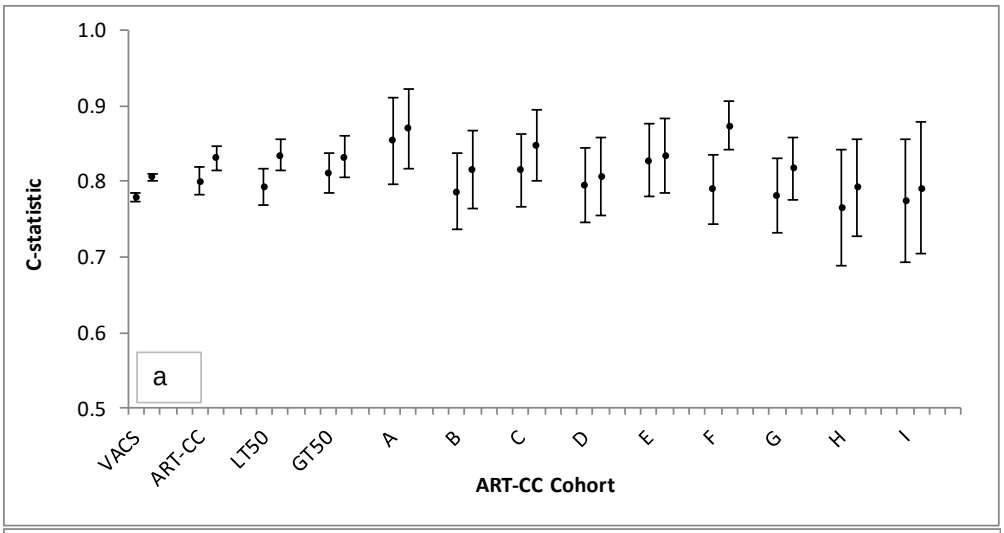
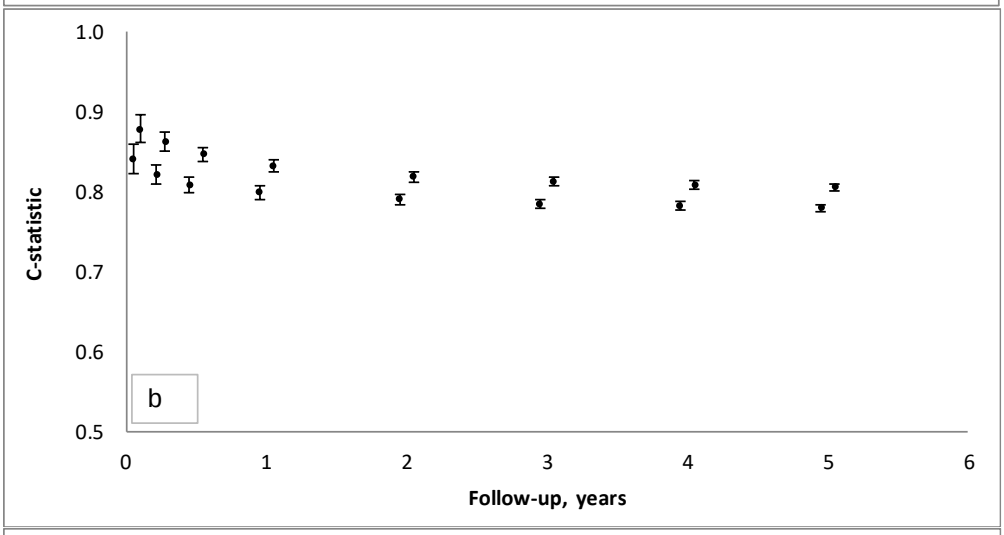
Table 1. Characteristics of patients at a randomly selected visit date between 2000 and 2014, after a minimum of 1 year of antiretroviral therapy, in the development sample (VACS) and validation sample (ART-CC).

	VACS (N = 28390)		ART-CC (N = 12109)	
Random visit date				
2000-2004	6587	(23)	1307	(11)
2005-2009	7753	(27)	4744	(39)
2010-2014	14050	(49)	6058	(50)
ART Initiation				
1996-1998	7929	(28)	1696	(14)
1999-2002	6454	(23)	3282	(27)
2003-2007	6510	(23)	3958	(33)
2008-2014	7497	(26)	3173	(26)
Years on ART				
Median (IQR)	4.2	(2.2-7.6)	4.2	(2.2-7.4)
Age (years)				
Median (IQR)	52	(46-59)	43	(36-49)
Male	27696	(98)	8972	(74)
Race				
White	11576	(41)	6840	(56)
Black	13722	(48)	1403	(12)
Hispanic	2225	(8)	255	(2)
Other/unknown	867	(3)	3611	(30)
CD4 cell count (cells/ul)				
Median (IQR)	435	(249-643)	500	(335-690)
HIV-1 RNA <= 500 copies/mL				
	21561	(76)	10650	(88)
Hemoglobin (g/dl)				
Median (IQR)	14.0	(12.8-15.1)	14.3	(13.0-15.3)
FIB-4				
<1.45	15782	(56)	8994	(74)
1.45-3.25	9722	(34)	2459	(20)
>3.25	2886	(10)	656	(5)
eGFR (ml/min)				
Median (IQR)	90	(73-105)	101	(87-113)
Hepatitis C infection	5523	(19)	1803	(15)
Albumin (g/dl)				
Median (IQR)	4.0	(3.7-4.3)	4.3	(4.0-4.5)
White blood count (k/ml)				
Median (IQR)	5.5	(4.3-6.9)	5.8	(4.7-7.2)
Body mass index, kg/m^2				
Median (IQR)	25.3	(22.4-28.7)	24.2	(21.7-27.2)
Low-risk*	6907	(24)	7303	(60)

*Age <50 years, CD4 >= 200, and HIV-1 RNA <= 500





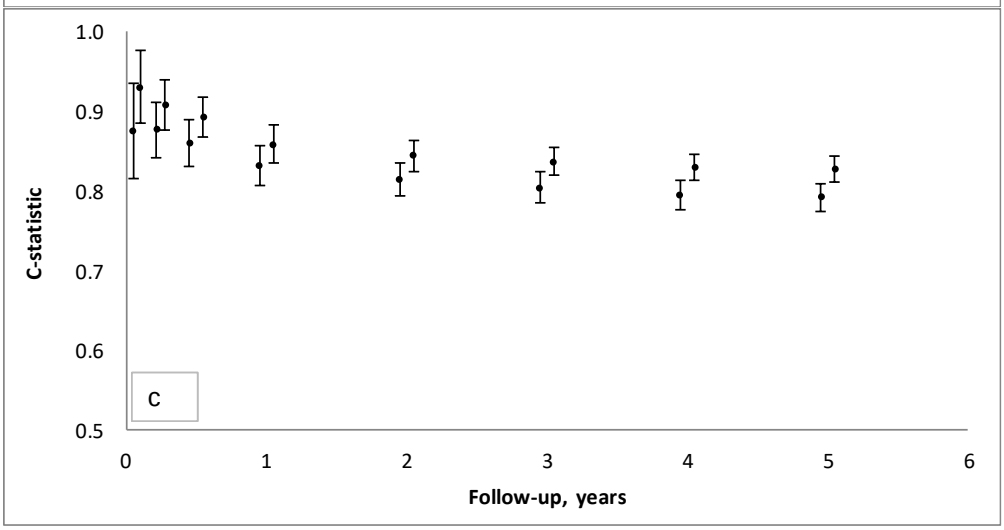
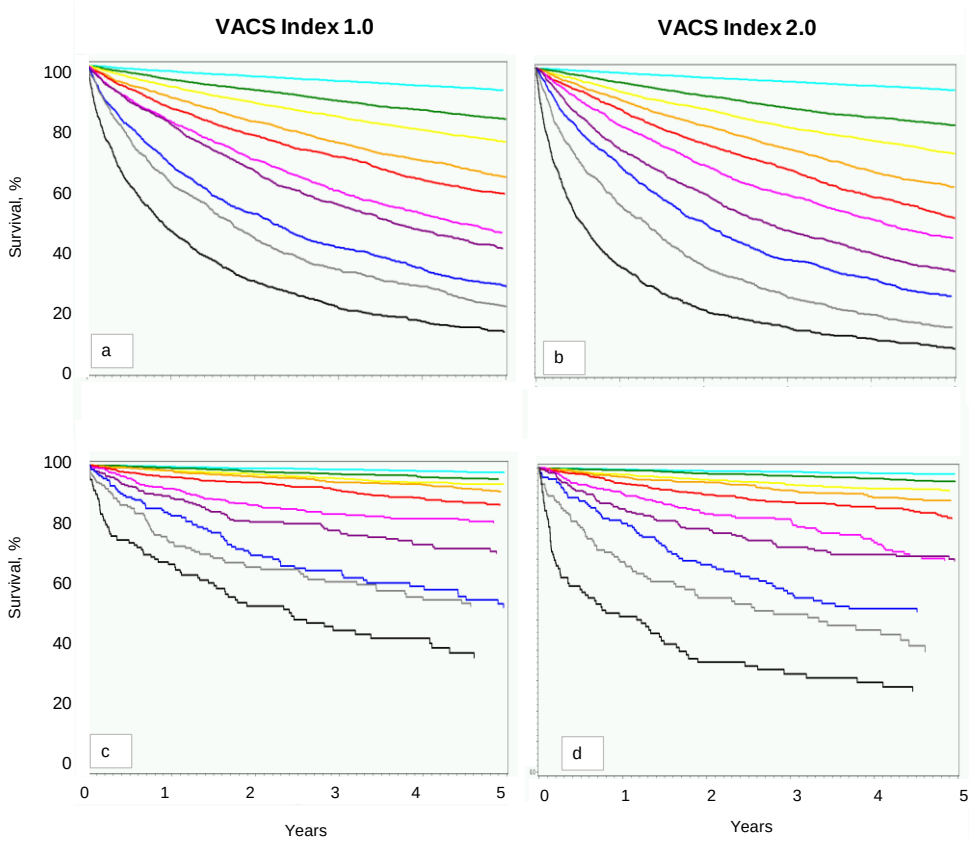


Figure 1. Discrimination of 5-year, all-cause mortality, for VACS Index 1.0 (left) and VACS Index 2.0 (right): a. VACS, ART-CC and individual ART-CC cohorts. LT50 = ART-CC, complete data available for less than 50% of eligible, GE50= ART-CC, complete data available for at least 50% of eligible; b. VACS; c. ART-CC



	One-year survival VACS Index		Five-year survival VACS Index	
Decile	1.0	2.0	1.0	2.0
1	98%	99%	92%	93%
2	95%	95%	82%	81%
3	93%	92%	75%	72%
4	90%	90%	63%	61%
5	86%	87%	58%	51%
6	82%	81%	45%	44%
7	81%	73%	40%	33%
8	68%	68%	28%	25%
9	62%	55%	21%	15%
10	46%	35%	13%	8%
1	99%	99%	97%	98%
2	99%	99%	95%	95%
3	98%	98%	94%	92%
4	98%	97%	91%	89%
5	96%	95%	87%	83%
6	92%	91%	81%	69%
7	89%	86%	71%	69%
8	83%	81%	53%	52%
9	74%	69%	52%	37%
10	67%	51%	35%	25%

Figure 2. Kaplan-Meier plots for all-cause mortality by decile of risk according to VACS Index 1.0 and VACS Index 2.0, in development sample, VACS (a and b) and validation sample, ART-CC (c and d). Further detail available in Appendix Table 4.

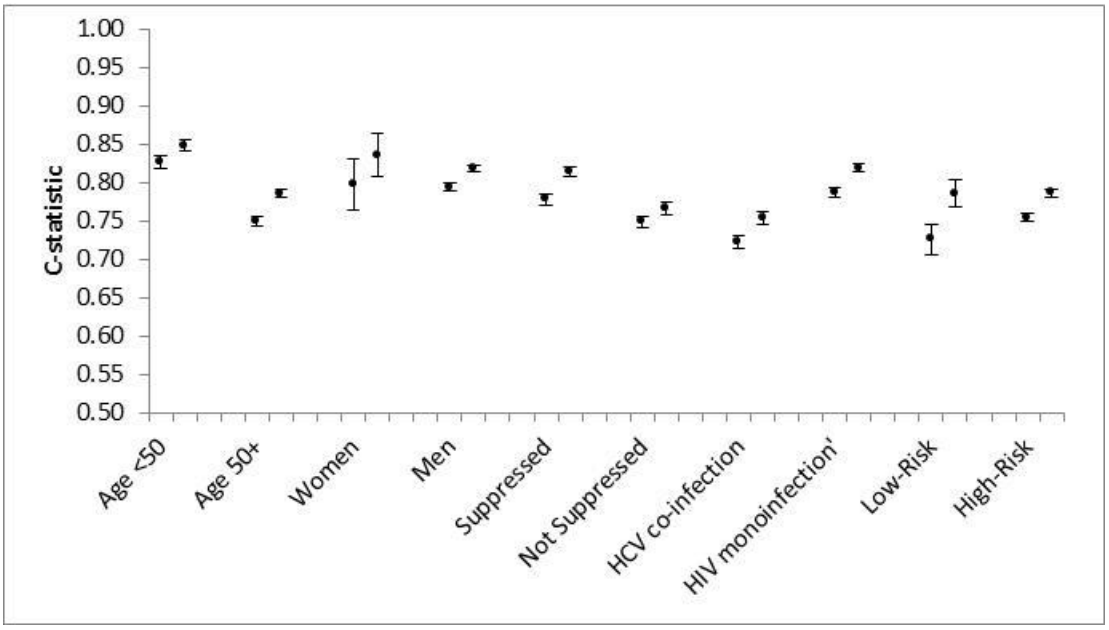


Figure 3. Discrimination of 5-year, all-cause mortality, for VACS Index 1.0 (left) and VACS Index 2.0 (right), in combined VACS and ART-CC data subgroups. Low-Risk = age <50 years, CD4 count $\geq$ 200 cells/μl, andHIV-RNA $\leq$ 500 copies/mL. High-Risk = all others.

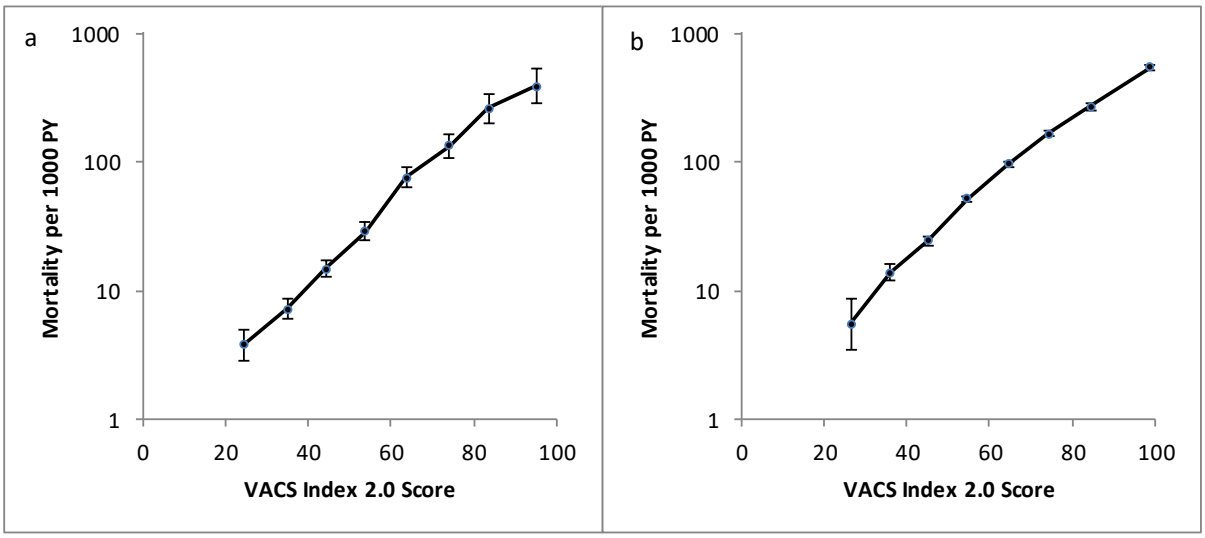


Figure 4. All-cause mortality rates during 5 years of follow-up by VACS Index 2.0 score. a. Low risk patients (age <50 years, CD4 ≥200 cells/ml, HIV-1 RNA ≤500 copies/mL), b. High risk patients (all others).

Appendix Table 1. VACS Index 2.0 Cox proportional hazards model, for 5-year, all-cause mortality, estimated in Veterans Aging Cohort Study, varying length of last value carried forward (LVCF)..

	Main analysis LVCF 180 days					Sensitivity LVCF 1 year				
N	28390					28830				
deaths	7293					7479				
Parameter	PE	SE	χ^2	p	HR (95% CI)	PE	SE	χ^2	p	HR (95% CI)
Age (years), censored at 30-75, centered at (age-50)										
X	0.056	0.012	22	<.0001	1.06 (1.03-1.08)	0.058	0.012	24	<.0001	1.06 (1.04-1.09)
X^2	-0.004	0.004	2	0.22	1.00 (0.99-1.00)	-0.006	0.004	3	0.11	0.99 (0.99-1.00)
X^3	0.005	0.001	29	<.0001	1.01 (1.00-1.01)	0.005	0.001	30	<.0001	1.01 (1.00-1.01)
CD4 cell count (cells/ml), censored at 0-1000, as ln (1000-CD4)										
X	-0.056	0.025	5	0.03	0.95 (0.90-0.99)	-0.048	0.025	4	0.05	0.95 (0.91-1.00)
X^2	-0.153	0.023	46	<.0001	0.86 (0.82-0.90)	-0.149	0.023	43	<.0001	0.86 (0.82-0.90)
X^3	0.024	0.002	94	<.0001	1.02 (1.02-1.03)	0.023	0.002	86	<.0001	1.02 (1.02-1.03)
HIV-1 RNA (log copies/ml), censored at 1.3- 5.0, centered at (logVL - 2)										
X	0.513	0.033	247	<.0001	1.67 (1.57-1.78)	0.518	0.032	257	<.0001	1.68 (1.58-1.79)
X^2	-0.422	0.041	109	<.0001	0.66 (0.61-0.71)	-0.412	0.040	106	<.0001	0.66 (0.61-0.72)
X^3	0.098	0.011	77	<.0001	1.10 (1.08-1.13)	0.095	0.011	73	<.0001	1.10 (1.08-1.12)
Hemoglobin (g/dl), censored at 9-16, centered at (14 - hemoglobin)										
X	-0.134	0.011	141	<.0001	0.88 (0.86-0.89)	-0.132	0.011	142	<.0001	0.88 (0.86-0.90)
X^2	0.026	0.006	16	<.0001	1.03 (1.01-1.04)	0.026	0.006	17	<.0001	1.03 (1.01-1.04)
X^3	0.005	0.001	10	0.002	1.01 (1.00-1.01)	0.004	0.001	10	0.002	1.00 (1.00-1.01)
FIB-4, censored at .5 -7.5										
X	0.220	0.028	62	<.0001	1.25 (1.18-1.32)	0.213	0.028	59	<.0001	1.24 (1.17-1.31)
X^2	-0.009	0.003	7	0.008	0.99 (0.99-1.00)	-0.008	0.003	7	0.0106	0.99 (0.99-1.00)
eGFR (ml/min), censored at 0-180,*										
X1	-0.031	0.028	1	0.28	0.97 (0.92-1.03)	-0.014	0.028	0	0.61	0.99 (0.93-1.04)
X2	-0.077	0.045	3	0.0917	0.93 (0.85-1.01)	-0.107	0.045	6	0.0174	0.90 (0.82-0.98)
X3	0.106	0.027	16	<.0001	1.11 (1.06-1.17)	0.131	0.026	25	<.0001	1.14 (1.08-1.20)
X4	0.133	0.034	15	0.0001	1.14 (1.07-1.22)	0.093	0.033	8	0.0054	1.10 (1.03-1.17)
Hepatitis C co-infection										
Yes	0.342	0.028	147	<.0001	1.41 (1.33-1.49)	0.350	0.028	160	<.0001	1.42 (1.35-1.50)
Albumin (g/dl), censored at 2-5, centered at (albumin - 4)										
X	-0.443	0.034	165	<.0001	0.64 (0.60-0.69)	-0.467	0.034	189	<.0001	0.63 (0.59-0.67)
X^2	0.104	0.051	4	0.04	1.11 (1.00-1.23)	0.141	0.050	8	0.01	1.15 (1.04-1.27)
X^3	0.028	0.027	1	0.30	1.03 (0.98-1.08)	0.055	0.026	4	0.04	1.06 (1.00-1.11)
White blood count (k/ml), censored at 2.5-11, centered at (WBC - 5.5)										
X	0.126	0.011	130	<.0001	1.13 (1.11-1.16)	0.125	0.011	132	<.0001	1.13 (1.11-1.16)
X^2	0.020	0.004	30	<.0001	1.02 (1.01-1.03)	0.021	0.004	35	<.0001	1.02 (1.01-1.03)
X^3	-0.004	0.001	23	<.0001	1.00 (0.99-1.00)	-0.005	0.001	27	<.0001	1.00 (0.99-1.00)
Body mass index, kg/m2, censored at 15-35, centered at (BMI - 25)										
X	-0.055	0.003	388	<.0001	0.95 (0.94-0.95)	-0.055	0.003	407	<.0001	0.95 (0.94-0.95)
X^2	0.004	0.000	62	<.0001	1.00 (1.00-1.01)	0.004	0.000	62	<.0001	1.00 (1.00-1.00)

*X1 = eGFR/10, X2 = (eGFR-35)/10, X3 = (eGFR-65)/10, X4 = (eGFR-115)/10.

Appendix Table 2. Range of plausible values and associated VACS Index 2.0 score, setting all other predictors to their median value.

Predictor	Median	Range of plausible values*									
Age (years)											
Value	52	30	35	40	45	50	55	60	65	70	75
Score	**	32	38	41	43	44	45	47	49	53	59
CD4 cell count (cells/ml)											
Value	435	10	100	200	300	400	500	600	700	800	900
Score	**	55	53	51	48	45	43	40	37	34	32
HIV-1 RNA (log copies/mL)											
Value	1.7	1.3	1.5	1.8	2.0	2.5	3.0	3.5	4.0	4.5	5
Score	**	37	41	46	48	51	52	51	50	51	55
Hemoglobin (g/dl)											
Value	14	9	9.5	10	10.5	11	12	13	14	15	16
Score	**	58	58	57	55	54	51	47	44	42	42
FIB-4											
Value	1.34	0.50	1.00	1.45	2.00	3.25	4.00	5.00	6.00	7.00	7.50
Score	**	41	43	45	47	51	53	56	58	60	61
eGFR (ml/min)											
Value	90	0	20	40	60	80	100	120	140	160	180
Score	**	53	51	49	45	44	44	46	51	55	60
Hepatitis C co-infection											
Value	No	Yes									
Score	**	51									
Albumin (g/dl)											
Value	4	2.00	2.25	2.50	2.75	3.00	3.25	3.5	4.00	4.50	5.00
Score	**	65	62	59	57	54	52	49	44	41	39
White blood count (k/ml											
Value	5.5	2.5	3	4	5	6	7	8	9	10	11
Score	**	43	42	42	43	46	49	51	54	55	55
Body mass index (kg/m2)											
Value	25.3	15	17	18	20	22	24	26	28	30	35
Score	**	62	57	55	51	48	46	44	42	41	41

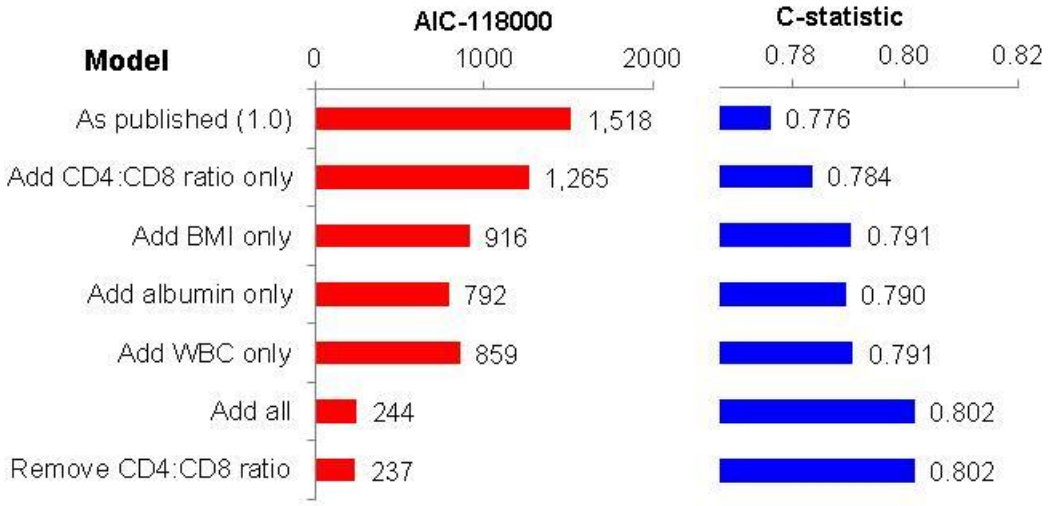
* Clinically meaningful values between lowest and highest values used in development model.
**Score = 44 when all values are set to their median and Hepatitis C is set to no.

Appendix Table 3. Number at risk, number of deaths, distribution of VACS Index 2.0 scores, and all-cause mortality hazard ratio (HR) per 5 points, in the development sample (VACS) and validation sample (ART-CC), overall and by individual cohort (A-I).

			VACS Index 2.0 Score					Risk of all-cause mortality, per 5 points	
	N	Deaths	Median	25th	75th	1st	99th	HR	(95% CI)
VACS	28,390	7,293	51	39	66	15	111	1.31	(1.30-1.31)
ART-CC	12,109	722	41	33	52	14	97	1.37	(1.35-1.39)
A	1,011	40	41	31	52	14	91	1.41	(1.32-1.52)
B	944	95	42	34	53	17	98	1.38	(1.31-1.44)
C	1,872	112	35	27	46	11	93	1.37	(1.32-1.42)
D	1,509	78	44	36	54	18	89	1.38	(1.31-1.45)
E	863	73	42	33	54	15	104	1.34	(1.28-1.41)
F	1,899	111	42	34	53	17	102	1.38	(1.33-1.43)
G	2,231	120	42	34	54	16	94	1.40	(1.34-1.46)
H	891	53	44	34	54	19	103	1.34	(1.27-1.42)
I	889	40	41	33	50	17	95	1.40	(1.30-1.51)

Appendix Table 4. Number at risk, number of deaths, distribution of VACS Index 2.0 scores, and all-cause mortality hazard ratio (HR) per 5 points, in the development sample (VACS) and validation sample (ART-CC), overall and by individual cohort (A-I).

		30 days			6 months			1 year			5 years		
	N	Died	Survival	Left	Died	Survival	Left	Died	Survival	Left	Died	Survival	Left
VACS sample													
Overall	28390	348			1706			2833			7293		
Decile													
VACS Index 1.0													
1	10646	12	100%	10634	113	99%	10533	199	98%	10447	732	92%	5247
2	4763	17	100%	4745	109	98%	4653	220	95%	4543	737	82%	2325
3	3249	21	99%	3228	122	96%	3127	225	93%	3023	723	75%	1469
4	2239	27	99%	2211	141	94%	2097	233	90%	2005	737	63%	898
5	1864	28	98%	1835	140	92%	1722	260	86%	1603	718	58%	700
6	1449	29	98%	1419	157	89%	1291	264	82%	1185	729	45%	427
7	1268	30	98%	1237	148	88%	1119	242	81%	1026	716	40%	353
8	1083	45	95%	1033	215	80%	867	351	68%	731	743	28%	204
9	962	41	96%	920	226	76%	733	370	62%	592	728	21%	137
10	867	98	88%	763	335	61%	531	469	46%	398	730	13%	64
VACS Index 2.0													
1	12381	10	100%	12371	100	99%	12281	185	99%	12196	729	93%	5586
2	4275	16	100%	4259	96	98%	4179	196	95%	4079	729	81%	2324
3	2853	24	99%	2827	105	96%	2747	220	92%	2633	730	72%	1405
4	2029	14	99%	2014	108	95%	1919	207	90%	1821	730	61%	878
5	1597	23	99%	1573	116	93%	1480	213	87%	1383	729	51%	593
6	1391	19	99%	1371	140	90%	1249	260	81%	1130	729	44%	437
7	1149	19	98%	1128	175	85%	974	305	73%	844	729	33%	279
8	1016	35	96%	979	203	80%	812	324	68%	691	729	25%	183
9	888	61	93%	827	264	70%	623	397	55%	491	729	15%	95
10	811	127	84%	678	399	51%	411	526	35%	285	730	8%	41
ART-CC sample													
Overall	12109	47			192			318			722		
Decile													
VACS Index 1.0													
1	4824	2	100%	4789	10	100%	4443	23	99%	3915	72	97%	1398
2	2087	1	100%	2065	8	100%	1928	19	99%	1745	64	95%	694
3	1824	5	100%	1800	16	99%	1688	31	98%	1539	82	94%	610
4	1148	1	100%	1138	10	99%	1057	20	98%	960	68	91%	394
5	824	2	100%	816	20	97%	739	31	96%	670	75	87%	258
6	492	4	99%	485	21	95%	428	35	92%	376	72	81%	149
7	362	7	98%	350	24	93%	300	36	89%	254	73	71%	82
8	206	4	98%	202	21	89%	169	32	83%	141	71	53%	39
9	196	9	95%	186	26	86%	153	46	74%	120	72	52%	43
10	146	12	91%	130	36	74%	97	45	67%	78	73	35%	19
VACS Index 2.0													
1	5838	1	100%	5785	10	100%	5356	27	99%	4662	73	98%	1559
2	2397	1	100%	2379	10	100%	2224	16	99%	2051	72	95%	865
3	1247	3	100%	1240	14	99%	1169	26	98%	1070	72	92%	489
4	884	1	100%	876	12	99%	812	24	97%	755	71	89%	335
5	618	4	99%	609	12	98%	557	29	95%	501	73	83%	197
6	359	1	100%	355	19	94%	305	28	91%	267	73	69%	83
7	311	3	99%	302	22	92%	255	38	86%	213	72	69%	84
8	190	6	97%	182	20	89%	159	33	81%	133	72	52%	46
9	151	11	92%	139	29	80%	109	44	69%	88	71	37%	15
10	114	16	85%	95	44	59%	61	53	51%	47	73	25%	15



Appendix Figure 1. Model development in VACS Cohort comparing model fit using Akaike's information criterion (AIC) and discrimination using Harrell's c-statistic