An internationally generalizable risk index for mortality after one year of antiretroviral therapy

Janet P. Tate[a], Amy C. Justice[a], Michael D. Hughes[b], Fabrice Bonnet[c], Peter Reiss[d], Amanda Mocroft[e], Jacob Nattermann[f], Fiona C. Lampe[e], Heiner C. Bucher[g], Timothy R. Sterling[h], Heidi M. Crane[i], Mari M. Kitahata[j], Margaret May[k] and Jonathan A.C. Sterne[k]

Objective: Despite the success of antiretroviral therapy (ART), excess mortality continues for those with HIV infection. A comprehensive approach to risk assessment, addressing multiorgan system injury on ART, is needed. We sought to develop and validate a practical and generalizable mortality risk index for HIV-infected individuals on ART.

Design and methods: The Veterans Aging Cohort Study (VACS) was used to develop the VACS Index, based on age, CD4 cell count, HIV-1 RNA, hemoglobin, aspartate and alanine transaminase, platelets, creatinine and hepatitis C status, and a Restricted Index based on age, CD4 cell count and HIV-1 RNA with an outcome of death up to 6 years after ART initiation. Validation was in six independent cohorts participating in the ART Cohort Collaboration (ART-CC).

Results: In both the development (4932 patients, 656 deaths) and validation cohorts (3146 patients, 86 deaths) the VACS Index had better discrimination than the Restricted Index (c-statistics 0.78 and 0.72 in VACS, 0.82 and 0.78 in ART-CC). The VACS Index also demonstrated better discrimination than the Restricted Index for HIV deaths and non-HIV deaths, in men and women, those younger and older than 50 years, with and without detectable HIV-1 RNA, and with or without HCV coinfection.

Conclusions: Among HIV-infected patients treated with ART, the VACS Index more accurately discriminates mortality risk than traditional HIV markers and age alone. By accounting for multiorgan system injury, the VACS Index may prove a useful tool in clinical care and research.

AIDS 2013, **27**:563–572

Keywords: anemia, cohort study, comorbidity, FIB-4, HIV, mortality, prognostic index

Introduction

Among HIV-infected individuals on antiretroviral therapy (ART), AIDS-defining events are rare [1,2], and HIV-1 RNA is often undetectable. Yet compared with behaviorally and demographically similar controls, excess mortality in these individuals remains and is not explained by CD4 cell count alone [3,4]. The Strategies

[a]Yale University School of Medicine and the Veterans Affairs Healthcare System, West Haven, Connecticut, [b]Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, USA, [c]Université Bordeaux, ISPED, Centre Inserm U897-Epidemiologie-Biostatistique, Bordeaux, France, [d]Division of Infectious Diseases and Department of Global Health, Amsterdam Institute for Global Health and Development, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [e]Research Department of Infection and Population Health, UCL Medical School, London, UK, [f]Department of Internal Medicine, University of Bonn, Germany, [g]Basel Institute for Clinical Epidemiology & Biostatistics, University Hospital Basel, Basel, Switzerland, [h]Department of Medicine, Vanderbilt University, Nashville, Tennessee, [i]Clinical Epidemiology and Health Services Research Core, Center for AIDS Research, [j]Department of Medicine, University of Washington, Seattle, Washington, USA, and [k]Department of Social Medicine, University of Bristol, Bristol, UK.

Correspondence to Janet P. Tate, ScD, VA Connecticut Health Systems, 950 Campbell Avenue, West Haven, CT 06516, USA.
Tel: +1 203 932 5711 X 5371; fax: +1 203 937 4926; e-mail: Janet.Tate2@va.gov
Received: 21 June 2012; revised: 10 October 2012; accepted: 16 October 2012.

DOI:10.1097/QAD.0b013e32835b8c7f

for Management of Anti-Retroviral Therapy trial [5] and observational studies [6,7] suggest that HIV-associated inflammation, hypercoagulability, and increased risk of aging-associated organ system injury may contribute to this excess. To monitor patients in care, and identify potentially modifiable risk factors, we need to consider biomarkers beyond traditional measures of HIV disease progression in overall risk estimation.

Although a number of novel biomarkers have been considered [5,6,8], it is sensible to begin by considering the information gained from routine clinical data [9]. In addition to regular measurements of CD4 cell count and HIV-1 RNA, current guidelines recommend screening for hepatitis C, and frequent monitoring of hemoglobin, platelets, aspartate and alanine transaminases, and creatinine [10,11]. These measures are associated with all-cause mortality, after adjustment for CD4 cell count and HIV-1 RNA [12–15], and correlated with biomarkers of inflammation [7]. At the time of ART initiation, a composite index incorporating these measures predicts mortality more accurately than one restricted to CD4 cell count, HIV-1 RNA, and age [16].

However, because most patients will be on ART for extended periods, an on-treatment index is much more relevant to health professionals and HIV-positive people, for evaluating prognosis after starting treatment. The previously reported relationships between biomarkers and mortality may differ once treatment is established. It is also important to evaluate the stability of the on-treatment weightings with increasing length of time on ART. In addition, validation in an external cohort, is a critical step in prognostic model development, particularly when the development cohort is restricted to male veterans.

Therefore, we refined our original model [16] to create the Veterans Aging Cohort Study (VACS) Risk Index, designed to predict mortality in HIV patients who have been treated for 1 year, and devised a simple scoring system. The VACS Index was developed in HIV-infected US veterans and validated in independent cohorts from the United States and Europe participating in the Antiretroviral Therapy Cohort Collaboration (ART-CC). We also evaluated discrimination of the index by cause of death and in important patient subgroups.

Methods

The ART-CC, described in detail elsewhere [17,18], is an international collaboration that combines data on HIV-infected individuals, who were antiretroviral-naive when they started ART, from participating cohorts in Europe and North America. Here, eligible patients were HIV-infected, age at least 18 years, who initiated ART between 2000 and 2007. All had CD4 cell count measured in the 3 months before ART initiation, and HIV-1 RNA more than 500 copies/ml in the same period. Included cohorts [VACS; the AIDS Therapy Evaluation Project Netherlands (ATHENA); Cologne-Bonn Cohort, Germany; Royal Free Hospital Cohort, London United Kingdom; Swiss HIV Cohort Study; Vanderbilt-Meharry Center for AIDS Research Cohort; and the University of Washington HIV Cohort, Seattle, USA] contributed data on all biomarkers of interest for at least 60% of patients (when routinely collected), and reported at least 25 deaths in such patients. Institutional review boards from each cohort approved analysis of routinely collected data.

Prognostic indices were developed using data from men in VACS, a cohort of more than 33 000 HIV-infected veterans for whom data on inpatient and outpatient diagnoses, laboratory results and pharmacy fills are obtained from the time the patient is first identified within the Veterans Administration as having HIV infection [17]. VACS includes all HIV-infected veterans in Veterans Administration care, and ascertainment of deaths is excellent [19,20]. Indices were validated in the remaining six cohorts. Development and validation datasets were combined to evaluate index performance within important patient subgroups [women, those with HIV-1 RNA <500 copies/ml, and hepatitis C (HCV) coinfected patients]. We refer to these three datasets as 'VACS', 'ART-CC' (meaning ART-CC without VACS data), and 'combined'.

We adapted our original prognostic model [16] for use in patients after 1 year of ART. To be included, predictors should be as follows: first, be widely available in clinical practice and research databases; second, be accurately and reliably measured; third, predict mortality and show a net reclassification improvement when added to an existing model. We dropped AIDS events because they are increasingly rare among those on ART [2] and the effect on subsequent risk of death varies widely by condition [1], alcohol/drug abuse because there are no standard measures for these conditions and hepatitis B infection because it is not collected in many research databases and is often correlated with HCV infection. We also considered whether to add IDU and sex, and whether to keep age. The final model is based on nine quantifiable measures.

Prognostic factors used in the VACS index include age, CD4 cell count, HIV-1 RNA and laboratory measurements of hemoglobin, aspartate and alanine transaminase (AST, ALT), platelets, creatinine and HCV status. Composite markers of liver and renal injury [FIB-4 and estimated glomerular filtration rate (eGFR)] are computed. FIB-4, composed of AST, ALT, platelets and age, is a validated indicator of liver fibrosis [FIB-4 = (years of age $\times$ AST)/(platelets in 100/l $\times$ sqrt of ALT)] [21]. eGFR, based on the Modification of

Table 1. Characteristics after 1 year of antiretroviral therapy of 4932 HIV-infected male veterans and 3146 HIV-infected patients from six other cohorts who initiated antiretroviral therapy between 2000 and 2007.

	VACS ($N=4932$) N (%)	ART-CC ($N=3146$) N (%)
Year of ART initiation		
2000–2003	2752 (56)	1350 (43)
2004–2007	2180 (44)	1796 (57)
Sex		
Male	4932 (100)	2271 (72)
Race		
White	1282 (26)	1586 (50)
Black	2241 (45)	592 (19)
Other/unknown	1409 (29)	968 (31)
Age (years)		
<50	2660 (54)	2687 (85)
50–64	2030 (41)	406 (13)
≥65	242 (5)	53 (2)
Median (IQR)	49 (43–55)	39 (33–45)
CD4 cell count (cells/μl)		
≥500	1079 (22)	905 (29)
350–499	1032 (21)	896 (28)
200–349	1284 (26)	860 (27)
100–199	841 (17)	366 (12)
50–99	309 (6)	63 (2)
<50	387 (8)	56 (2)
Median (IQR)	307 (166–473)	385 (258–524)
HIV-1 RNA (copies/ml)		
<500	3206 (65)	2735 (87)
$500–1\times10^5$	1358 (28)	338 (11)
$\geq1x10^5$	368 (7)	73 (2)
Median (IQR)	400 (50–4406)	50 (40–51)
Hemoglobin (g/dl)		
≥14	2421 (49)	1517 (48)
12–13.9	1899 (39)	1204 (38)
10–11.9	499 (10)	356 (11)
<10	113 (2)	69 (2)
Median (IQR)	13.9 (12.8–14.9)	13.9 (12.7–14.9)
FIB-4		
<1.45	3102 (63)	2646 (84)
1.45–3.25	1429 (29)	434 (14)
>3.25	401 (8)	66 (2)
Median (IQR)	1.2 (0.9–1.8)	0.9 (0.7–1.2)
eGFR (ml/min)		
≥60	4505 (91)	3073 (98)
45–59.9	242 (5)	49 (2)
30–44.9	69 (1)	12 (0)
<30	116 (2)	12 (0)
Median (IQR)	93 (77–109)	101 (88–117)
Hepatitis C infection	1555 (32)	371 (12)

ART-CC, Antiretroviral Therapy Cohort Collaboration; ALT, alanine transaminase; AST, aspartate transaminase; ART, antiretroviral therapy; eGFR, estimated glomerular filtration rate; IQR, interquartile range; Hepatitis C: diagnosis, positive antibody test or detectable virus; VACS, Veterans Aging Cohort Study. FIB-4: (years of age × AST)/(platelets in 10^9/l × square root of ALT). eGFR: 186.3 × (serum creatinine $^{-1.154}$) × (age $^{-0.203}$) × (0.742 for women) × (1.21 if black). $P<0.001$ for comparison of veterans and ART-CC by category for all but hemoglobin, $P=0.39$.

Diet in Renal Disease equation, [$eGFR = 186.3 \times (\text{creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ for women}) \times (1.21 \text{ if Black})$] is a validated indicator of impaired renal function [22]. HCV infection status was based on documented diagnosis, a positive antibody test or detectable plasma HCV-RNA. Once tested, patients were assumed to remain either positive or negative. For comparison, we created a Restricted Index that included only age and conventional HIV risk factors (CD4 cell count and HIV-1 RNA). Each prognostic factor was categorized into levels for ease of subsequent application in clinical settings (Table 1). The number of categories of CD4 cell count, HIV-1 RNA, anemia and renal function were expanded compared with previous analyses [16]. We considered using predictors as continuous measures. Although there was a slight increase in discrimination, we chose to maintain the simplicity and transparency of categorical measures, as the continuous model required multiple transformations and quadratic terms.

Cause of death (COD) was classified as HIV related, non-HIV related, and unnatural (includes accidental and violent). VACS recently obtained underlying cause of death from death certificates coded by the National Death Index according to International Classification of Diseases, Tenth Revision (ICD-10). Unnatural deaths (ICD-10 categories V, W, X, Y; and codes F10, F11, F14, F19) included homicide, suicide, and substance abuse. HIV deaths were ICD-10 B20-B24. All other deaths with known cause were classified as non-HIV. In ART-CC, deaths were classified based both on ICD codes and on relevant clinical information, using the code classification system, as described previously [23,24]. VACS COD information was not available at the time of the ART-CC adjudication process.

Primary analyses used Cox models for 5-year, all-cause mortality from 1 year after initiation of ART. Observation time ended at the earlier of death, the date of last follow-up, or 6 years after ART initiation. First, using VACS data, we modeled mortality using components of the VACS Index and the Restricted Index. We derived point values by multiplying the log of each estimated hazard ratio by 25 for the VACS Index and 30 for the Restricted Index. These multipliers were chosen so that each index had an approximate working range of 0–100, although higher scores are theoretically possible. Next, in both datasets, patients' index scores were calculated by summing the points associated with each prognostic factor level. Risk index scores were used for the remaining analyses.

Discrimination (prognostic accuracy) of the VACS and Restricted Indices was compared using Harrell's c-statistic (P values from transformation of Somers' D) [25]. C-statistics are a commonly employed metric for evaluating the discrimination of prognostic indices [26]. C-statistics between 0.50 and 0.59 are considered poor; 0.60 and 0.69, fair; 0.70 and 0.79, good; 0.80 and 0.89 very good; and above 0.89, excellent [27]. Analyses were done separately for the development and validation datasets, adjusting for ART-CC cohort with indicator variables. We further evaluated performance of the

indices according to cause of death. We assessed the linearity of the relationship between score and mortality by plotting mortality rate per 1000 person-years [log scale, with 95% confidence intervals (CI)] versus the median of five point intervals of score, collapsed if necessary to maintain at least five deaths in each interval. To demonstrate the additional prognostic information available from the VACS Index we plotted rates for patients classified by the Restricted Index as low risk (age <50 years, undetectable HIV-1 RNA, CD4 cell count ≥200 cells/μl). Five-year cumulative mortality was estimated using the Kaplan–Meier method. We used SAS version 9.2 (SAS Institute, Cary, North Carolina, USA) for all analyses, except calculation of Harrell's c-statistic that used Stata version 11 (Stata Corp., College Station, Texas, USA).

In sensitivity analyses we explored the performance of the VACS Index at ART initiation and at 6 months, 2, 3, 4, and 5 years after ART initiation. We used the biomarker measurement date closest to the time point of interest and within specified time intervals around each point (Appendix Figure 1, http://links.lww.com/QAD/A274), so that measurements could be assigned to one time point only. The interval was limited to 180 days before at ART initiation, ±90 days for the 6-month time point, 90 days before to 180 days after the 1-year time point, and ±180 days from the relevant anniversary of ART initiation for the remaining intervals. Patients with incomplete measurements at ART initiation were excluded. Missing measurements in subsequent periods were interpolated by averaging values in adjacent periods, on the assumption of approximately linear trajectories between measurements. Findings based on multiple imputation of missing values, which assumes data were 'missing at random' [28], were similar, so are not reported. To examine sensitivity of our results to the width of the time window, we also constrained the 1-year score to measurements obtained within 60 days of the anniversary of ART initiation.

Results

Among 13 582 men initiating ART in VACS between 2000 and 2007, 7823 had CD4 cell count and HIV-1 RNA at least 500 copies/ml in the 3 months prior to ART initiation, of whom 6324 (81%) had complete biomarker measurements. Of 5127 ART-CC patients meeting inclusion criteria 3747 (73%) had complete measurements at ART initiation, varying from 61 to 92% by cohort. At 1 year, complete measurements were available for 4932 (85%) of 5794 VACS and 3146 (92%) of 3434 ART-CC patients who were alive and not lost to follow-up. VACS patients were all men, more likely to have initiated ART before 2004, and median 10 years older than ART-CC patients (Table 1). At 1 year, median CD4 cell count was lower in VACS than ART-CC patients, (307 versus 385 cells/μl), the proportion with CD4 cell count <50 cells/μl was higher (8 versus 2%), and HIV-RNA was more frequently detectable (35 versus 13%, range over ART-CC cohorts 7–32%). Fewer than 5% of patients in each cohort had severe anemia (hemoglobin <10 g/dl); FIB-4 more than 3.25, eGFR less than 60 ml/min per 1.73 m^2 and HCV infection were all more common in VACS. During five additional years of follow-up, from 1 year after initiation of ART, there were 655 (13%) deaths in VACS and 86 (3%) in ART-CC.

We explored adding IDU and sex, and omitting age. The study sample included 287 patients with IDU, of whom 16 died. IDU was associated with increased risk of death [hazard ratio 1.97, (95% CI 1.10–3.50), $P = 0.02$] in unadjusted analysis, but the risk was attenuated [hazard ratio 1.12, (95% CI 0.65–2.13), $P = 0.59$] in multivariable models. We found a protective effect of female sex in multivariable models [hazard ratio 0.56 (95% CI 0.34–0.93), $P = 0.03$], but there were too few events (21 deaths/875 women) for a precise estimate. In a model without age, the hazard ratio for CD4 cell count and HIV-RNA decreased by more than 10% and those for FIB-4 increased by more than 10% compared with the full model, suggesting confounding by age. Thus, we did not include IDU or sex in our final prognostic model, but retained age.

The VACS and Restricted Indices are shown in Table 2. Age at least 65 years, CD4 cell count less than 100 cells/μl and HIV-1 RNA at least 5 $\log_{10}$ copies/ml were strong predictors of mortality in both indices. Their effect was attenuated after including measures of anemia, liver fibrosis and renal function. Hazard ratios for hemoglobin less than 12 g/dl, FIB-4 more than 3.25 and eGFR less than 30 ml/min (compared with reference groups) were each greater than two. Point values derived from log hazard ratios showed a gradient across levels of predictors. Maximum theoretical scores were 164 for the VACS Index and 115 for the Restricted Index. However, 99% of values were below 100 for both indices, in both cohorts. No value exceeded 124. The median and interquartile range for the two indices were similar within each dataset (Table 3). Using continuous rather than categorical predictors slightly increased the c-statistics (0.789 versus 0.782 for the VACS Index and 0.728 versus 0.720 for the Restricted Index).

Restricted Index and VACS Index scores 1 year after ART initiation (Table 3) were higher in VACS (median 30 and 28) than in ART-CC (10 and 16). Of note, 2000 (64%) of ART-CC patients were considered low risk by traditional HIV measures (age <50 years, undetectable HIV-1 RNA, and CD4 cell count ≥200 cells/μl), and thus had Restricted Index scores of 0 (CD4 cell count ≥500) or 10 (CD4 cell count 200–499). However, more than half of these patients ($n = 1101$) had abnormalities of hemoglobin, FIB-4 or eGFR. In VACS, 1263 patients

Table 2. Adjusted hazard ratios and point values for Restricted Index (age, CD4 and HIV-1 RNA) and VACS Index, derived in 4932 male Veterans after one year of antiretroviral therapy (ART) using Cox models.

	Hazard ratios (95% CI)		Points	
	Restricted Index	VACS Index	Restricted Index	VACS Index
Age (years)				
<50	1.0	1.0	0	0
50–64	2.2 (1.8–2.6)	1.6 (1.4–1.9)	23	12
>65	4.3 (3.3–5.7)	3.0 (2.2–4.0)	44	27
CD4 cell count (cells/μl)				
>500	1.0	1.0	0	0
350–499	1.5 (1.1–2.0)	1.4 (1.0–1.9)	10	6
200–349	1.3 (1.0–1.8)	1.2 (0.9–1.6)	10	6
100–199	1.9 (1.4–2.5)	1.5 (1.1–2.0)	19	10
50–99	3.8 (2.8–5.3)	3.0 (2.2–4.2)	40	28
<50	4.6 (3.4–6.3)	3.2 (2.4–4.4)	46	29
HIV-1 RNA (copies/ml)				
<500	1.0	1.0	0	0
$500–1\times10^5$	1.5 (1.2–1.7)	1.3 (1.1–1.6)	11	7
$>1\times10^5$	2.3 (1.8–2.9)	1.8 (1.4–2.3)	25	14
Hemoglobin (g/dl)				
>14		1.0		0
12–13.9		1.5 (1.3–1.8)		10
10–11.9		2.4 (1.9–3.1)		22
<10		4.7 (3.4–6.4)		38
FIB-4				
<1.45		1.0		0
1.45–3.25		1.3 (1.1–1.6)		6
>3.25		2.7 (2.2–3.4)		25
eGFR (ml/min)				
>60		1.0		0
45–59.9		1.3 (0.9–1.7)		6
30–44.9		1.4 (0.9–2.2)		8
<30		2.8 (2.1–3.8)		26
Hepatitis C infection		1.2 (1.0–1.4)		5
Theoretical maximum index score			115	164

ALT, alanine transaminase; AST, aspartate transaminase; cART, combination antiretroviral therapy; eGFR, estimated glomerular filtration rate; IQR, interquartile range. FIB-4: (years of age × AST)/(platelets in 109/l × square root of ALT). eGFR: 186.3 × (serum creatinine $^{-1.154}$) × (age $^{-0.203}$) × (0.742 for women) × (1.21 if black). Hepatitis C: diagnosis, positive antibody test or detectable virus.

(29%) had restricted index scores 10 or less and half of these ($n = 630$) had abnormalities of hemoglobin, FIB-4 or eGFR. Thus, at least half the patients who would have been considered to be at low risk based on the Restricted Index were classified as intermediate or higher risk based on the VACS Index. The hazard ratio for 5-year, all-cause mortality associated with a five-point increment of score was similar in each cohort: VACS [Restricted Index, hazard ratio 1.18 (95% CI 1.16–1.20)] and [VACS Index, hazard ratio 1.22 (1.21–1.24)], ART-CC [Restricted Index, hazard ratio 1.33 (1.27–1.39)] and [VACS Index, hazard ratio 1.32 (1.27–1.38)]. However, discrimination was better with the VACS Index than the Restricted Index, in both VACS (c-statistics 0.78 versus 0.72, $P < 0.001$) and ART-CC (c-statistics 0.82 versus 0.78, $P = 0.06$).

Better discrimination with the VACS Index persisted when stratified by cause of death and in subgroups. When deaths were categorized as HIV, non-HIV or unnatural the VACS Index discriminated risk of both HIV and non-HIV deaths better than the Restricted Index (Table 3). Both the Restricted Index and the VACS index performed better for HIV than non-HIV deaths, particularly in ART-CC. Corresponding differences were less marked in VACS, perhaps because classification of death in VACS was based on ICD codes but not clinical information. In VACS less than 25% of deaths occurred in the first year of follow-up, regardless of cause of death. In ART-CC 48% of the HIV deaths and 35% of the non-HIV deaths occurred in the first year.

Among subgroups of interest in the combined data (Table 4), discrimination was consistently better with the VACS Index than the Restricted Index, with the greatest improvement in discrimination among those aged at least 50 years. hazard ratio for each cause of death strata and subgroup were within the confidence intervals for all-cause mortality (data not shown).

Associations between mortality rates and index scores were log-linear across the range of both indices, in both VACS (Fig. 1, panels a and c) and ART-CC (panels b and d). The VACS index provided additional discrimination among patients with good prognosis based on traditional markers of HIV disease progression

Table 3. Distribution of Restricted Index and Veterans Aging Cohort Study Index scores evaluated 1 year after initiation of ART, in the development (VACS) and validation (ART-CC) datasets and their discrimination of 5-year, all-cause mortality measured with Harrell's c-statistic.

		VACS development cohort ($N = 4932$)	ART-CC validation cohor ($N = 3146$)	
Restricted Index score, median (IQR), max.		28 (16–43), 124	10 (10–21), 94	
VACS Index score, median (IQR), max.		30 (10–44), 115	16 (6–24), 118	
Five-year mortality	Deaths	c (95% CI)	Deaths	c (95% CI)
All causes of death				
Restricted Index	656	0.72 (0.70–0.74)	86	0.78 (0.72–0.84)
VACS Index		0.78 (0.76–0.80)		0.82 (0.77–0.87)
HIV and non-HIV deaths				
Restricted Index	590	0.73 (0.71–0.75)	54	0.82 (0.76–0.89)
VACS Index		0.79 (0.77–0.81)		0.85 (0.79–0.91)
HIV deaths only				
Restricted Index	370	0.77 (0.75–0.79)	23	0.90 (0.83–0.98)
VACS Index		0.82 (0.80–0.85)		0.93 (0.88–0.98)
Non-HIV deaths				
Restricted Index	220	0.69 (0.65–0.72)	31	0.77 (0.67–0.86)
VACS Index		0.77 (0.74–0.80)		0.78 (0.69–0.88)

ART-CC, antiretroviral therapy Cohort Collaboration; CI, confidence interval; VACS, Veterans Aging Cohort Study.VACS Index: age, CD4 cell count, HIV-1 RNA, hemoglobin, FIB-4, eGFR and hepatitis C. Restricted Index: age, CD4 cell count, HIV-1 RNA. Deaths were categorized as HIV, non-HIV and unnatural. Unnatural deaths are included in all causes and excluded from other groupings.

(Restricted Index scores 10 or less, panels e and f). There was substantial variation in mortality risk across the range of the VACS Index: estimated 5-year cumulative mortality in VACS patients varied from 2.8% in 676 patients (13 deaths) with scores less than 10, to 55% in 543 patients (238 deaths) with scores at least 60. Corresponding estimated mortality risks in ART-CC were 1.6% (920 patients, seven deaths) and 41% (63 patients, 17 deaths), respectively.

In sensitivity analyses, results were similar over a wide range of time on ART and length of follow-up (Appendix Table, http://links.lww.com/QAD/A274). Hazard ratios and c-statistics remained consistent from 1 to 5 years after ART initiation. Both discrimination and association were weaker using index scores measured at ART initiation. C-statistics were higher with shorter follow-up times in both VACS and ART-CC. Constraining the interval to measurements obtained within 60 days of the anniversary of ART initiation resulted in 25% fewer patients, but distribution of scores and mortality associations were little changed (data not shown).

Discussion

The VACS Index, based on routinely obtained traditional HIV markers and generic biomarkers of organ system injury, consistently predicted mortality after 1 year of treatment more accurately than an index restricted to age, CD4 cell count and HIV-1 RNA (Restricted Index). This was true in VACS (the development cohort) and in a validation dataset assembled from other European and US cohorts participating in ART-CC. In both VACS and ART-CC discrimination of the VACS Index was better than the Restricted Index, overall and within important patient subgroups, and for HIV and non-HIV deaths. The superior accuracy of the VACS Index was particularly evident among those categorized as low risk by the Restricted Index and among those aged 50 years and older – a growing proportion of patients in care. These results persisted across a range of times on ART and length of follow-up. Estimated 5-year cumulative mortality varied approximately 20-fold between patient groups at lowest and highest risk, in both development and validation datasets.

Our study has important strengths. We assembled large datasets, validated our findings in multinational independent cohorts and evaluated performance of the VACS Index among important subgroups under-represented in VACS (women and younger patients). We also considered performance over differing intervals of follow-up (1–5 years) and using different clinical points of care (at treatment initiation and up to 5 years of treatment). The consistently superior discrimination of the VACS Index, compared with the Restricted Index, suggests excellent generalizability in high-income settings [29]. Discrimination of the VACS Index is comparable to that of indices in clinical use such as the Framingham Risk Score for cardiovascular events (c-statistics of 0.73 in men and 0.71 in women) [30] and many indices recommended for geriatric populations [27]. Somewhat surprisingly, c-statistics were higher in the validation dataset than in the development dataset, most notably with respect to HIV deaths. This finding underscores the generalizability of the VACS Index and may reflect the fact that any prognostic index is likely to be more accurate in predicting shorter term rather than longer term events (a greater proportion of deaths occurred in the first year of follow-up in ART-CC than in VACS). The VACS Index

uses laboratory measurements recommended for routine management of HIV-infected patients, thus, providing improved prognostic accuracy without added cost.

Limitations of our study are related to use of observational data from multiple countries. Of eligible subjects in our analyses, 27% had incomplete data at ART initiation. We explored characteristics of patients with and without complete data and found no consistent patterns of association between indicators of disease severity and completeness. Further, results using multiple imputations were consistent with those from complete case analyses. As hazard ratios were not substantively different with or without interpolation or multiple imputations, we believe our results to be robust. Mortality rates varied dramatically between European and US cohorts and in part depend on access to national death registries. Nevertheless, performance of the VACS Index was better in the validation dataset than in VACS, for which ascertainment of deaths is excellent. Although mortality rate differences make calibration of the VACS Index difficult, they should not interfere with evaluation of discrimination of mortality [9].

When constructing a clinical prognostic index it is important to keep the goal in mind. Our goal was to develop a parsimonious index based on routinely available clinical data that would accurately predict mortality. Because age is a strong predictor and a confounder of other important predictors (CD4 cell count, HIV RNA and FIB-4) it makes sense to include this nonmodifiable risk factor to help ensure accurate risk estimates. Our goal was not to identify all modifiable mediators of mortality. Many mediators may directly or indirectly affect VACS Index score and so do not need to be included in the Index. For example, we have shown that smokers have higher VACS Index scores, as do those with hypertension or hazardous alcohol use. [31]. Now that an accurate risk assessment tool is available, it can be used to quantify the impact of interventions on a host of modifiable risk factors. We are currently exploring the change in VACS Index scores after patients modify levels of smoking and alcohol use. Categorical predictors were chosen for ease of implementation. Using continuous predictors provided slight increases in c-statistic, but the added complexity might obscure interpretation of the findings and make it difficult to calculate the VACS Index manually [32]. Scores based on continuous measures could be generated as part of laboratory reports, but categories might be preferable as they are less affected by extremes due to possible laboratory error, because the range of values is constrained.

It remains to be seen whether additional variables can further improve the accuracy of the VACS Index. In this study we considered IDU and sex. Addition of IDU did not improve the accuracy of the index and there were too few events among the women to obtain precise estimates. In other analyses we have explored the effect of blood pressure, smoking, cholesterol and markers of chronic inflammation [interleukin 6 (IL-6), D-dimer, sCD14]. Although blood pressure, smoking and cholesterol were associated with mortality among those with HIV infection in unadjusted analyses, these factors resulted in very modest risk reclassification when added to the VACS Index (<1%) [31]. In contrast, addition of D-dimer or sCD14 resulted in somewhat more risk reclassification (4–7%) [7]. In the future, the VACS Index may be improved by adding D-dimer, sCD14 or other novel biomarkers. New variables such as these should only be included if they can be reliably measured, and their added costs are justified by clinically important improvements in prognostic accuracy.

The VACS Index outperformed the Restricted Index among older patients (50 or more years), a group that represents the future majority of people living with HIV in North America and Europe [4,33]. Mortality among

Table 4. Subgroup analyses: Restricted Index and Veterans Aging Cohort Study Index discrimination of 5-year mortality hazard ratio associated with a five point increment of score.

			Restricted Index	VACS Index
Subgroup	*N*	Deaths	c (95% CI)	c (95% CI)
Overall	8078	742	0.77 (0.75,0.78)	0.81 (0.80,0.83)
Sex				
Men	7203	721	0.76 (0.74–0.78)	0.81 (0.80–0.83)
Women	875	21	0.69 (0.55–0.83)	0.75 (0.65–0.86)
Age, years				
<50	5347	322	0.77 (0.74-0.80)	0.83 (0.80–0.85)
≥50	2731	420	0.67 (0.64–0.70)	0.74 (0.72–0.77)
HIV-1 RNA, copies/ml				
<500	5941	360	0.74 (0.71–0.77)	0.80 (0.78–0.82)
≥500	2137	382	0.73 (0.71–0.76)	0.79 (0.76–0.81)
Hepatitis C infection				
Yes	1926	303	0.69 (0.66–0.73)	0.76 (0.73–0.79)
No	6152	439	0.79 (0.77–0.82)	0.82 (0.80–0.84)

CI, confidence interval; VACS, Veterans Aging Cohort Study.

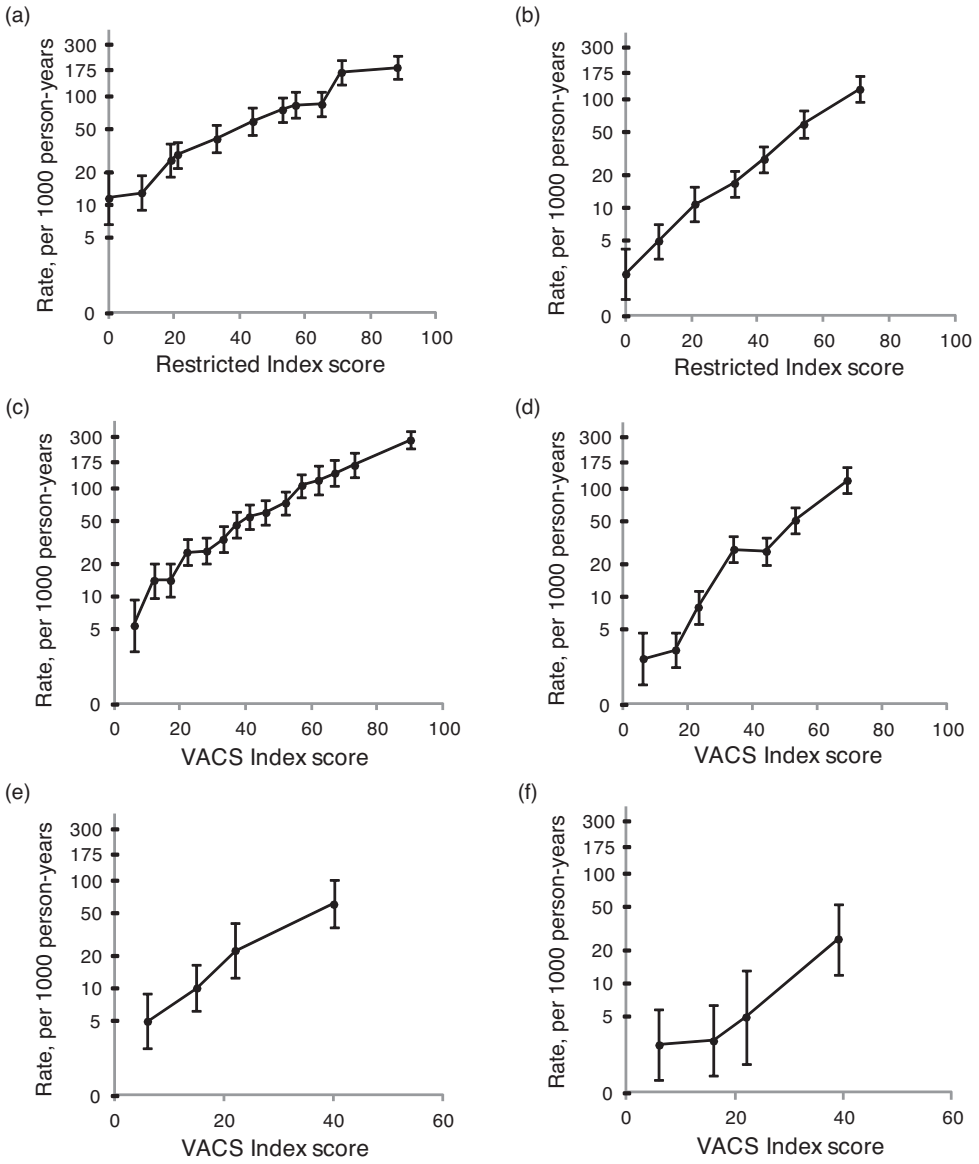

Fig. 1. All-cause, 5-year mortality rates by risk score. (a) VACS cohort, Restricted Index. (b) ART-CC cohorts, Restricted Index. (c) VACS cohort, VACS Index. (d) ART-CC cohorts, VACS Index. (e) VACS cohort, VACS Index, low risk. (f) ART-CC cohorts, VACS Index, low risk. Low risk: age less than 50, CD4 cell count more than 200 cells/μl, undetectable HIV-1 RNA. ART-CC, antiretroviral therapy cohort collaboration; VACS, Veterans Aging Cohort Study.

HIV-infected patients on ART is increasingly influenced by 'non-AIDS' events [24,34] that represent combined effects of HIV, aging, comorbid disease and treatment toxicity [4]. The VACS Index had better discrimination than the Restricted Index for both HIV and non-HIV deaths. This is the best evidence to date that biomarkers of organ system injury offer independent insight into HIV disease progression. HIV contributes to excess mortality by exacerbating aging associated pathophysiologic mechanisms including microbial translocation, inflammation, and hypercoagulation [3,4,33,35]. Biomarkers of pathophysiologic aging, including IL-6, soluble CD14 cell count and D-dimer, are associated with mortality in those with HIV infection [5,36–38]. Interestingly, the VACS Index is more strongly correlated with these markers than the Restricted Index [7]. After adjustment for the VACS Index, IL-6 is no longer associated with mortality and the association of D-dimer and sCD14 is diminished. Taken together, these findings suggest that the added discrimination offered by the VACS Index reflects improved detection of HIV-associated pathophysiology as well as aging associated comorbidity.

The VACS Index combines nine pieces of information into a single score, indicative of disease burden. A composite index offers at least two major improvements over the individual biomarkers. First, a score gives

the clinician an overall sense of the patient's condition and can be used to predict mortality. The simplicity of a single number is appealing for ease of interpretation by both clinician and patient. This is exemplified by the enduring use of the Apgar score, a composite of five characteristics of newborns, introduced 50 years ago [39]. Second, thresholds for concern of these routinely monitored measurements have typically been more extreme than those identified by the index. The exercise of calculating the integrated impact of several biomarkers can help clinicians recognize the importance of more moderate abnormalities that may still be associated with disease. For example, the Framingham Index has helped providers realize that moderate levels of blood pressure and cholesterol elevation are of concern. Similarly, the thresholds identified by the VACS Index for hemoglobin, creatinine, AST, ALT and platelets are less extreme. For example, men are not considered anemic unless their hemoglobin is less than 13 [40], yet the VACS Index indicates increased risk of death when hemoglobin is less than 14. Even more subtle abnormalities are of concern among older patients because the composite measures FIB-4 and eEGFR vary with age. In a 50-year old with normal platelets (200), AST and ALT values as low as 35 equate to a FIB-4 of 1.48 and six points of VACS Index score. In a 50-year old, a creatinine of 1.1 connotes a clinically significant decreased eGFR of less than 60 ml/min. The VACS Index can also help clinicians balance opposing outcomes (such as undetectable HIV-1 RNA and good CD4 cell count response, but development of mild anemia, liver injury or renal insufficiency) that might be addressed by changing ART components. Index guided management has the advantage of enabling providers to optimize patients' overall health, rather than narrowly focusing on traditional markers of HIV disease progression.

Conclusion

We have demonstrated that the VACS Index for treated HIV-infected patients, including women, is transportable across settings in Europe and the United States, and predicts mortality better than an index restricted to CD4 cell count, HIV-1 RNA and age. These findings reinforce the importance of non-HIV specific markers in predicting mortality and HIV disease progression in HIV-infected patients and suggest that the VACS Index may prove a useful tool in clinical care and research.

Acknowledgements

We thank all patients, doctors, and study nurses associated with the participating cohort studies.

M.D.H. declares being a paid member of data monitoring committees for Boehringer Ingelheim, Medicines Development, Pfizer and Tibotec.

Role of the authors: J.P.T., A.C.J., M.D.H. and J.A.C.S. designed the study. J.P.T. performed the analysis and wrote the first draft. A.C.J. and J.A.C.S. made major revisions. All authors contributed to editing the manuscript and reviewed and approved the submission.

The Antiretroviral Therapy Cohort Collaboration (ART-CC): Writing group: J.P.T. (VACS), A.C.J. (VACS), M.D.H. (HSPH), F.B. (Aquitaine), P.R. (ATHENA), A.M. (EuroSIDA), J.N. (Koln/Bonn), F.C.L. (Royal Free), H.C.B. (SHCS), T.R.S. (Vanderbilt), H.M.C., M.M.K. (Washington), M.M., J.A.C.S. (Bristol).

Funding/Support: The Veterans Aging Cohort Study is supported by National Institutes of Health: NIAAA (U10-AA13566), NHLBI (R01-HL095136; R01-HL090342; RCI-HL100347), NIA (R01-AG029154), NIAID (U01-A1069918), NIMH (P30-MH062294), and the Veterans Health Administration Office of Research and Development (VA REA 08–266). The ART Cohort Collaboration is supported by the UK Medical Research Council (grant G0700820). M.D.H. received support from NIH/NIAID AI024643-23A1. J.P.T. was supported by the Training Program in Environmental Epidemiology funded under grant no. T32 ES07069.

Conflicts of interest

There are no conflicts of interest.

References

1. Mocroft A, Sterne JA, Egger M, May M, Grabar S, Furrer H, *et al*. **Variable impact on mortality of AIDS-defining events diagnosed during combination antiretroviral therapy: not all AIDS-defining conditions are created equal.** *Clin Infect Dis* 2009; **48**:1138–1151.
2. D'Arminio MA, Sabin CA, Phillips A, Sterne J, May M, Justice A, *et al*. **The changing incidence of AIDS events in patients receiving highly active antiretroviral therapy.** *Arch Intern Med* 2005; **165**:416–423.
3. Deeks SG, Phillips AN. **HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity.** *BMJ* 2009; **338**: a3172.
4. Justice AC. **HIV and aging: time for a new paradigm.** *Curr HIV/AIDS Rep* 2010; **7**:69–76.
5. Kuller LH, Tracy R, Belloso W, De WS, Drummond F, Lane HC, *et al*. **Inflammatory and coagulation biomarkers and mortality in patients with HIV infection.** *PLoS Med* 2008; **5**:e203.
6. Sandler NG, Wand H, Roque A, Law M, Nason MC, Nixon DE, *et al*. **Plasma levels of soluble CD14 independently predict mortality in HIV infection.** *J Infect Dis* 2011; **203**:780–790.
7. Justice AC, Freiberg MS, Tracy R, Kuller L, Tate JP, Goetz MB, *et al*. **Does an index composed of clinical data reflect effects of inflammation, coagulation, and monocyte activation on mortality among those aging with HIV?** *Clin Infect Dis* 2012; **54**:984–994.
8. Neuhaus J, Jacobs DR Jr, Baker JV, Calmy A, Duprez D, La RA, *et al*. **Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection.** *J Infect Dis* 2010; **201**:1788–1795.
9. Vasan RS. **Biomarkers of cardiovascular disease: molecular basis and practical considerations.** *Circulation* 2006; **113**: 2335–2362.

10. Panel on Clinical Practices for Treatment of HIV Infection. *Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents*. Washington, DC: Department of Health and Human Services/Henry J. Kaiser Family Foundation; 2005. pp. 1–97.
11. Aberg JA, Kaplan JE, Libman H, Emmanuel P, Anderson JR, Stone VE, *et al*. **Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America.** *Clin Infect Dis* 2009; **49**:651–681.
12. May M, Royston P, Egger M, Justice AC, Sterne JA, ART-CC. **Development and validation of a prognostic model for survival time data: application to prognosis of HIV positive patients treated with antiretroviral therapy**. *Stat Med* 2004; **23**:2375–2398.
13. Srasuebkul P, Lim PL, Lee MP, Kumarasamy N, Zhou J, Sirisanthana T, *et al*. **Short-term clinical disease progression in HIV-infected patients receiving combination antiretroviral therapy: results from the TREAT Asia HIV observational database.** *Clin Infect Dis* 2009; **48**:940–950.
14. Lundgren JD, Mocroft A, Gatell JM, Ledergerber B, D'Arminio MA, Hermans P, *et al*. **A clinically prognostic scoring system for patients receiving highly active antiretroviral therapy: results from the EuroSIDA study.** *J Infect Dis* 2002; **185**:178–187.
15. Harris RJ, Sterne JA, Abgrall S, Dabis F, Reiss P, Saag M, *et al*. **Prognostic importance of anaemia in HIV type-1-infected patients starting antiretroviral therapy: collaborative analysis of prospective cohort studies.** *Antivir Ther* 2008; **13**:959–967.
16. Justice AC, McGinnis KA, Skanderson M, Chang CC, Gibert CL, Goetz MB, *et al*. **Towards a combined prognostic index for survival in HIV infection: the role of 'non-HIV' biomarkers.** *HIV Med* 2010; **11**:143–151.
17. Fultz SL, Skanderson M, Mole LA, Gandhi N, Bryant K, Crystal S, *et al*. **Development and verification of a 'virtual' cohort using the National VA Health Information System.** *Med Care* 2006; **44 (8 Suppl 2)**:S25–S30.
18. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, *et al*. **Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies.** *Lancet* 2002; **360**:119–129.
19. Boyle CA, Decoufle P. **National sources of vital status information: extent of coverage and possible selectivity in reporting.** *Am J Epidemiol* 1990; **131**:160–168.
20. Fisher SG, Weber L, Goldberg J, Davis F. **Mortality ascertainment in the veteran population: alternatives to the National Death Index.** *Am J Epidemiol* 1995; **141**:242–250.
21. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, *et al*. **Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection.** *Hepatology* 2006; **43**:1317–1325.
22. Stevens LA, Coresh J, Greene T, Levey AS. **Assessing kidney function: measured and estimated glomerular filtration rate.** *N Engl J Med* 2006; **354**:2473–2483.
23. Kowalska JD, Friis-Moller N, Kirk O, Bannister W, Mocroft A, Sabin C, *et al*. **The Coding Causes of Death in HIV (CoDe) Project: initial results and evaluation of methodology.** *Epidemiology* 2011; **22**:516–523.
24. Antiretroviral Therapy Cohort Collaboration (ART-CC). **Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: collaborative analysis of 13 HIV cohort studies**. *Clin Infect Dis* 2010; **50**:1387–1396.
25. Newson R. **Confidence intervals for rank statistics: Somers' D and extensions.** *Stata J* 2006; **6**:309–334.
26. Cook NR. **Use and misuse of the receiver operating characteristic curve in risk prediction.** *Circulation* 2007; **115**:928–935.
27. Yourman LC, Lee SJ, Schonberg MA, Widera EW, Smith AK. **Prognostic indices for older adults: a systematic review.** *JAMA* 2012; **307**:182–192.
28. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. **Review: a gentle introduction to imputation of missing values.** *J Clin Epidemiol* 2006; **59**:1087–1091.
29. Justice AC, Covinsky KE, Berlin JA. **Assessing the generalizability of prognostic information.** *Ann Intern Med* 1999; **130**:515–524.
30. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. **Prediction of coronary heart disease using risk factor categories.** *Circulation* 1998; **97**:1837–1847.
31. Tate J, Freiberg M, Justice AC. **Do risk factors for cardiovascular disease improve VACS Index prediction of all cause mortality?** *16th International Workshop on HIV Observational Databases*, Athens; 2012.
32. Sullivan LM, Massaro JM, D'Agostino RB Sr. **Presentation of multivariate data for clinical use: The Framingham Study risk score functions.** *Stat Med* 2004; **23**:1631–1660.
33. Deeks SG. **Immune dysfunction, inflammation, and accelerated aging in patients on antiretroviral therapy.** *Top HIV Med* 2009; **17**:118–123.
34. Leone S, Gregis G, Quinzan G, Velenti D, Cologni G, Soavi L, *et al*. **Causes of death and risk factors among HIV-infected persons in the HAART era: analysis of a large urban cohort.** *Infection* 2011; **39**:13–20.
35. Effros RB, Fletcher CV, Gebo K, Halter JB, Hazzard WR, Horne FM, *et al*. **Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions.** *Clin Infect Dis* 2008; **47**:542–553.
36. Phillips AN, Neaton J, Lundgren JD. **The role of HIV in serious diseases other than AIDS.** *AIDS* 2008; **22**:2409–2418.
37. Silverberg MJ, Neuhaus J, Bower M, Gey D, Hatzakis A, Henry K, *et al*. **Risk of cancers during interrupted antiretroviral therapy in the SMART study.** *AIDS* 2007; **21**:1957–1963.
38. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, *et al*. **CD4+ count-guided interruption of antiretroviral treatment.** *N Engl J Med* 2006; **355**:2283–2296.
39. Casey BM, McIntire DD, Leveno KJ. **The continuing value of the Apgar score for the assessment of newborn infants.** *N Engl J Med* 2001; **344**:467–471.
40. Beutler E, Waalen J. **The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration?** *Blood* 2006; **107**:1747–1750.