

HIV Associated Non AIDS (HANA) Conditions and “Inflammation”

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Learning Objectives:

At the conclusion of this presentation, learners should be better able to:

- Optimize management strategies for HIV Associated Non AIDS (HANA) conditions in those aging with HIV
- Accurately interpret the VACS Index score in order to use it to help tailor and prioritize care for patients aging with HIV infection

Outline: HANA Conditions

- Define and review larger context
- Update in detail: coronary artery disease; liver disease; and osteoporosis
 - Major risk factors
 - Strength of association with HIV
 - Screening and management recommendations
- Provide an approach to multi-morbidity

Larger Context

HIV Associated Non AIDS (HANA) Conditions

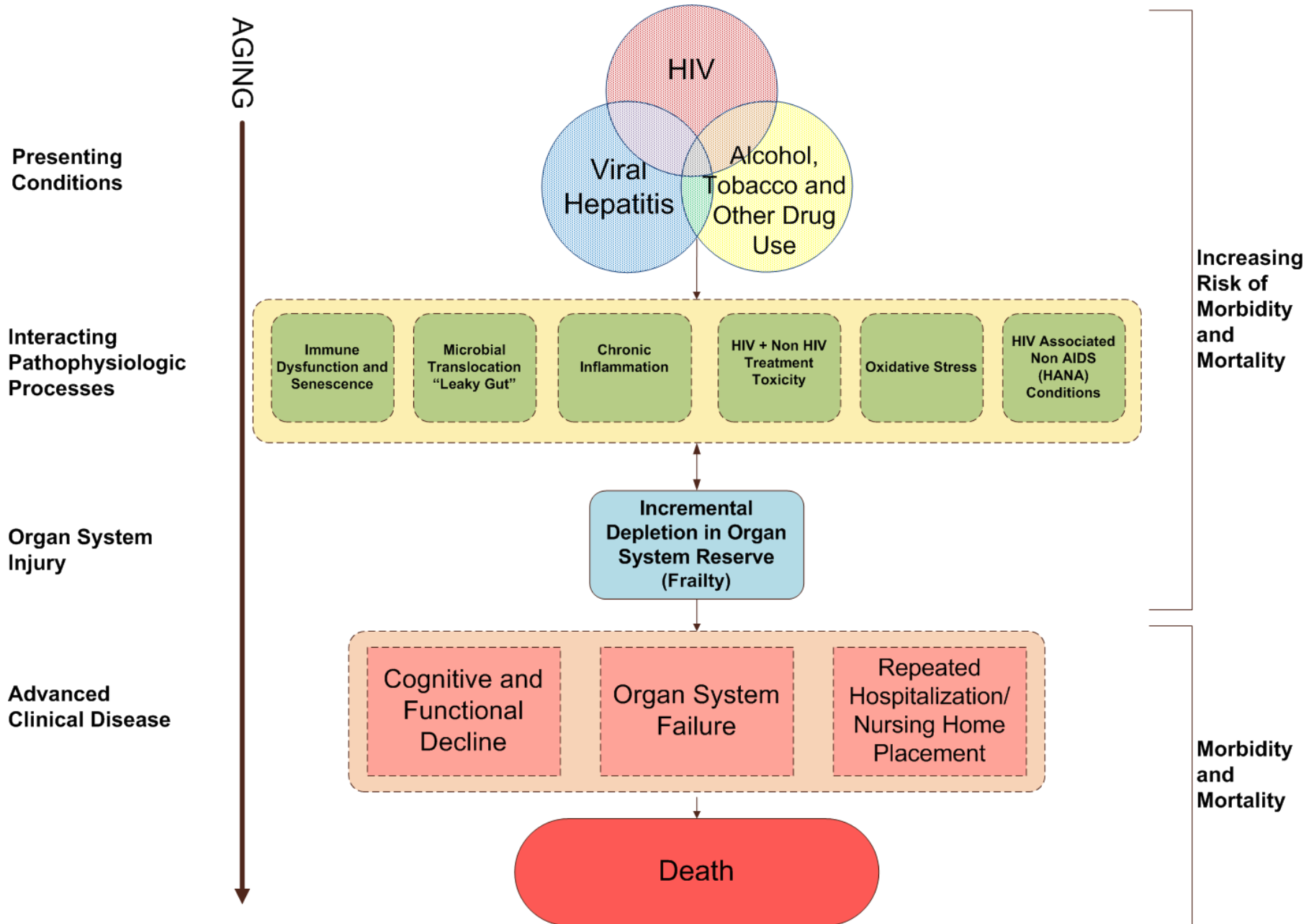
- After adjustment for usual risk factors, HIV association remains
 - Usual risk factors determine most of the risk
 - Increasing age and substance use often important
- Subset of comorbid disease we are seeing
- May be due to HIV, to ART or both
 - May or may not be associated with usual markers of HIV disease (CD4 count or HIV-1 RNA)

Likely HANA Conditions

- Vascular: Coronary Artery Disease, Congestive Heart Disease, Thrombosis, Stroke
- Liver: risk of and rapid progression to cirrhosis and hepatoma
- Cancer: Infection related Cancers- e.g. Anal; Non infection related Cancers- e.g. Lung
- Bone: Osteoporosis, Avascular Necrosis
- Bone Marrow: anemia, thrombocytopenia
- Renal: most is not HIVAN
- Neurological: Peripheral neuropathy, ?dementia

Of Note

- Range of relative risk with HIV variable
 - Fragility fracture risk modest (1.3)
Womack J. et al. PLoS ONE February 2011 | Volume 6 | Issue 2 | e17217
 - Cardiovascular risk may be substantial (>2 fold)
Freiberg M et al. HIV Associated with Clinically Confirmed MI. CROI 2011 Abstract# W-176
- Incidence/prevalence of a particular condition separate issue from that of relative risk
 - Relative risk of anal cancer very high
 - Incidence/prevalence lower than for lung cancer
- Consider competing risk of death
- Multimorbidity is the rule



Non HIV Causes of Inflammation

- Smoking: oxidative stress
- Alcohol: microbial translocation
- Immune stimulation: other viruses
- Liver disease: decreased immune function causing prolonged stimulation
- Obesity: oxidative stress

Cardiovascular Disease



HIV status and the risk of AMI

Risk Factors	HR for AMI with 95% CI
HIV infection	1.94 (1.58-2.37)
Age (10 yrs)	1.39 (1.26-1.54)
Race/ethnicity	
African American	0.79 (0.64-0.98)
Hispanic	1.39 (1.03-1.88)
Other	0.42 (0.22-0.80)
Hypertension	1.36 (1.10-1.68)
Diabetes	2.01 (1.68-2.53)
Hypercholesterolemia	1.30 (1.06-1.59)
Ever Smoking	1.87 (1.38-2.52)
HCV infection	1.10 (0.88-1.38)
EGFR<30 ml/min/1.73m ²	4.93 (3.12-7.77)
BMI ≥ 30kg/m ²	0.90 (0.72-1.12)
History of cocaine abuse or dependence	1.42 (0.97-2.09)
History of alcohol abuse or dependence	0.80 (0.56-1.11)

Coronary Artery Disease Recommendations

- Observational data in HIV+/- cohorts
 - Risk substantial--manage risk factors in all
- Observational data in HIV+/- cohorts and well established in general population
 - Address substance use: smoking, alcohol, cocaine
 - Aggressive hypertension control
 - Avoid excess weight gain
 - Lipid management

Liver Disease

Evolving Problem

- Rising incidence of hepatocellular cancer
- Rising incidence of symptomatic cirrhosis
- Causes:
 - HCV and alcohol major causes
 - HBV, HIV and non HIV treatment contribute
- FIB 4 scores improve on ART
- Soon, more effective treatments (not less toxic)

Liver Disease Recommendations

- Observational data in HIV+/- cohorts and established findings in general population
 - Address in all alcohol, toxic medications, HBV vaccination and treatment
 - FIB 4 to identify those at risk
 - Routine screening of AST, ALT, and platelets recommended by guidelines
 - Not all liver disease is HCV
- Possibly, wait for more effective HCV treatment

Osteoporosis



Fragility Fractures HIV+/- (n= 125,259)

	HIV Model	Full Model	HIV+ Men
HIV	1.32 (1.20, 1.47)	1.10 (0.97, 1.25)	--
Age (10 yr increments)	--	1.32 (1.25, 1.40)	1.52 (1.39, 1.66)
White race	--	1.80 (1.60, 2.03)	1.85 (1.52, 2.25)
Alcohol abuse	--	1.80 (1.50, 2.17)	1.50 (1.12, 2.02)
Liver disease	--	1.38 (1.10, 1.73)	1.39 (1.03, 1.87)
Smoker	--	1.21 (1.04, 1.42)	1.30 (1.00, 1.67)
Any PPI use	--	1.70 (1.51, 1.92)	1.55 (1.28, 1.89)
BMI	--	0.82 (0.79, 0.85)	0.87 (0.77, 0.99)
BMI ²	--	1.002 (1.002, 1.003)	1.00 (1.00, 1.00)
Current corticosteroid use	--	1.45 (1.21, 1.74)	1.41 (1.06, 1.88)
CD4/100 cells/mm ³	--	--	1.01 (0.98, 1.05)
Current TDF use	--	--	1.29 (0.99, 1.70)
Current PI use	--	--	1.41 (1.16, 1.70)

Osteoporosis Recommendations

- *Observational data in HIV+/- cohorts and established findings in general population*
 - Weight bearing exercise
 - Avoid wasting
 - Smoking and alcohol cessation
 - Avoid steroids and proton pump inhibitors
 - Vitamin D among those with deficiency
 - Treatment if fracture or BMD below 2.5 SD

Multimorbidity

ARS Question 1

50 year old, HIV infected male on ART with an HIV-1 RNA<500, CD4 count 500, normal hemoglobin, creatinine, AST, ALT, and platelets. HCV negative.

If you see that his hemoglobin is 12 g/dL, does this change his risk of mortality?

1. No
2. Yes, modestly
3. Yes, substantially

*In all cases referring to estimated 5 year mortality risk.

ARS Question 2

A 50 year old woman with CD4 count (500 cells /mm³), undetectable HIV-1 RNA, normal hemoglobin, and creatinine, HCV- (estimated 5 year mortality 4%).

If you are told that her AST is 52, ALT is 30, and her platelets are 140K (FIB 4 is 3.39); how does this change her risk of mortality?

1. Minor abnormalities in AST, ALT, no change
2. Risk is doubled
3. Risk is more than 4 times as high

ARS Question 3

50 year old Black woman started on Atripla achieves excellent response (CD4 increases from 350 to 700, HIV-1 RNA <50) but develops a stable, low grade, renal insufficiency (eGFR 44 mL/min). Should you change her ARVs?

1. No, don't mess with success
2. Maybe
3. Definitely, so long as she has other options

Multimorbidity

- Patients have multiple conditions that interact
- Need to consider cumulative injury not just a subset of diagnoses
- Need a means of
 - Tracking cumulative injury and overall risk of adverse outcomes
 - Identifying modifiable mediators of risk

Rationale for Multivariable Risk Index

- A single, summary measure of disease
- Identifies important thresholds for lab tests
- Resolves conflicting results
- Informs prioritization
- Has major statistical advantages
 - Decreased measurement error
 - Each person has a measurable outcome at any time point

Example: Framingham Index

- Assigns points based on 6 factors (5 modifiable)
- Estimates risk of MI or death over the next 5-10 years ranging from 1% to >56%
- Assumes that change in risk due to smoking cessation is same as never having smoked, etc.

Framingham Risk Assessment

ssessment Tool for ...

NATIONAL CHOLESTEROL EDUCATION PROGRAM
Third Report of the Expert Panel on
Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

The [risk assessment tool](#) below uses recent data from the Framingham Heart Study to estimate 10-year risk for "hard" coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes. Use the calculator below to estimate 10-year risk.

Age: years

Gender: Female Male

[Total Cholesterol:](#) mg/dL

[HDL Cholesterol:](#) mg/dL

[Smoker:](#) No Yes

[Systolic Blood Pressure:](#) mm/Hg

Currently on any medication to treat high blood pressure. No Yes

TOP **Total cholesterol** - Total cholesterol values should be the average of at least two measurements obtained from lipoprotein analysis.

TOP **HDL cholesterol** - HDL cholesterol values should be the average of at least two measurements obtained from lipoprotein analysis.

TOP **Smoker** - The designation "smoker" means any cigarette smoking in the past month.

TOP **Systolic blood pressure** - The blood pressure value used is that

Results View:

Risk score results:

Age:	60
Gender:	male
Total Cholesterol:	280 mg/dL
HDL Cholesterol:	100 mg/dL
Smoker:	Yes
Systolic Blood Pressure:	120 mm/Hg
On medication for HBP:	No
Risk Score*	10%

* The risk score shown was derived on the basis of an equation. Other NCEP materials, such as ATP III print products, use a point-based system to calculate a risk score that approximates the equation-based one.

To interpret the risk score and for specific information about CHD risk assessment as part of detection, evaluation, and treatment of high blood cholesterol, see [ATP III Executive Summary](#) and [ATP III At-a-Glance](#).

Uses of Framingham Index

- Assesses relative importance of CHD risk for individual patients
- Quantifies absolute level of CHD risk for individual patients
- Allows clinicians and patients to match the level of treatment to the level of risk
- CHD guidelines are based on these estimates

Veterans Aging Cohort Study Risk Index (VACS Index)

- Composed of age and laboratory tests currently recommended for clinical management
 - HIV Biomarkers: HIV-1 RNA, CD4 Count, AIDS defining conditions
 - “non HIV Biomarkers”: Hemoglobin, hepatitis C, composite markers for liver and renal injury
- Developed in US veterans, validated in Europe and North America



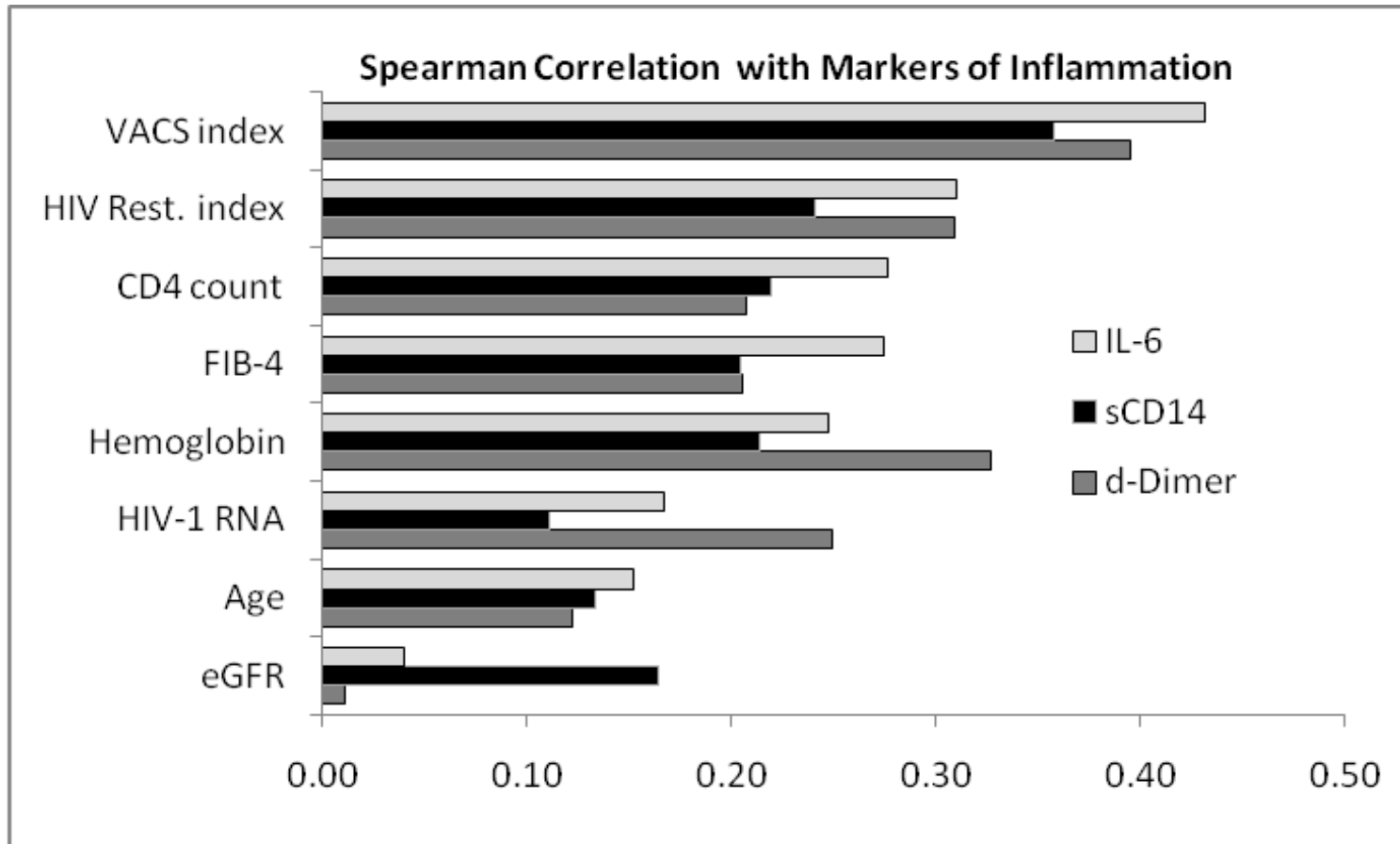
VACS Index for External Validation

		Index Score		
		Restricted	VACS	
Age	Age (years)	<50	0	0
		50 to 64	23	12
		≥ 65	44	27
HIV Specific Biomarkers	CD4 cells/mm³	≥ 500	0	0
		350 to 499	10	6
		200 to 349	10	6
		100 to 199	19	10
		50 to 99	40	28
		< 50	46	29
	HIV-1 RNA copies/ml	< 500	0	0
	500 to 1x10 ⁵	11	7	
	≥ 1x10 ⁵	25	14	
Biomarkers of General Organ System Injury	Hemoglobin g/dL	≥ 14		0
		12 to 13.9		10
		10 to 11.9		22
		< 10		38
	FIB-4	< 1.45		0
		1.45 to 3.25		6
		> 3.25		25
	eGFR mL/min	≥ 60		0
		45 to 59.9		6
		30 to 44.9		8
< 30			26	
Hepatitis C Infection				5





VACS Index Correlated with Biomarkers of Inflammation



Justice AC et al, "Biomarkers of Inflammation, Coagulation, and Monocyte Activation are Strongly Associated with the VACS Index among Veterans on cART" CROI 2011 Poster # 796

Accuracy Characterized in Two Ways:

- **Discrimination:** ability to rank observations according to relative risk of the outcome
 - Typical measure: c statistic (probability that any two random pairs will be accurately ordered based on risk)
 - Easiest to achieve, most emphasized, not very clinically relevant
- **Calibration:** the ability to correctly estimate the probability of outcome for a group
 - Much more useful in clinical decision making
 - Difficult to quantify, can be inspected using calibration curves
 - New approach: use reclassification tables



Discrimination of VACS vs. Restricted Index

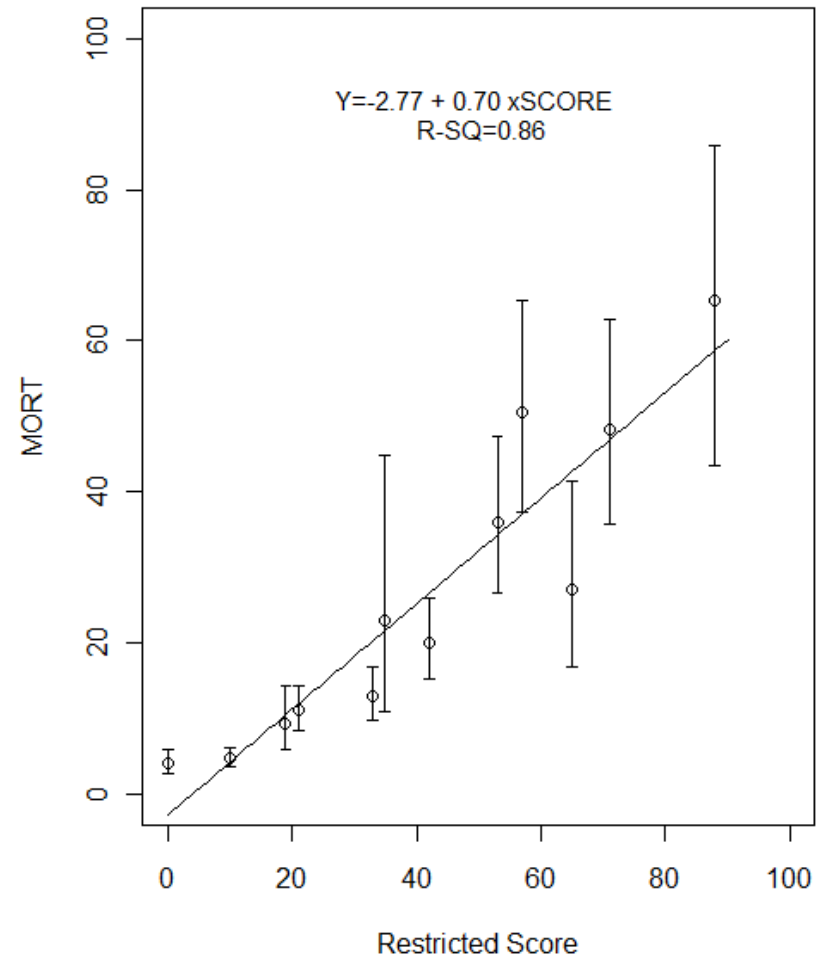
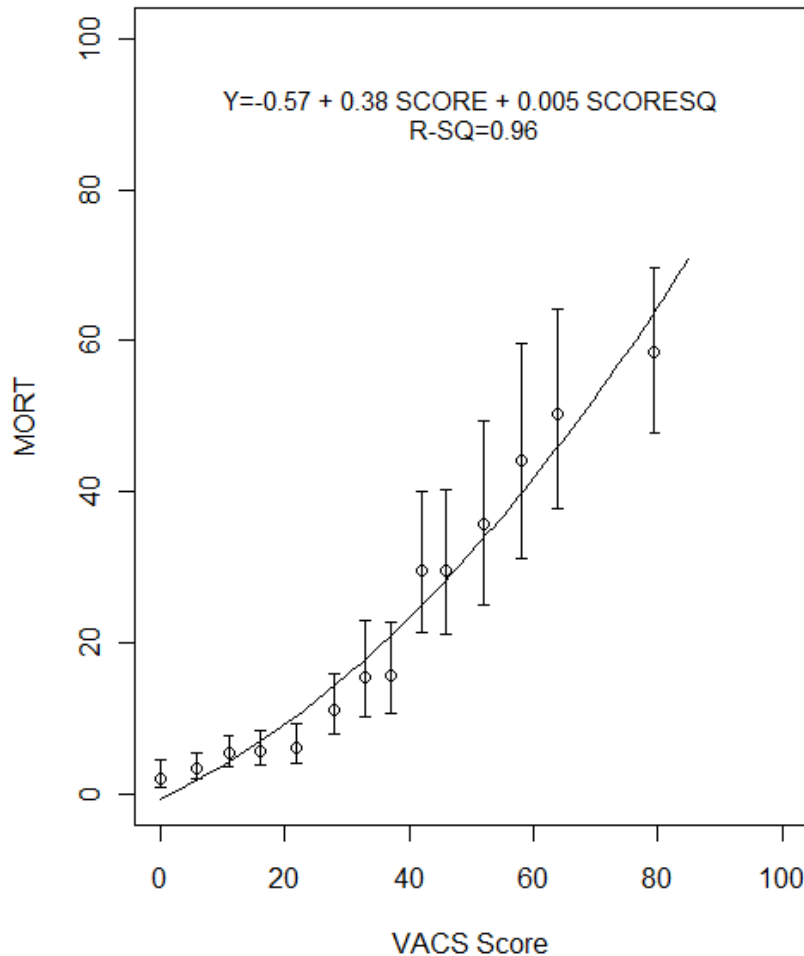
Subgroup	VACS Index C-stat	Restricted Index C-stat	p-value**
Overall	0.80	0.75	<0.0001
Male	0.81	0.75	<0.001
Female	0.81	0.77	<0.001
White	0.79	0.74	<0.001
Black	0.81	0.76	<0.001
Hispanic	0.90	0.78	<0.001
Age			
<50	0.81	0.75	<0.001
>= 50	0.74	0.69	<0.0001
HIV-1 RNA			
<500	0.77	0.68	<0.0001
>=500	0.78	0.74	<0.0001



Calibration of VACS vs. Restricted Index (5 Year Mortality)

3a. VACS Index

3b. Restricted Index





Risk Reclassification (5 Year Mortality)

VACS % Risk Restricted	0-<5	5-<10	10-<15	15-<20	>=20	Total
0-<5	2884 9%	226 16%	42 38%	18 44%	11 65%	3181
5-<10	582 7%	716 4%	141 12%	29 28%	44 13%	1512
10-<15	12 17%	205 7%	96 8%	27 25%	37 31%	377
15-<20	0	38 13%	41 16%	21 21%	19 27%	119
>=20	0	13 15%	80 6%	56 21%	146 22%	295
Total	3478	1198	400	151	257	5484



Risk Reclassification by Subgroup (5 Year Mortality)

Group	n	Higher Risk	Lower Risk	Total Reclassified
Women	969	25% (24%)	7% (11%)	32% (36%)
HIV RNA<500 copies/ml	4216	10% (11%)	15% (21%)	26% (32%)
Black Race	1684	18% (18%)	15% (20%)	33% (39%)
Hispanic Ethnicity	494	9% (8%)	22% (24%)	31% (32%)
Overall	5484	11% (11%)	19% (26%)	30% (37%)

Summary: VACS Index

- Is calibrated and discriminating for mortality among patients with access to ART in North America
- Can be applied at any point in care
- Offers substantially more information than CD4, HIV RNA, and age alone, or in combination
- Shows promise as surrogate endpoint
- Has fulfilled all the same criteria as the Framingham index (with similar or better results)

Why Should Clinicians Care?

- Uses lab tests currently part of routine care
- Identifies modifiable risk at earlier thresholds
- Incorporates age, and effects of HANA and toxicity
- Computation easy, can be included in lab reports and available through websites/apps
- Offers approach to prioritizing care that goes beyond CD4 count and HIV-1 RNA
- May offer a more nuanced approach to the questions of when to: start, switch, or stop

Case 1 (ARS Question 1)

50 year old, HIV infected male on ART with an HIV-1 RNA<500, CD4 count 500, normal hemoglobin, creatinine, AST, ALT, and platelets. HCV negative.

score 8; expected mortality* 4%

–CD4 count 400 cells/mm³, score 18; expected mortality* 9%

–Hemoglobin 12-13.9 g/dL, score 28; expected mortality* 15%

–Hemoglobin 10-11.9 g/dL, score 40; expected mortality* 24%

*In all cases referring to estimated 5 year mortality risk.

Case 2 (ARS Question 2)

A 50 year old woman with CD4 count (500 cells /mm³), undetectable HIV-1 RNA, normal hemoglobin, and creatinine, HCV- (estimated 5 year mortality 4%).

If you are told that her AST is 52, ALT is 30, and her platelets are 140K (FIB 4 is 3.39) how much does this change her risk of mortality?

Her risk has gone from 4% to 19% (risk is more than quadrupled)

Case 3(ARS Question 3)

50 year old Black woman started on Atripla achieves excellent response (CD4 increases from 350 to 700, HIV-1 RNA <50) but develops a stable, low grade, renal insufficiency (eGFR 45-59.9 mL/min). Should you change her ARVs?

The Index would suggest that benefit gained by CD4 response counteracted by harm from renal insufficiency—so long as an alternative regimen can achieve viral suppression.

Interventions to Improve VACS Score

- Usual approach to CD4 count, HIV-1 RNA
- Fib 4 abnormal: ART adherence, alcohol reduction, HCV treatment, HBV vaccination, weight control, med review for toxins (e.g., acetaminophen, statins, ketoconazole, herbal remedies); ? treatment intensification?
- Anemic: ART adherence, alcohol reduction, ART review for toxins (e.g. AZT, D4T), work up for reversible causes; ?treatment intensification?
- eGFR abnormal: blood pressure control, glucose control, med review for toxins (e.g. NSAIDS, Tenofovir)



National VACS Project Team 2010



Veterans Aging Cohort Study

- **PI and Co-PI:** AC Justice, DA Fiellin
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