

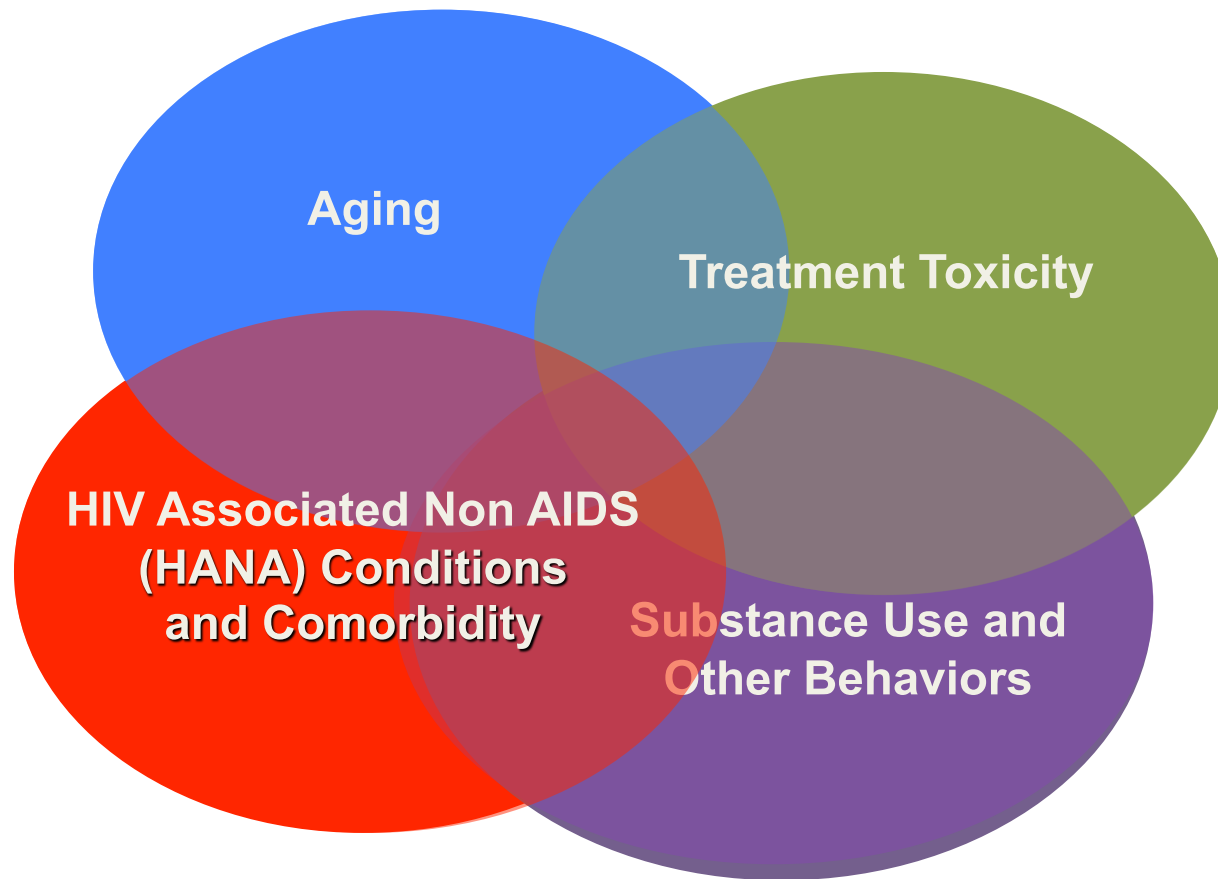
HIV, Comorbidity, and Toxicity: How Can We Most Effectively Improve Patient Outcomes?

Amy C. Justice, MD, PhD

Professor, Yale University School of Medicine
Section Chief, General Internal Medicine, VA Connecticut

OAR Working Group on HIV and Aging, April 15, 2011
NIH, Fishers Lane Conference Center, Rockville MD

Non AIDS Conditions Among Those Aging with HIV



HIV Associated Non AIDS Conditions (HANA)

- After adjustment for usual risk factors, HIV association remains
 - Usual risk factors determine most of the risk
 - Increasing age and substance use often important
- Additional risk may be due to HIV, to ART or both
 - May/may not be associated with CD4 or HIV-1 RNA
 - Chronic viral infection
 - Chronic inflammation (possibly, even among those free of substantial viral replication)

Overlapping Risks

Condition	HIV or HCV – Associated?	Aging- Associated?	Substance Use- Associated?	ARV, other Medication- Associated?
Myocardial Infarction	Both	Yes	Tobacco, Cocaine	Possibly PIs
Diabetes	HCV	Yes	Alcohol	PIs
Stroke	Both	Yes	Cocaine	Anticoagulants
Fragility Fractures	HIV	Yes	Alcohol, Tobacco	Steroids, PPIs
Liver Cirrhosis	Both	Yes	Alcohol	Lots
“Infectious” Cancers	Liver-HCV Anal-HIV, HPV	Yes	Liver-Alcohol	Unknown
Non-Infectious Cancers	Lung-HIV	Yes	Lung-Tobacco	Unknown
Pneumonia	HIV	Yes	Tobacco, Alcohol	Unknown
Obstructive Lung Disease	HIV	Yes	Tobacco	Unknown



Not
Adjusted
for
Competing
Risk of
Death

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)



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

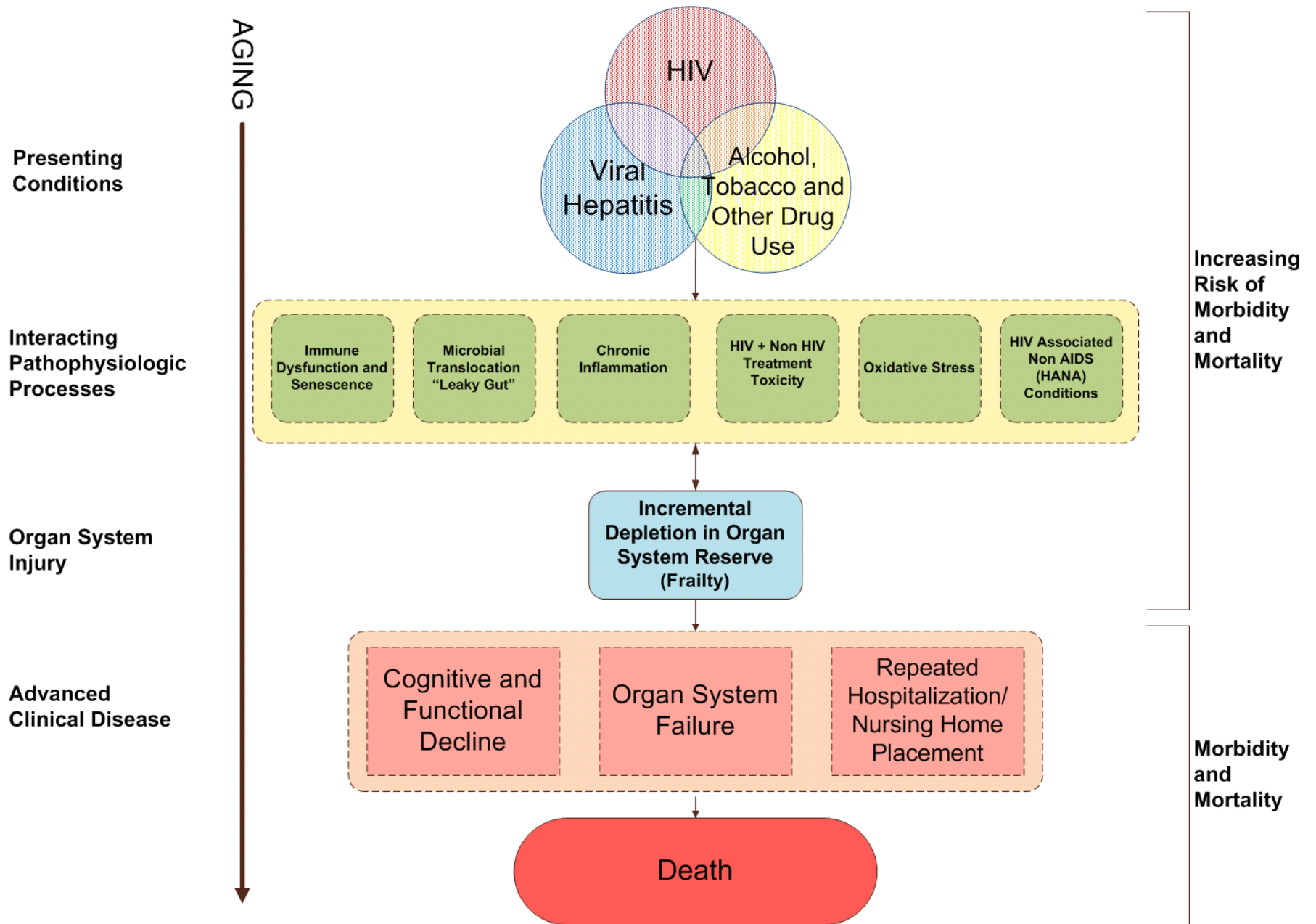
	HIV Model	Full Model	HIV+ Men
HIV	1.32 (1.20, 1.47)	1.10 (0.97, 1.25)	--
Age (10 yr increments)	--	1.32 (1.25, 1.40)	1.52 (1.39, 1.66)
White race	--	1.80 (1.60, 2.03)	1.85 (1.52, 2.25)
Alcohol abuse	--	1.80 (1.50, 2.17)	1.50 (1.12, 2.02)
Liver disease	--	1.38 (1.10, 1.73)	1.39 (1.03, 1.87)
Smoker	--	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)

Note

- Range of relative risk with HIV variable
 - Fragility fracture risk modest (1.3)
 - Cardiovascular risk may be substantial (>2 fold)
- 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

Multimorbidity

- Patients have multiple, clinically significant, conditions that likely interact
- Need to consider cumulative injury on major organ systems and overall functional compromise not just a subset or count of diagnoses
- Need a means of tracking these



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

Framingham Index

- Assigns points based on 6 factors (5 modifiable) to estimate risk of MI or CVD death over 10 years (from 1% to >56%)
- Assumes that change in risk due to change in factor is same as never having had the factor
- Quantifies absolute level of CHD risk for individual patients and allows level of treatment to be matched to level of risk
- CHD guidelines are based on these estimates, has been used as an outcome in RCTs

D'Agostino RB. Et al. Validation of the Framingham Coronary Heart Disease Prediction Scores: Results of a Multiple Ethnic Groups Investigation. JAMA 2001;286:180-187

Veterans Aging Cohort Study Risk Index (VACS Index)

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



Composite Biomarkers

$$\text{FIB 4} = \frac{\text{AGE} * \text{AST}}{\text{PLT} * \text{sqrt}(\text{ALT})}$$

$$\text{eGFR} = 186.3 * \text{CREAT}^{-1.154} * \text{AGE}^{-0.203} * \text{FEM_VAL} * \text{BLACK_VAL}$$

FEM_VAL = 0.742 if female, 1 if male

BLACK_VAL = 1.21 if black, 1 otherwise

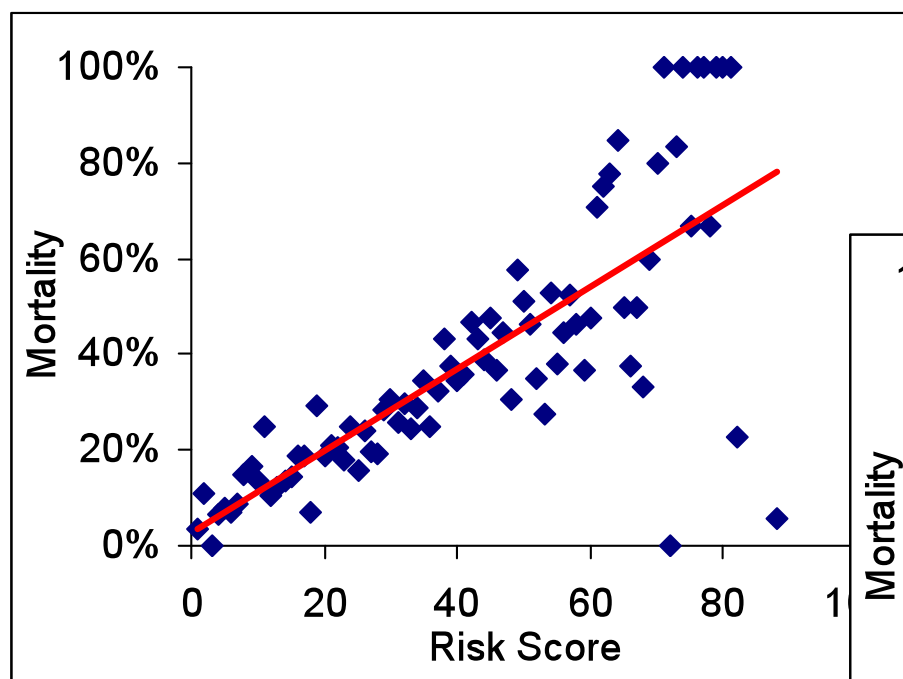
VACS Index Thresholds and Points

			Index Score	
			Restricted	VACS
Age	Age (years)	<50	0	0
		50 to 64	23	12
		≥ 65	44	27
HIV Specific Biomarkers	CD4 cells/mm ³	≥ 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
Biomarkers of General Organ System Injury		500 to 1x10 ⁵	11	7
		≥ 1x10 ⁵	25	14
	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

Tate J. et al. IDSA 2010 Vancouver, BC October 21-24th. Poster 1136

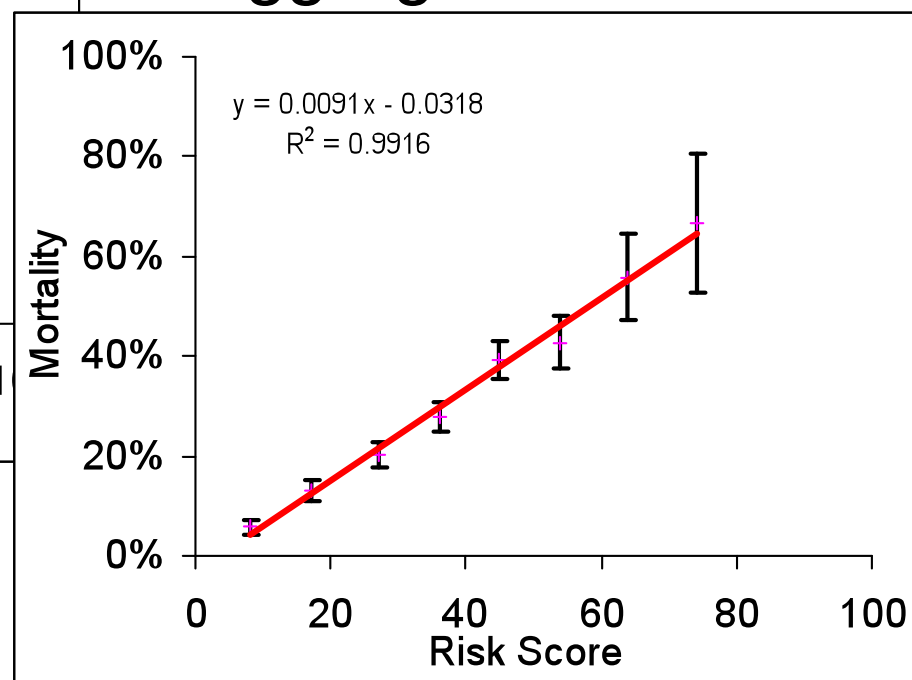


VACS Index Highly Predictive of Long Term (5 Year) All Cause Mortality



Individual Scores

Aggregated Scores



Justice, AC. et. al, *HIV Med.* 2010 Feb;11(2):143-51. Epub 2009 Sep 14.

Justice AC. *HIV and Aging: Time for a New Paradigm.* *Curr HIV/AIDS Rep.* 2010 May;7(2):69-76



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

Justice AC. et al. A Prognostic Index for those Aging with HIV. CROI 2011 Poster # 793



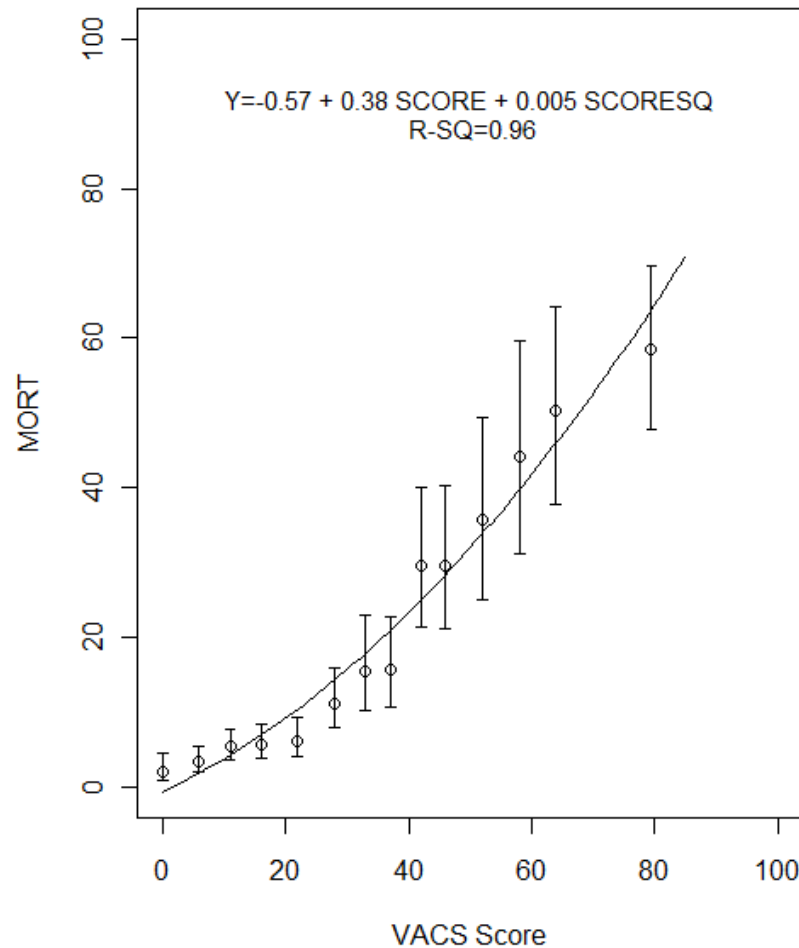
Risk Reclassification by Subgroup (5 Year Mortality)

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%)

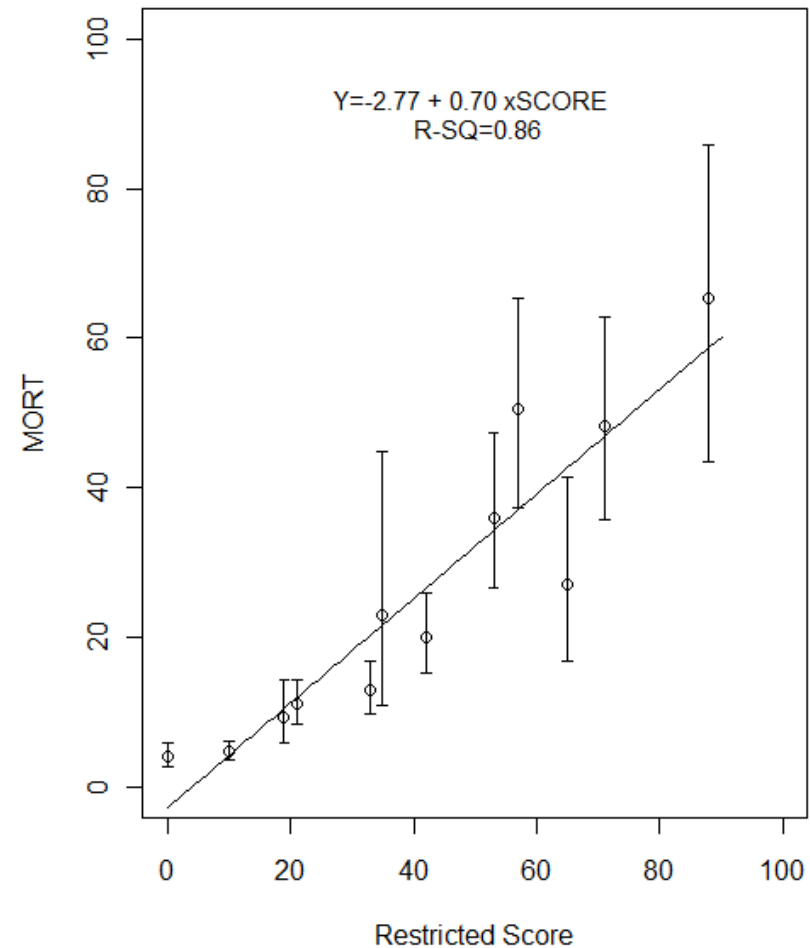


Calibration of VACS vs. Restricted Index (5 Year Mortality)

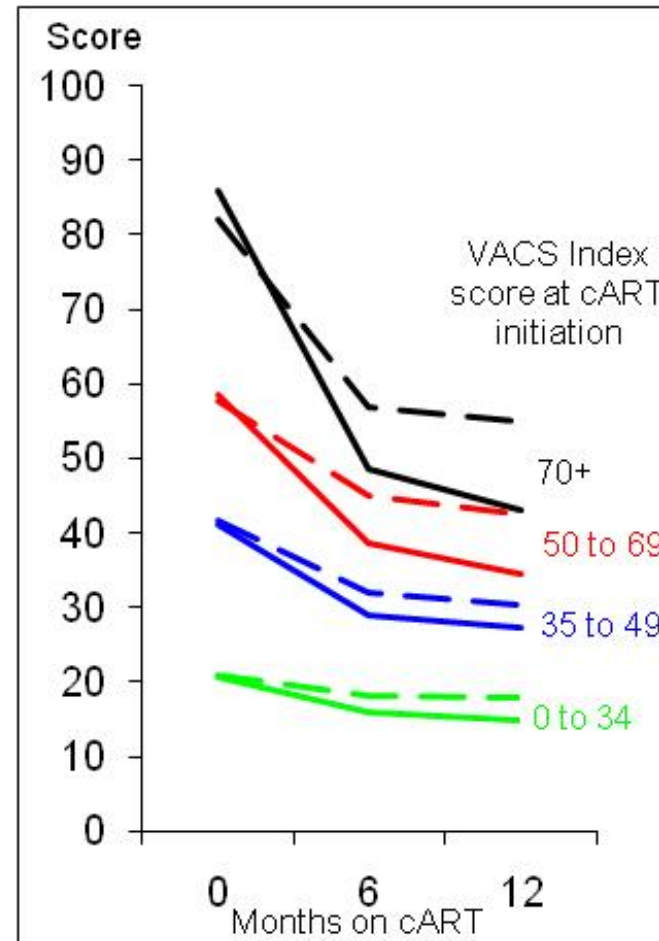
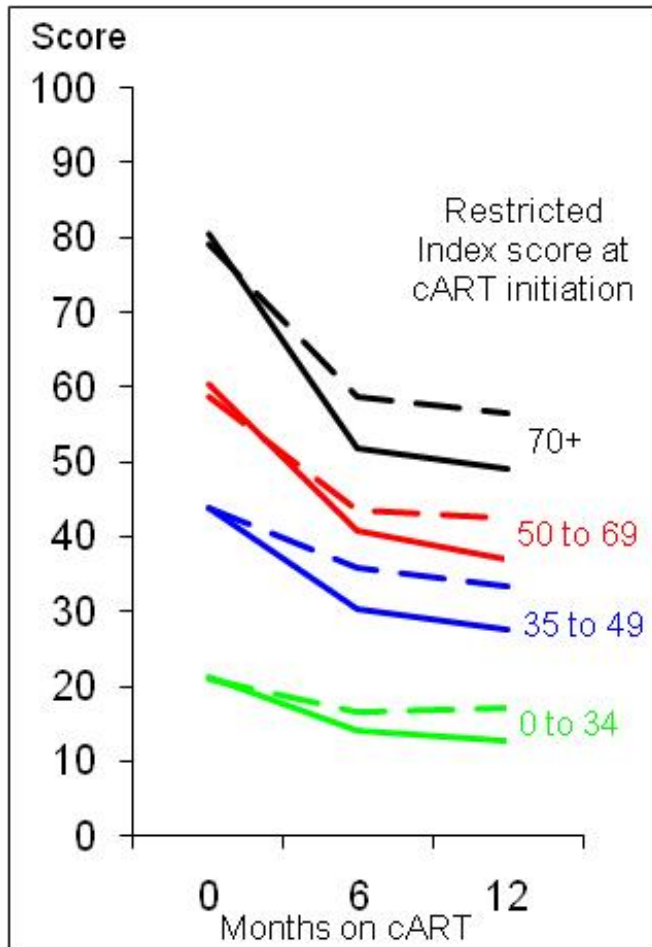
3a. VACS Index



3b. Restricted Index



Response to 1st Year of cART (+/- 80% adherence)



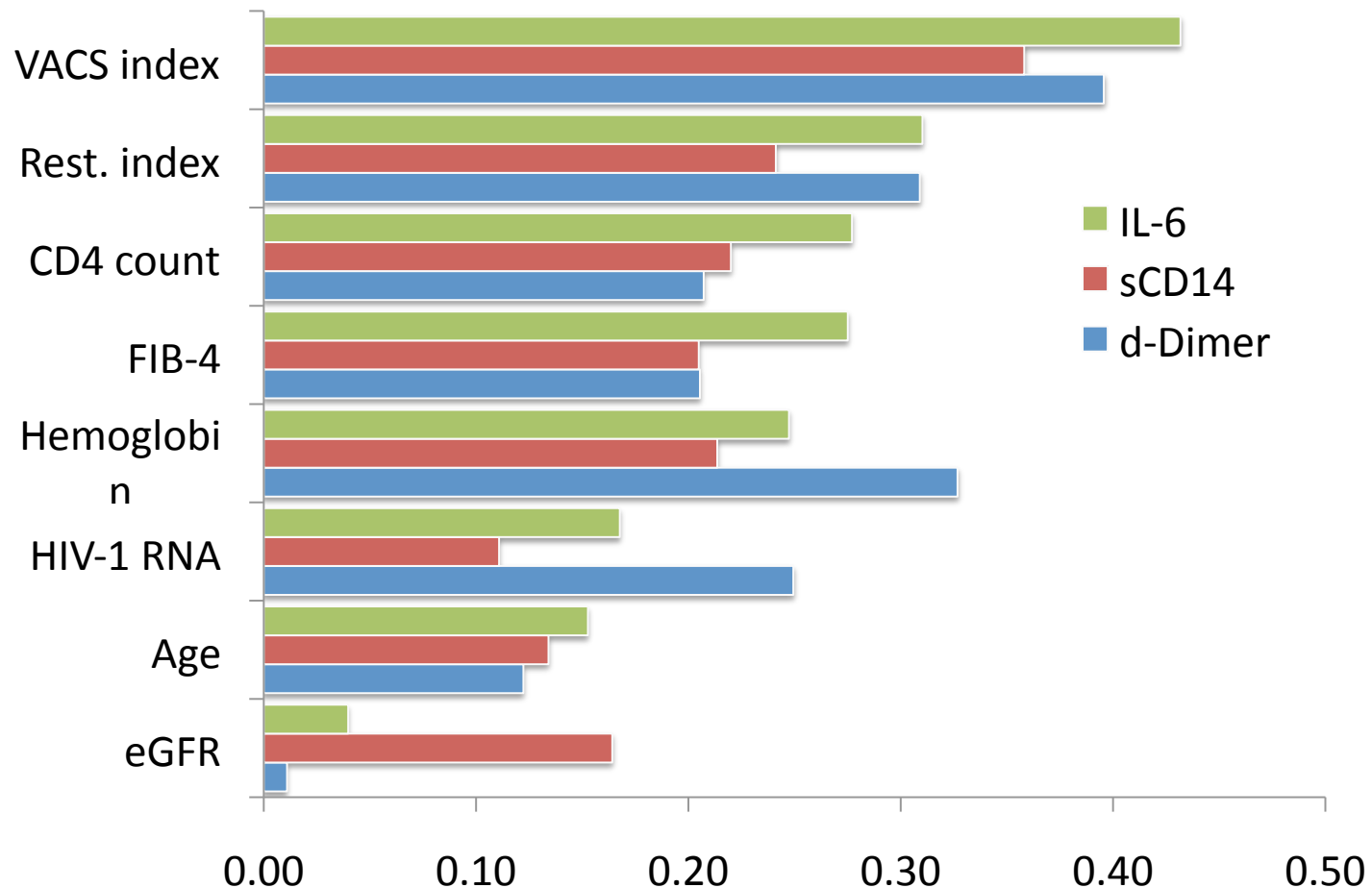
Solid lines indicate $\geq 80\%$ adherence

Tate J. et al. IDSA 2010 Vancouver, BC October 21-24th. Poster 1136





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

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
- Has fulfilled the same criteria as the Framingham index (with similar or better results)
- Might test whether Index improved by adding D-dimer, hypertension, BMI, or functional capacity.

Advantages

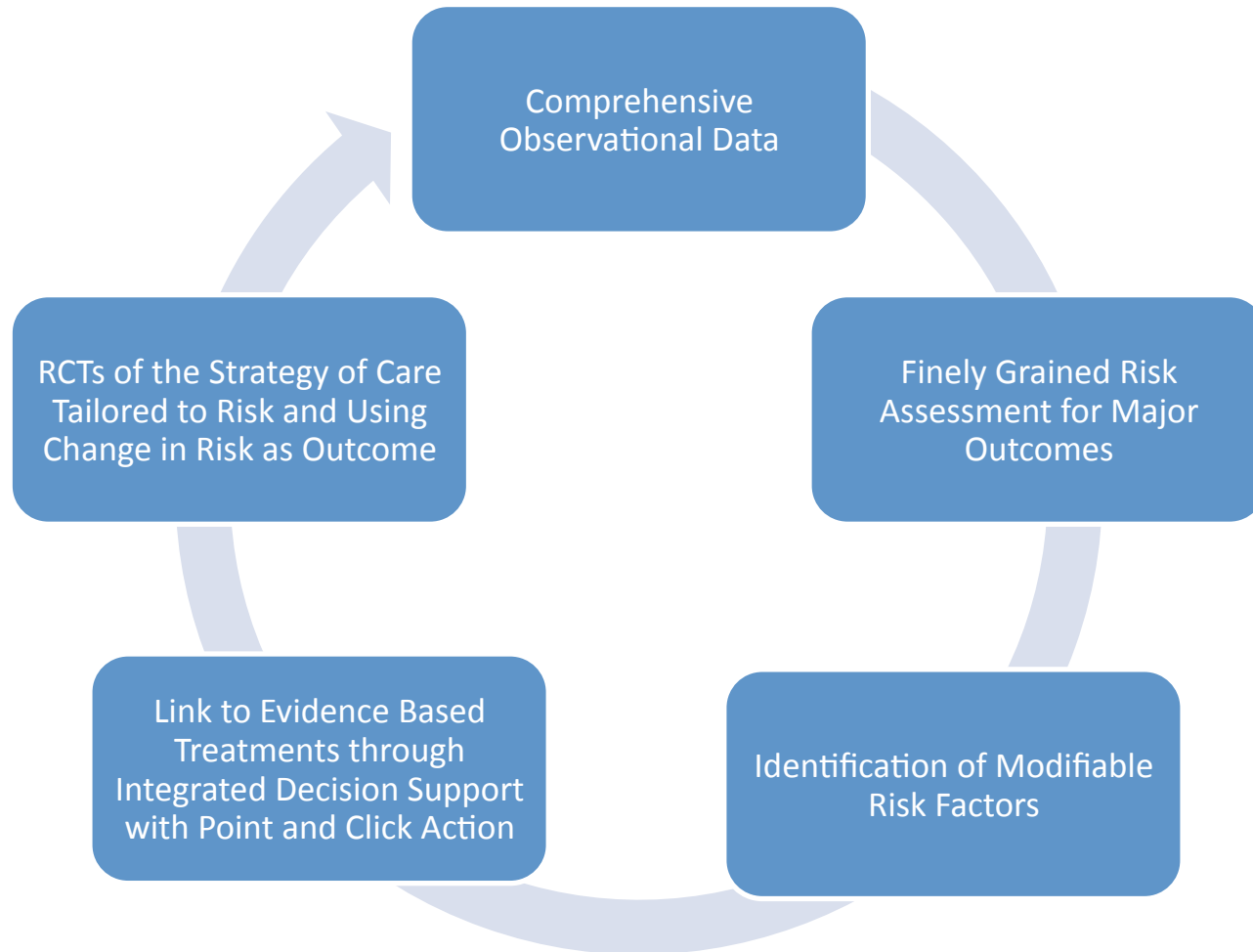
- Computationally easy, widely valid, well calibrated
- Uses lab tests currently part of routine care; but extends well beyond CD4 and HIV-1 RNA
- Identifies modifiable risk early in course of disease
 - To prioritize care
 - To motivate behavior change
- Offers a means of comparing effectiveness of diverse interventions (behavior to therapeutics)
- A new approach to when to start, switch, or stop

Potential Interventions to Lower VACS Risk Index

	CD4 and HIV-1 RNA	Hemoglobin	eGFR	FIB 4	HCV
ARV optimization (choice, timing, and adherence)	+++	+++/-	+/-	++/-	NA
Alcohol Cessation	++ (adherence)	+	NA	+++	NA
HCV Treatment	NA	+	NA	++/-	+++
HBV Treatment	NA	+	NA	++/-	NA
Medication Review	+	++	+++	++	NA
Blood Pressure Control	NA	NA	+++	NA	NA

So, how can we most effectively
improve outcomes among
patients aging with HIV
infection?

Risk and Optimized Care





National VACS Project Team 2010



Veterans Aging Cohort Study

- **PI and Co-PI:** AC Justice, DA Fiellin
- **Scientific Officer (NIAAA):** K Bryant
- **Participating VA Medical Centers:** Atlanta (D. Rimland), Baltimore (KA Oursler, R Titanji), Bronx (S Brown, S Garrison), Houston (M Rodriguez-Barradas, N Masozera), Los Angeles (M Goetz, D Leaf), Manhattan-Brooklyn (M Simberkoff, D Blumenthal, H Leaf, J Leung), Pittsburgh (A Butt, E Hoffman), and Washington DC (C Gibert, R Peck)
- **Core Faculty:** K Akgun, S Braithwaite, C Brandt, K Bryant, R Cook, K Crothers, J Chang, S Crystal, N Day, R Dubrow, M Duggal, J Erdos, M Freiberg, M Gaziano, M Gerschenson, A Gordon, J Goulet, N Kim, M Kozal, K Kraemer, V LoRe, S Maisto, K Mattocks, P Miller, P O'Connor, C Parikh, C Rinaldo, J Samet
- **Staff:** H Bathulapalli, T Bohan, D Cohen, A Consorte, P Cunningham, A Dinh, C Frank, K Gordon, J Huston, F Kidwai, F Levin, K McGinnis, L Park, C Rogina, J Rogers, L Sacchetti, M Skanderson, J Tate, E Williams
- **Major Collaborators:** VA Public Health Strategic Healthcare Group, VA Pharmacy Benefits Management, Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), Yale Center for Interdisciplinary Research on AIDS (CIRA), Center for Health Equity Research and Promotion (CHERP), ART-CC, NA-ACCORD, HIV-Causal
- **Major Funding by:** National Institutes of Health: NIAAA (U10-AA13566), NIA (R01-AG029154), NHLBI (R01-HL095136; R01-HL090342; RCI-HL100347), NIAID (U01-A1069918), NIMH (P30-MH062294), and the Veterans Health Administration Office of Research and Development (VA REA 08-266) and Office of Academic Affiliations (Medical Informatics Fellowship).