Aging with HIV: Multimorbidity, Risk Assessment, and Personalized Health Care

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No Conflict
Key Considerations When Caring for Older HIV-Infected Patients*

- **Comorbid disease complicates management**
- **HIV may effect biology of aging**
- Reduced mucosal/immune defenses and changes in risk behavior may increase transmission
- Less screening leads to delayed diagnosis

*DHHS Guidelines accessed 11/5/2012, Key Considerations When Caring for Older HIV-Infected Patients.
DHHS Call for Personalized Rx*

• ART regimen choice should be informed by comprehensive review of other medical conditions

• Older individuals may be at greater risk of adverse effects and drug-drug interactions
  – Liver and kidney disease

• Regimen simplification and discontinuation of unnecessary medications may be necessary

*DHHS Guidelines accessed 11/5/2012, HIV, Aging and Antiretroviral Therapy
Polypharmacy

• Typically defined as >5 drugs

• Associated with diminished marginal benefit from additional medication due to:
  – Nonadherence
  – Adverse drug events (confusion, falls, renal failure, etc.)

• Risk of adverse events increases approximately 10% with each additional medication

Gandhi TK. N Engl J Med 2003;348:1556-64
Swiss Cohort

NB: most patients on 3 ARVs in addition to these medications, polypharmacy is the norm at 50 years.

Primary Care Recommendations*

“...are the same for HIV-infected and HIV-uninfected adults and focus on identifying and managing risks of conditions such as heart, liver, and renal disease; cancer; and bone demineralization.”

*DHHS Guidelines accessed 11/5/2012, Non-AIDS HIV-Related Complications and Other Comorbidities
Guideline Overload

• Applied guidelines for 10 common chronic diseases to a closed panel of 2500 primary care patients
  – Age, sex, and disease prevalence matched to US
  – Did not allow for new problems or new patients

• Estimated MD time/workday required assuming
  – All stable (3.5 hours/day)
  – Some active disease (10.6 hours/day)

• HIV-infected patients have even more guidelines!

Decision to Screen/Treat Comorbid Disease is a Risk Balancing Act

**Favors** Screening/Treatment

- Disease Risk
- Benefits of Treatment

**Against** Screening/Treatment

- Short Life Expectancy
- Harms of Screening/Rx

It appears to me a most excellent thing for the physician to cultivate Prognosis...He will manage the cure best who has foreseen what is to happen from the present state of matters....for he will be the better able to treat those aright who can be saved.

---excerpt from The Book of Prognostics, a Hippocratic treatise

Value of Prognosis is Not New:

Hippocrates, the father of Western medicine
460 BC-370 BC
What is New Since Hippocrates?

• Multimorbidity the norm—no longer treating only one condition

• Plethora of
  – Biomarkers and indices
  – Treatment options

• **New opportunity:** EMRs can collect “Big Data” and calculate and interpret indices
Risk Assessment is Integral to Care

At each decision node, inaccuracy in risk estimation can cost time, money, and lives.
How Do We Assess Risk?

• Clinical judgment
  – History, exam, experience
  – On average good, but variable
  – Heuristics /bias

• Clinical judgment + individual biomarkers
  – Subject to reproducibility, accuracy, availability
  – Biomarkers disagree
  – Threshold for action not obvious
Clinical Judgment + Prognostic Indices

• Integration of 100s-1000s more patient observations than any provider has in a lifetime
• Can decrease variability and improve accuracy
• By combining biomarkers, indices reduce susceptibility to error for any single marker
• Prior to EMRs, indices were inconsistently used
• Results of head to head comparisons of clinical judgment vs. index prediction are mixed
Common Indices

• Disease Specific (simple, often memorized):
  – Framingham Risk Index: myocardial infarction
  – Child-Pugh Score: liver cirrhosis
  – Gold Criteria: chronic obstructive pulmonary disease

• General (often complex):
  – MICU mortality: APACHE
  – Geriatric mortality: ePrognosis
Note: an Index that Doesn’t Include All Sources of Risk Can Be Useful

• Not possible to include all sources
  – May not be measured or known
  – Likely “upstream”

• A responsive estimate of risk enables:
  – Mapping progress
  – Comparing effectiveness
  – Planning care intensity
Note: Accuracy May Vary by Outcome Predicted

- Mortality or specific events are most common
- That which predicts one outcome may or may not predict other outcomes
- Ability to predict multiple relevant outcomes is a test of robustness
Tailor Screening and Treatment to Individual Risk

• Use prediction tools to estimate net benefit
  – Accounting for treatment disutilities
  – Accounting for payoff time

• Requires two inputs:
  – Accurate estimation of risk
  – Risk reduction associated with interventions

The Veterans Aging Cohort Index

VACS Index
Components of VACS Index

• Age

• HIV Biomarkers: HIV-1 RNA, CD4 Count

• General Biomarkers: Hemoglobin, HCV, Composite markers for liver and renal injury

• Assessed among those initiating treatment

• Adjusted to predict among those on treatment
Composite Biomarkers

FIB 4 = \frac{AGE \times AST}{PLT \times \sqrt{ALT}}

eGFR = 186.3 \times CREAT^{-1.154} \times AGE^{-0.203} \times FEM\_VAL \times BLACK\_VAL

FEM\_VAL = \begin{cases} 0.742 & \text{if female, 1 if male} \\ 1 & \text{otherwise} \end{cases}

BLACK\_VAL = \begin{cases} 1.21 & \text{if black, 1 otherwise} \\ 1 & \text{otherwise} \end{cases}
<table>
<thead>
<tr>
<th></th>
<th>Index Score</th>
<th>Restricted</th>
<th>VACS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>50 to 64</td>
<td>23</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>&gt; 65</td>
<td>44</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td><strong>CD4 cells/mm³</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 500</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>350 to 499</td>
<td>10</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>200 to 349</td>
<td>10</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>100 to 199</td>
<td>19</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>50 to 99</td>
<td>40</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>46</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td><strong>HIV-1 RNA copies/ml</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 500</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>500 to 1x10⁵</td>
<td>11</td>
<td>7</td>
<td></td>
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<tr>
<td>≥ 1x10⁵</td>
<td>25</td>
<td>14</td>
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<tr>
<td><strong>Hemoglobin g/dL</strong></td>
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<tr>
<td>≥ 14</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>12 to 13.9</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>10 to 11.9</td>
<td>22</td>
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<tr>
<td>&lt; 10</td>
<td>38</td>
<td></td>
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<tr>
<td><strong>FIB-4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1.45</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1.45 to 3.25</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3.25</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>eGFR mL/min</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥ 60</td>
<td>0</td>
<td>0</td>
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<tr>
<td>45 to 59.9</td>
<td>6</td>
<td>6</td>
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</tr>
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<td>30 to 44.9</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>26</td>
<td></td>
<td></td>
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<tr>
<td><strong>Hepatitis C Infection</strong></td>
<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>
VACS Index Predicts Mortality
VACS Index Equally Predictive of Cardiovascular as All Cause Deaths (n=4932)

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Age Only</th>
<th>Restricted Index</th>
<th>VACS Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.67 (0.58-0.76)</td>
<td>0.70 (0.61-0.78)</td>
<td>0.77 (0.70-0.85)</td>
</tr>
<tr>
<td>All Cause</td>
<td>na</td>
<td>na</td>
<td>0.78 (0.76-0.80)</td>
</tr>
</tbody>
</table>

Justice A. et al. Reply to Chow. CID 2012
### Discrimination (C Statistic) of VACS Vs. Restricted Index (n=3146; VA omitted)

<table>
<thead>
<tr>
<th>Mortality Outcome</th>
<th>Restricted Index</th>
<th>VACS Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause</td>
<td>0.78 (0.72, 0.84)</td>
<td>0.82 (0.77, 0.87)</td>
</tr>
<tr>
<td>HIV</td>
<td>0.90 (0.83, 0.98)</td>
<td>0.93 (0.88, 0.98)</td>
</tr>
<tr>
<td>Non HIV</td>
<td>0.77 (0.67, 0.86)</td>
<td>0.78 (0.69, 0.88)</td>
</tr>
</tbody>
</table>

Tate J et al. The VACS Index: An internationally generalizable risk index for mortality after one year of antiretroviral therapy. AIDS in press,
Accuracy of VACS Index for All Cause Mortality in NA-ACCORD

## Discrimination

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>VACS Index</th>
<th>Restricted Index</th>
<th>p**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.80</td>
<td>0.75</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>0.81</td>
<td>0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.81</td>
<td>0.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>0.79</td>
<td>0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>0.81</td>
<td>0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.90</td>
<td>0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>0.81</td>
<td>0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;= 50</td>
<td>0.74</td>
<td>0.69</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HIV-1 RNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500</td>
<td>0.77</td>
<td>0.68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;=500</td>
<td>0.78</td>
<td>0.74</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

1-5 Year Mortality Rates

Justice AC. et al. A Prognostic Index for those Aging with HIV. CROI 2011 Poster # 793
A. NA-ACCORD (N=10835)
B. VACS (N=5066)

C. Men (N = 12785)
D. Women (N = 3116)

E. Age < 50 years (N = 11191)
F. Age >50 years (N = 4710)

G. Black (N = 5878)
H. White (N = 6079)

I. Undetectable VL (N=8715)
J. Detectable VL (N = 7186)
Risk Reclassification Index

- 25% of NA-ACCORD subjects with an undetectable viral load were correctly reclassified using the VACS Index compared to an index restricted to CD4 count, HIV-1 RNA and age.

- >80% of HIV+ patient on cART in most clinical settings have an undetectable viral load.
VACS Index Predicts 30 Day Mortality in HIV+/- Veterans

Table 3. Multivariable analyses of 30-day mortality after MICU admission, 83 deaths in 588 patients with VA MICU admission.  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>10.9 (0.73, 163)</td>
</tr>
<tr>
<td>VACS Index on MICU admission/5 points in HIV+</td>
<td>1.22 (1.14, 1.30)</td>
</tr>
<tr>
<td>VACS Index on MICU admission/5 points in uninfected</td>
<td>1.50 (1.29, 1.76)</td>
</tr>
<tr>
<td>Non-Black race/ethnicity (reference Black)</td>
<td>1.55 (0.85, 2.83)</td>
</tr>
<tr>
<td><strong>Hospital admission admission code</strong> (reference cardiovascular)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>26.8 (5.25, 137)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>11.7 (2.46, 55.9)</td>
</tr>
<tr>
<td>Other&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.59 (1.47, 29.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Significant interaction identified between HIV and VACS Index score at MICU admission (p=0.01); C-statistic = 0.87, with Hesmer-Lemeshow lack of fit p = 0.57.

<sup>b</sup> Other diagnostic categories include cancer, GI and liver, renal, endocrine, neurologic and other.

Akgun K. Critical Care Medicine, in press.
VACS Index Correlated with Inflammatory Biomarkers, Functional Performance, and Neurocognitive Function
Justice AC et al, "Biomarkers of Inflammation, Coagulation, and Monocyte Activation are Strongly Associated with the VACS Index among Veterans on cART" CID published online 1/15/2012
Oursler K. et al. Co-morbidity is predictive of muscle strength in HIV veterans: results from the VACS Index. CROI 2012 Poster #859
Higher veterans aging cohort study (VACS) index scores are associated with concurrent risk of neurocognitive impairment

M.J. Marquine¹, D.J. Moore¹, D.J. Gouaux¹, A. Rooney¹, S.P. Woods¹, S.L. Letendre², R.J. Ellis³, I. Grant³

¹University of California San Diego, Psychiatry, San Diego, USA; ²University of California San Diego, Medicine, San Diego, USA; ³University of California San Diego, Neurosciences, San Diego, USA

- **VACS Index strongly associated with NCI** (p<0.001)
  - Age, hemoglobin, HCV independently associated
  - HIV-1 RNA, CD4 count, FIB 4, eGFR less so (need to know how much variation present)
  - Overall index did as well as components

- **1274 HIV+ subjects**

- Frascati consistent neurocognitive battery sensitive to HIV associated cognitive deficits
VACS Index is Predictive of Major Morbidity
MICU Admission Over 6 Years

Kaplan-Meier Survival Estimates

HIV Restricted Index

VACS Index

Akgun K. et al. JAIDS In Press
VACS Index is Responsive to Change in Risk
VACS Index Response to 1st Year of cART

Solid lines indicate >80% adherence

Tate J. et al. Change in a prognostic index for survival in HIV infection after one year on cART by level of adherence. IDSA 2010
OPTIMA Trial

- Options in Management with Antiretrovirals
- Multi-national collaboration (US Department of Veterans Affairs, Canadian Institutes for Health Research, UK Medical Research Council) conducted from 2001-2007
- Randomized 339 patients with advanced multi-drug resistant HIV infection
- 2X2 factorial design of standard ARV regimen (3-4 drugs) or (>=5 drugs) with or without an initial 3 month treatment interruption
- Time to all-cause mortality or new AIDS defining event
- Showed no significant difference between interventions in either primary endpoints (52%) or death (36% of patients)
Application of VACS Index to OPTIMA Data

- VACS Index scores determined at baseline and every 3 months from data obtained during regularly scheduled study visits.
- VACS Index was highly responsive to treatment changes as were traditional biomarkers ("Restricted").

KA Kirkwood, VACS Index as a Surrogate Outcome for HIV/AIDS Clinical Trials. Joint Statistical Meeting August 2, 2012
Mortality was accurately predicted by baseline VACS Score (ROC $c = .753$)

Compared with Restricted Index, Reclassifying percentage of deaths with the VACS Index leads to a 23.2% improvement
5 Point Change in VACS Index Associated with Change in Risk

KA Kirkwood, VACS Index as a Surrogate Outcome for HIV/AIDS Clinical Trials. Joint Statistical Meeting August 2, 2012
VACS Index Summary

- Is accurate among patients with access to cART in the US and Europe
- Offers more than CD4, HIV RNA, and age
- Encompasses aspects of frailty
- Is responsive to change in risk and can be used to map burden of disease over time
- A means of comparing effectiveness of diverse interventions
- May be a promising surrogate outcome
Implementation

Please help us make this as useful as possible.
Individualized Risk Portal
HTTP://VACS.MED.YALE.EDU

Last month: >1000 hits

VACS Index Calculator

- **Age:** 52 years
- **Sex:** Male
- **Race:** Black
- **CD4:** > 500 cells/mm³
- **HIV-1 RNA:** < 500 copies/ml
- **Hemoglobin:** > 14 g/dL
- **AST:** 44 U/L
- **ALT:** 35 U/L
- **Platelet count:** 140 x 10⁹/L
- **FIB-4:** 2.76
- **Serum Creatinine:** 1.2
- **eGFR:** 82 ml/min
- **Hepatitis C:** No

**VACS Index:** 39

**5 Year Mortality Risk:** 18%

[What does this mean?]  [Comments]
Interpretation

On average, if 100 people with HIV infection taking antiretroviral treatment had this VACS Score, 82 of them would be alive 5 years from now and 18 would be dead.
Comment Page

Would you like to help us make the VACS Index calculator even better?

Please leave us a comment

Would you like to register to receive updates when new VACS Index information is posted?
Email

Are you a
Clinician
What other?

Submit
With thanks to participants in VACS, ART-CC, and NA-ACCORD
Veterans Aging Cohort Study

- **Consortium PI**: AC Justice*
- **Scientific Officer (NIAAA)**: K Bryant
- **Affiliated PIs**: N Berliner, S Braithwaite, K Crothers*, DA Fiellin*, M Freiberg*, V LoRe*
- **Participating VA Medical Centers**: Atlanta (D. Rimland*, J Guest), 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 and Workgroup Chairs**: C Brandt, R Dubrow, N Gandhi, J Lim, K McGinnis, C Parikh, J Tate, E Wang, J Womack
- **Staff**: H Bathulapalli, T Bohan, J Ciarleglio, D Cohen, A Consorte, P Cunningham, A Dinh, L Erickson, C Frank, K Gordon, J Huston, F Kidwai-Khan, G Koerbel, F Levin, M Mezes, L Piscitelli, C Rogina, S Shahrir, M Skanderson, A Varcas
- **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
- **Cross Cohort Collaborators**: Richard Moore (NA-ACCORD), Jonathan Stern (ART-CC), Brian Agan (DoD), Miguel Hernan (HIV-Causal)
- **Major Funding by**: National Institutes of Health: AHRQ (R01-HS018372), NIAAA (U10-AA13566, U24-AA020794, U01-AA020790), 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, VA IRR Merit Award) and Office of Academic Affiliations (Medical Informatics Fellowship)

*Indicates individual is also the Chair of a Core or Workgroup
Want to know more?

Study Website: [www.vacohort.org](http://www.vacohort.org)

Index Calculator: [HTTP://VACS.MED.YALE.EDU](http://HTTP://VACS.MED.YALE.EDU)