HIV and Aging: One Size Does Not Fit All

Amy C. Justice, MD, PhD
PI, Veterans Aging Cohort Study
Professor of Medicine and Public Health
Yale University
Preface
Most medical treatments have been designed for the “average patient.” As a result of this “one-size-fits-all-approach,” treatments can be very successful for some ...but not for others.

Accessed 10/6/2015
https://www.whitehouse.gov/precision-medicine
Precision Medicine Initiative

Mission statement:

To enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized* treatments.

*[taking] into account individual differences in people’s genes, environments, and lifestyles.

Accessed 10/6/2015
https://www.whitehouse.gov/precision-medicine
Ironic, Isn’t It?

• We can talk about aging with HIV because of the survival benefit of antiretroviral therapy (ART)
  – Developed based on “average patient” response

• ART also decreases HIV transmission

• With the exception of viral resistance assays, neither genetics nor metabolomics have had much impact on HIV or aging

• So, why doesn’t “one size fit all”? 
Bill, age 77

Sue, age 73

Anna, age 64
An Approach to Precision Medicine for those Aging with HIV:

Individualized Prioritization, Simplification, and Patient Empowerment
Current Status
Percentage of Adults Living with HIV Aged 50+ By Year and Region

Source: UNAIDS 2012 estimates.
## Life Expectancy Not “Normal”

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cohort/study name</th>
<th>Country of study</th>
<th>LE in HIV-positive population</th>
<th>LE in general population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakagawa <em>et al.</em> [8]</td>
<td>Computer simulation (HIV Synthesis)</td>
<td>UK</td>
<td>LE at birth: 75.0 years if diagnosed with HIV with high CD4 count; 71.5 years if diagnosed with HIV with low CD4 count</td>
<td>LE at birth: estimated from model to be 82.0 years if not infected with HIV</td>
</tr>
<tr>
<td>The Antiretroviral Therapy Cohort Collaboration [9]</td>
<td>ART-CC (Europe and North America)</td>
<td>Multi-country study</td>
<td>LE at age 20: 43.1 years. LE at age 35: 31.7 years</td>
<td>Not stated</td>
</tr>
<tr>
<td>Johnson <em>et al.</em> [10]</td>
<td>leDEA-SA</td>
<td>South Africa</td>
<td>LE at age 20: 276 years in men; 368 years in women. LE at age 60: 10.1 years in men; 144 years in women</td>
<td>Not stated</td>
</tr>
<tr>
<td>Losina <em>et al.</em> [12]</td>
<td>Computer simulation (CEPAC)</td>
<td>USA</td>
<td>LE at age 33: 2266 years if optimally diagnosed and treated; 19.36 years if treated with cART and adherence follows normal patterns</td>
<td>LE at age 33: 42.91 years for general population; 3458 years if risk profile similar to those with HIV</td>
</tr>
<tr>
<td>Bor <em>et al.</em> [17]</td>
<td></td>
<td>KwaZulu-Natal, South Africa</td>
<td>No specific estimates</td>
<td>LE at birth: 523 years in 2000; 492 years in 2003; 60.5 years in 2011</td>
</tr>
<tr>
<td>May <em>et al.</em> [23]</td>
<td>UK Collaborative HIV Cohort Study</td>
<td>UK</td>
<td>LE at age 20: 39.5 years in men; 50.2 years in women. LE at age 35: 30.1 years in men; 37.7 years in women</td>
<td>LE at age 20: 57.8 years in men; 61.6 years in women. LE at age 35: 43.5 years in men; 46.9 years in women</td>
</tr>
<tr>
<td>van Sighem <em>et al.</em> [41]</td>
<td>ATHENA Cohort</td>
<td>The Netherlands</td>
<td>LE at age 25: 527 years in men; 57.8 years in men</td>
<td>LE at age 25: 53.1 years in men; 58.1 years in women</td>
</tr>
</tbody>
</table>

*Abbreviations: cART, combination antiretroviral therapy; LE, life expectancy.*

Barriers to Detection in Older Individuals

• HIV screening not practiced (recommended for individuals 13-64 years of age by CDC and USPTF)
• False belief that sex and drug use cease with age
• Common alternative causes of symptoms
• Unaware that verbal consent is sufficient
• Lack of appreciation of the growing prevalence/incidence in this population
Risk of Transmission Will Grow: Sex Doesn’t End at 50

• Sexual activity
  – US: 84% of men and 62% of women in last year\(^1\)
  – SA: 63% of men and 30% of women in last month\(^2\)

• Risk of transmission greater given exposure:
  – In US, men 50+ years 6X less likely to use condoms \(^3\)
  – Ugandan men 50+ years:
    • More likely to have STDs than younger men \(^4\)
    • 40% remained sexually active after HIV dx \(^4\)
  – Women have thinner vaginal wall, increasing risk \(^5\)

\(^5\) Menopause Int 2008;14:134–5
Aging with HIV is Complicated

• Before aging was an issue, “mix” included:
  – ART regimens susceptible to non adherence, resistance, and toxicity
  – Major co infections (HCV, TB, MDR-TB)
  – Socioeconomic issues: stigma, addiction, incarceration, homelessness, under nutrition

• Aging is nearly synonymous with multimorbidity

• HIV increases age associated injury from other viral infections, inflammation, and immune dysregulation
ART Initiation
Maintaining HIV-1 RNA Suppression
After Aging Takes Its Toll
Generalized gamma models adjusted for age, race, smoking, HCV, obesity, diabetes and site. 13 biomarkers “normalized” in 1 year, 12 remained distinct from uninfected. After 1 year, values stabilized. Median ages (years): 42 uninfected, 38 ART naïve, and 48 suppressed.

Resting Energy Expenditure (kJ) per kg Fat-Free Mass in HIV-positives and Healthy Controls

BATTERHAM

Study
Kotler(3)  Kotler(3)
Hommes(4)  Hommes(49)
Melchion(47)  Melchion(47)
Mulligan(52)  Mulligan(52)
Melchion(50)  Melchion(50)
Salehian(92)  Salehian(92)
Macallan(53)  Macallan(53)
Godfried(54)  Godfried(54)
Sharpstone(45)  Sharpstone(45)
Schwenk(58)  Schwenk(58)
Sharpstone(46)  Sharpstone(46)
McNurlan(88)  McNurlan(88)
Heijligenberg(60)  Heijligenberg(60)
Jimenez-Exposito(66,94)  Jimenez-Exposito(66,94)
Lane(75)  Lane(75)
Coors(79)  Coors(79)
Korach(82)  Korach(82)
Hadigan(81)  Hadigan(81)
Sehkar(83)  Sehkar(83)
Batterham(87)  Batterham(87)
Luzi(86)  Luzi(86)
Kosmiski(85)  Kosmiski(85)
Crenn(93)  Crenn(93)
Overall

Mean difference
95% CI

-34.31 (-57.11, -11.51)
20.91 (10.57, 31.24)
14.76 (7.19, 22.34)
31.50 (21.15, 41.85)
13.00 (7.46, 18.54)
21.00 (15.52, 26.48)
15.90 (9.40, 26.90)
15.06 (9.14, 20.99)
13.00 (2.36, 23.64)
8.42 (4.26, 12.59)
0.42 (-6.95, 7.79)
0.84 (-12.98, 14.65)
9.71 (-0.62, 20.04)
6.30 (-2.87, 15.46)
14.10 (7.61, 20.58)
6.28 (-0.57, 13.12)
4.31 (-6.41, 15.03)
-6.00 (-16.53, 4.53)
12.55 (0.85, 24.25)
21.63 (0.81, 44.07)
13.32 (6.26, 20.38)
11.30 (6.25, 28.85)
23.59 (12.78, 34.41)
25.86 (14.61, 37.11)
11.93 (8.44, 15.43)

Mean difference
(95% CI)

REE/FFM higher in control subjects
REE/FFM higher in HIV-positive subjects

Veterans Aging Cohort Study (VACS)

- Large, characterized cohort based on national VA electronic medical record data
  - >50,000 HIV+ matched to >100,000 HIV-
  - Nested survey cohort of >7,000 (half HIV+)
  - Nested tissue bank of ~2,500 (2/3 HIV+)
  - ~15 yrs. of longitudinal data
Weight Change after ART And Mortality
(Normal n=2226 Vs. Overweight/Obese n=1842)

*Adjusted for VACS Index at ART Initiation

Incidence of Diabetes by BMI at Baseline and Weight Gain Over 12 Months

HIV-negative and HIV-positive patients were compared across different BMI categories and weight gain groups. The graph shows a higher incidence of diabetes in HIV-positive patients compared to HIV-negative patients across all BMI categories and weight gain groups.

Tate J et al. CROI [Poster] Atlanta, Georgia, March 3-6, 2013. Under Review
HIV and Myocardial Infarction

Premature aging?

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th># of events</th>
<th>Mean age</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>56,456</td>
<td>286</td>
<td>55.3</td>
</tr>
<tr>
<td>HIV+</td>
<td>27,988</td>
<td>231</td>
<td>55.3</td>
</tr>
</tbody>
</table>

0.0 years crude difference

Adjusted mean difference in age:
-0.04 (-0.62, 0.54) years

No difference in age at diagnosis by HIV status

Greater risk?

<table>
<thead>
<tr>
<th></th>
<th>IR per 1,000 py</th>
<th>95% CI</th>
<th>aIRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>1.31</td>
<td>(1.17, 1.47)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>HIV+</td>
<td>2.18</td>
<td>(1.92, 2.48)</td>
<td>1.81</td>
<td>(1.49, 2.20)</td>
</tr>
</tbody>
</table>

An 81% increase in the rate in HIV+ compared to HIV-

Linear regression models to estimate the mean difference in age at diagnosis and Poisson regression models to estimate incidence rate ratios (aIRR) were adjusted for age, race, sex, body mass index, alcohol use, cigarette smoking, hepatitis C infection, anemia, diabetes, hyperlipidemia, lipid-lowering medications, hypertension, anti-hypertension medications, and statin use.

Altoff K et al. Comparison of Risk and Age at Diagnosis .... Clin Infect Dis 2015 Feb 15;60(4):627-38
HIV and “Associated” Cancers

*Anal, Hodgkins, Lung, Liver, Oral Cavity and Pharynx

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<tr>
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<th>N</th>
<th># of events</th>
<th>Mean age</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>66,991</td>
<td>565</td>
<td>57.8</td>
</tr>
<tr>
<td>HIV+</td>
<td>30,675</td>
<td>579</td>
<td>54.9</td>
</tr>
</tbody>
</table>

2.9 years crude difference

Adjusted mean difference in age:
-0.57 (-0.93, -0.21) years

7 month decrease in mean age at diagnosis in HIV+ compared to HIV-

Greater risk?

<table>
<thead>
<tr>
<th></th>
<th>IR per 1,000 py</th>
<th>95% CI</th>
<th>aIRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>2.15</td>
<td>(1.98, 2.33)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>HIV+</td>
<td>4.97</td>
<td>(4.59, 5.40)</td>
<td>1.84</td>
<td>(1.62, 2.09)</td>
</tr>
</tbody>
</table>

An 84% increase in the rate in HIV+ compared to HIV-

Linear regression models to estimate the mean difference in age at diagnosis and Poisson regression models to estimate incidence rate ratios (aIRR) were adjusted for age, race, sex, body mass index, alcohol use, cigarette smoking, hepatitis C infection, anemia, and diabetes.

Altoff K et al. Comparison of Risk and Age at Diagnosis .... Clin Infect Dis 2015 Feb 15;60(4):627-38
HIV and End-Stage Renal Disease

Premature aging?

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th># of events</th>
<th>Mean age</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>68,113</td>
<td>502</td>
<td>58.5</td>
</tr>
<tr>
<td>HIV+</td>
<td>31,139</td>
<td>346</td>
<td>55.3</td>
</tr>
</tbody>
</table>

3.2 years crude difference

Adjusted mean difference in age:
-0.23 (-0.69, 0.23) years

No difference in age at diagnosis by HIV status

Greater risk?

<table>
<thead>
<tr>
<th></th>
<th>IR per 1,000 py</th>
<th>95% CI</th>
<th>aIRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>1.88</td>
<td>(1.72, 2.05)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>HIV+</td>
<td>2.93</td>
<td>(2.63, 3.25)</td>
<td>1.43</td>
<td>(1.22, 1.66)</td>
</tr>
</tbody>
</table>

An 43% increase in the rate in HIV+ compared to HIV-

Linear regression models to estimate the mean difference in age at diagnosis and Poisson regression models to estimate incidence rate ratios (aIRR) were adjusted for age, race, sex, body mass index, alcohol use, cigarette smoking, hepatitis C infection, anemia, diabetes, hyperlipidemia, lipid-lowering medications, hypertension, anti-hypertension medications, and statin use.

Altoff K et al. *Comparison of Risk and Age at Diagnosis* .... Clin Infect Dis 2015 Feb 15;60(4):627-38
At ART Initiation
While Maintaining HIV-1 RNA Suppression
After Aging Takes Its Toll
Polypharmacy

• Typically defined as >5 chronic drugs

• Associated with diminished marginal benefit from additional medication due to:
  – Non adherence
  – Drug-drug interactions
  – Cumulative toxicity

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

• Interacts with alcohol, tobacco, other substances

Gandhi TK. N Engl J Med 2003;348:1556-64
Chronic Medication Count by Age and HIV Status (VACS)

Medication Count and Mortality (VACS)

Seven or more medications is associated with an increased risk of mortality after adjusting for HIV status and disease severity.

*Note: reference is 3 medications

Edelman EJ et al. IDSA [oral], San Francisco, California, October 2-6, 2013.
Substance Use

Alcohol, Tobacco, Opioids, and Benzodiazepines
Alcohol-Related Diagnoses and All-Cause Hospitalization Among HIV-Infected and Uninfected Patients: A Longitudinal Analysis of US Veterans from 1997-2011

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--Rentsch C et al. AIDS Behav 2015 Feb 26
High-dose Opioid Receipt by HIV Status

- a age ≤ 45 years.
- b age 45–64 years.
- c age ≥ 65 years.

Becker, WC et al. Trends in any and High-Dose Opioid Analgesic Receipt Among Aging Patients With and Without HIV, AIDS Behav published online 9/18/2015
HIV+ on ART and Uninfected in VACS Seen in 2009

<table>
<thead>
<tr>
<th></th>
<th>HIV+</th>
<th>Uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Smokers</td>
<td>55.6%</td>
<td>51.0%</td>
</tr>
<tr>
<td>Hazardous Alcohol</td>
<td>9.6%</td>
<td>12.0%</td>
</tr>
<tr>
<td>Alcohol Use Disorder</td>
<td>9.8%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Any Opioids</td>
<td>38.5%</td>
<td>43.4%</td>
</tr>
<tr>
<td>Long Term Opioids</td>
<td>15.0%</td>
<td>29.4%</td>
</tr>
<tr>
<td>Long Term Benzodiazepine</td>
<td>9.1%</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

## Polypharmacy, Alcohol, Tobacco, Opioids & Benzodiazepines

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n=64441)</th>
<th>Uninfected (n=47452)</th>
<th>HIV-infected (n=16989)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Long-term opioid receiptb</td>
<td>1.39 (1.21, 1.60)</td>
<td>&lt;0.001</td>
<td>1.35 (1.14, 1.61)</td>
</tr>
<tr>
<td>Long-term benzodiazepine receipt</td>
<td>1.33 (1.10, 1.62)</td>
<td>0.004</td>
<td>1.41 (1.12, 1.78)</td>
</tr>
<tr>
<td>Long-term opioid and benzodiazepine receipt</td>
<td>1.51 (1.22, 1.87)</td>
<td>0.0001</td>
<td>1.43 (1.10, 1.86)</td>
</tr>
<tr>
<td>Long-term medication countc</td>
<td>1.05 (1.04, 1.07)</td>
<td>&lt;0.001</td>
<td>1.04 (1.03, 1.06)</td>
</tr>
<tr>
<td>Alcohol use disorder</td>
<td>1.63 (1.39, 1.90)</td>
<td>&lt;0.001</td>
<td>1.56 (1.30, 1.88)</td>
</tr>
<tr>
<td>Drug use disorder</td>
<td>0.95 (0.81, 1.13)</td>
<td>0.59</td>
<td>0.88 (0.70, 1.11)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>1.14 (0.92, 1.40)</td>
<td>0.23</td>
<td>1.09 (0.86, 1.38)</td>
</tr>
<tr>
<td>Bipolar</td>
<td>0.92 (0.74, 1.14)</td>
<td>0.44</td>
<td>0.93 (0.71, 1.22)</td>
</tr>
<tr>
<td>Major Depression</td>
<td>0.95 (0.79, 1.15)</td>
<td>0.62</td>
<td>1.07 (0.84, 1.35)</td>
</tr>
<tr>
<td>PTSD</td>
<td>0.79 (0.68, 0.93)</td>
<td>0.004</td>
<td>0.75 (0.63, 0.91)</td>
</tr>
<tr>
<td>Acute paind</td>
<td>1.72 (1.43, 2.08)</td>
<td>&lt;0.001</td>
<td>1.76 (1.39, 2.23)</td>
</tr>
<tr>
<td>Chronic paine</td>
<td>0.93 (0.83, 1.05)</td>
<td>0.24</td>
<td>0.93 (0.81, 1.07)</td>
</tr>
<tr>
<td>Black vs. white</td>
<td>0.86 (0.77, 0.96)</td>
<td>0.006</td>
<td>0.81 (0.70, 0.92)</td>
</tr>
<tr>
<td>Hispanic vs. white</td>
<td>0.58 (0.45, 0.73)</td>
<td>&lt;0.001</td>
<td>0.56 (0.42, 0.75)</td>
</tr>
<tr>
<td>Other vs white</td>
<td>0.87 (0.63, 1.18)</td>
<td>0.37</td>
<td>0.88 (0.60, 1.29)</td>
</tr>
<tr>
<td>VACS Index score</td>
<td>1.12 (1.11, 1.13)</td>
<td>&lt;0.001</td>
<td>1.23 (1.21, 1.25)</td>
</tr>
<tr>
<td>Current smoking vs. never</td>
<td>1.87 (1.62, 2.15)</td>
<td>&lt;0.001</td>
<td>2.01 (1.69, 2.39)</td>
</tr>
<tr>
<td>Past smoking vs. never</td>
<td>1.43 (1.21, 1.70)</td>
<td>&lt;0.001</td>
<td>1.37 (1.11, 1.68)</td>
</tr>
</tbody>
</table>

Frailty¹,²

- Concept: decreased tolerance due to cumulative physiologic injury increasing risk of catastrophic declines

- Biological underpinnings:
  - Dysregulation across systems: Chronic inflammation, anabolic and catabolic hormones, insulin resistance, immune dysfunction/suppression (telomere length), oxidative stress, and micronutrient deficiencies

- Approaches to measurement vary:
  - Phenotypic (Fried et al.): Weight loss, exhaustion, weakness, slowness, low activity
  - Deficit accumulation (Rockwood et al.): 30 measures of function, symptoms, and diagnoses

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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

\[
FIB\ 4 = \frac{AGE \times AST}{PLT \times (ALT^{1/2})} \quad [1]
\]

\[
eGFR = 186.3 \times CREAT^{-1.154} \times AGE^{-0.203} \times \text{FEM}_\text{VAL} \times \text{BLACK}_\text{VAL} \quad [2]
\]

\[
\text{FEM}_\text{VAL} = 0.742 \text{ if female, } 1 \text{ if male}
\]

\[
\text{BLACK}_\text{VAL} = 1.21 \text{ if black, } 1 \text{ otherwise}
\]

<table>
<thead>
<tr>
<th>Biomarkers of General Organ System Injury</th>
<th>Restricted</th>
<th>VACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50 to 64</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>&gt;65</td>
<td>44</td>
<td>27</td>
</tr>
<tr>
<td>CD4 cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥500</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>350 to 499</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>200 to 349</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>100 to 199</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>50 to 99</td>
<td>40</td>
<td>28</td>
</tr>
<tr>
<td>&lt;50</td>
<td>46</td>
<td>29</td>
</tr>
<tr>
<td>HIV-1 RNA copies/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>500 to 1×10⁵</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>≥1×10⁵</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Hemoglobin g/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12 to 13.9</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>10 to 11.9</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>&lt;10</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>FIB-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.45</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1.45 to 3.25</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>&gt;3.25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>eGFR mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>45 to 59.9</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>30 to 44.9</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>&lt;30</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Hepatitis C Infection</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Association of VACS Index and a Restricted Index with Exercise Capacity and Body Composition in HIV-Infected Adults on Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>VACS Index(^a)</th>
<th>Restricted index(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endurance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic equivalents (METS)</td>
<td>6.0 (1.6)</td>
<td>-0.21 (0.1)</td>
<td>-0.25 (0.07)</td>
</tr>
<tr>
<td>Exercise time, median (range), min</td>
<td>12.0 (4-15)</td>
<td>-0.20 (0.2)(^b)</td>
<td>-0.23 (0.09)</td>
</tr>
<tr>
<td>6-min walk distance, m</td>
<td>533 (83)</td>
<td>-0.27 (0.05)</td>
<td>-0.10 (0.5)</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quadriceps strength, N</td>
<td>596 (163)</td>
<td>-0.45 (&lt;0.01)</td>
<td>-0.17 (0.2)</td>
</tr>
<tr>
<td>Grip strength, kg</td>
<td>40.5 (7.9)</td>
<td>-0.28 (0.04)</td>
<td>-0.18 (0.2)</td>
</tr>
<tr>
<td><strong>Body composition(^c)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total percent body fat, %</td>
<td>21.0 (9.0)</td>
<td>-0.04 (0.7)</td>
<td>0.01 (0.9)</td>
</tr>
<tr>
<td>Total lean mass, kg</td>
<td>56.1 (7.4)</td>
<td>-0.51 (&lt;0.001)</td>
<td>-0.22 (0.1)</td>
</tr>
<tr>
<td>Leg lean mass, kg</td>
<td>18.7 (2.8)</td>
<td>-0.49 (&lt;0.001)</td>
<td>-0.19 (0.2)</td>
</tr>
<tr>
<td>Quadriceps cross-sectional area, cm(^2)</td>
<td>68.6 (13.3)</td>
<td>-0.37 (&lt;0.01)</td>
<td>-0.12 (0.4)</td>
</tr>
</tbody>
</table>

\(^a\)Pearson.  
\(^b\)Spearman.  
\(^c\)By DXA (n=50) and CT (n=48).
FIG. 1. VACS index predicts quadriceps strength adjusted for muscle cross-sectional area (CSA).

Oursler KK et al. Association of the Veterans Aging Cohort Study Index with Exercise Capacity in HIV-Infected Adults AIDS Research and Human Retroviruses 2013; 29(9):1218-1223
The Veterans Aging Cohort Study Index is Associated With Concurrent Risk for Neurocognitive Impairment.


OBJECTIVE: The Veterans Aging Cohort Study (VACS) Index is predictive of mortality and combines age, traditional HIV biomarkers (HIV-1 plasma RNA and current CD4 count), and non-HIV biomarkers (indicators of renal and liver function, anemia, and hepatitis C coinfection). We examined the association between the VACS Index and HIV-associated neurocognitive impairment (NCI).

DESIGN AND METHODS: Participants included 601 HIV-infected adults enrolled in cohort studies at the University of California, San Diego, HIV Neurobehavioral Research Program (ages: 18-76 years; 88% male; 63% white; median current CD4 = 364 cells/mm; 63% on antiretroviral therapy; AIDS = 64%). Biomarkers used in calculating the VACS Index were measured in prospectively collected blood samples using conventional laboratory methods. NCI was defined using prospectively collected blood samples using conventional laboratory methods. NCI was defined using global and seven domain deficit scores.

RESULTS: Higher VACS Index scores were associated with concurrent risk for global NCI [P < 0.001; odds ratio = 1.21, confidence interval (CI): 1.12 to 1.32], even when adjusting for psychiatric comorbidities. This relation was statistically significant for most cognitive domains in adjusted models. Furthermore, the VACS Index predicted concurrent NCI beyond nadir CD4 and estimated duration of infection. Older age, lower hemoglobin, and lower CD4 counts were the VACS components most strongly linked to NCI.

CONCLUSIONS: The findings extend previous research on the potential usefulness of the VACS Index in predicting HIV-associated outcomes to include NCI. Although the effect size was relatively small, our findings suggest that demographic information, HIV-disease factors, and common comorbidities might each play important roles in the clinical manifestation of cognitive impairment among HIV-infected individuals. Additional research is needed to determine if a more sensitive and specific index can be developed.
### A. NA-ACCORD (N= 10835)

### B. VACS (N=5066)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C. Men (N = 12785)</td>
<td>D. Women (N = 3116)</td>
</tr>
<tr>
<td>E. Age &lt; 50 years (N = 11191)</td>
<td>F. Age &gt;50 years (N = 4710)</td>
</tr>
<tr>
<td>G. Black (N= 5878)</td>
<td>H. White (N = 6079)</td>
</tr>
<tr>
<td>I. Undetectable VL (N=8715)</td>
<td>J. Detectable VL (N= 7186)</td>
</tr>
</tbody>
</table>

Clinical Judgment

ROC Areas

VACS Index (dotted):
0.71, 95% CI 0.69-0.73

Judgment (grey):
0.67, 95% CI 0.65-0.70

Together (black):
0.75, 95% CI 0.72-0.78

VACS Index Predicts Fragility Fractures

VACS Index Scores Higher in HIV+

HIV +

Uninfected

Median 23, IQR 12-39

Median 12, IQR 6-27

Poster. 19th International Workshop on HIV Observational Databases (IWHOD), Sitges, Spain
VACS Index Also Predictive Among Veterans Aging Without HIV

Randomly selected score and followed for survival. Kaplan-Meier plots by VACS Index score for Hospitalization (top figures) and death (bottom figures) among HIV infected (left side) and uninfected (right side). Poster. 19th International Workshop on HIV Observational Databases (IWHOD), Sitges, Spain
Currently Active

Under Development

HTTP://VACS.MED.YALE.EDU
Modifiable Factors in Frailty in HIV

• Immune dysfunction
• Chronic immune stimulation
  – Microbial translocation (HIV and alcohol)
  – Viral activity
• Hepatitis C & B
• Ongoing substance use
• Polypharmacy
• Developing obesity
After diagnosing HIV and starting ART early,

how can we intervene on physiologic frailty?
Step 1: Treat Major Comorbidity & *Individualize* Primary Care Guidelines

- Cure HCV if possible
- Suppress HBV if possible
- Symptoms of Chronic Obstructive Lung Disease
- Discuss with patient how aggressively to treat
  - Hypertension
  - Diabetes
  - Cholesterol
Step 2: Polypharmacy

**Complete Medication Reconciliation**
- Perform annually and update with medication changes
- Assess medications taken, adherence and related symptoms
- Include assessment of over-the-counter medications and supplements

**Assess for Tobacco, Alcohol and Substance Use**
- Use standardized instruments

**Assess and Rank Each Medication According to Risks and Benefits**
- Prioritize ART and pharmacotherapy for alcohol/substance use disorders
- Use risk index, such as VACS Index, to assess mortality

**Prioritize and Plan with Patient**
- Incorporate goals and criteria for stopping treatment
- Develop strategies to monitor for medication-induced symptoms and other adverse events
- Incorporate patient preferences

Alcohol & Tobacco

• If one present, suspect other (and depression)
• Partner with addiction specialists
• Motivational Interviewing & cognitive behavioral therapy effective for many, especially if health is harmed by use
• Some require medication
  – Varenicline may have benefits for alcohol & tobacco
  – Naltrexone
    • Increasingly attractive for alcohol
    • If on opioids cannot use naltrexone
Prescribed Substances
Opioids and Benzodiazepines

• Co prescribing particularly problematic
• Long term (>90 days) requires careful intervention
• Partner with addiction specialists
• Motivational interviewing and cognitive behavioral therapy
• May require medication
  – Most commonly buprenorphine
Step 3: Substitute Exercise

- Decreases depression, hypertension, and metabolic syndrome
- Facilitates sleep, weight control, and pain management
- Helps prevent falls and fractures
- To start:
  - Partner with health psychology
  - Motivational interviewing
  - Write an exercise prescription
  - Apps (fitbit, myfitness pal, etc.)
  - Have patient do it with a friend
  - Achievable short term (5,000-10,000 steps) and long term goals
  - Add resistance training

http://nihseniorhealth.gov/exerciseandphysicalactivityhowtostart
At ART Initiation
While Maintaining HIV-1 RNA Suppression
As Aging Takes Its Toll
Frailty in Older Adults: Insights and Interventions
Sara Espinoza & Jeremy Walston
Cleveland Clinic Journal of Medicine, December 2005 (p1105-12)

Symptom relief
Setting patient-centered goals
Family and caregiver support

Exercise interventions

Comprehensive geriatric assessment and treatment
Geriatric evaluation and management (GEM)

GEM and Adult Care for Elders units,
programs for acute care for the elderly

Hospice care, maintain comfort and dignity

Increasingly frail

FIGURE 2. Potential interventions along the spectrum of frailty in older adults
What Don’t We Know?

• What happens after 65 years of age

• What happens when optimal ART is the first therapy provided

• Whether starting ART at high CD4 counts and maintaining viral suppression “normalizes” risks of aging associated conditions
The Secret to Managing Complexity:

Simplify, Prioritize with the Patient, Empower Patient to Develop & Achieve Health Goals
Veterans Aging Cohort Study (VACS)

The Veterans Aging Cohort Study (VACS) is a prospective, observational cohort study of HIV-positive and an age/race/site matched control group of HIV-negative veterans in care in the United States. The study’s aim is to understand the role of comorbid medical and psychiatric disease in determining clinical outcomes in HIV infection. It is funded primarily by the National Institute on Alcoholism and Alcohol Abuse, National Institutes of Health. The study has a special focus on the role of alcohol use and abuse in determining clinical outcomes.

The VACS study is built around the Veterans Health Administration (VA), the largest integrated health-care system in the United States, providing care to 5.6 million patients annually. The VA is also the largest single provider of HIV care in the nation, serving 15,000 HIV-positive veterans in 2003. The VA provides inpatient and outpatient medical care, pharmacy, mental-health services, substance-abuse treatment, long-term care, homeless care, and hospice services. The VA also has a national, fully electronic medical-record system that includes all routine clinical data, administrative data, and comprehensive follow-up data for mortality, as the VA pays some burial expenses for veterans.
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- **Consortium PI**: AC Justice*
- **Scientific Collaborator (NIAAA)**: K Bryant
- **Affiliated PIs**: S Braithwaite, K Crothers*, R Dubrow*, DA Fiellin*, M Freiberg*, V LoRe*
- **Participating VA Medical Centers**: Atlanta (D. Rimland*, V Marconi), Baltimore (M Sajadi, R Titanji), Bronx (S Brown, Y Ponomarenko), Dallas (R Bedimo), Houston (M Rodriguez-Barradas, N Másozera), Los Angeles (M Goetz, D Leaf), Manhattan-Brooklyn (M Simberkoff, D Blumenthal, H Leaf, J Leung), Pittsburgh (A Butt, K Kraemer, M Freiberg, E Hoffman), and Washington DC (C Gibert, R Peck)
- **Core and Workgroup Chairs**: C Brandt, J Edelman, N Gandhi, J Lim, K McGinnis, KA Oursler, C Parikh, J Tate, E Wang, J Womack
- **Staff**: H Bathulapalli, T Bohan, J Ciarleglio, A Consorte, P Cunningham, L Erickson, C Frank, K Gordon, J Huston, F Kidwai-Khan, G Köerbel, F Levin, L Piscitelli, C Rogina, S Shahrir, M Skanderson
- **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
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*Indicates individual is also the Chair of a Core or Workgroup
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