HIV and Aging: An Evolving Understanding

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Professor of Medicine and Public Health
Yale University
Mr. M

Patient: A 60 y/o white male with a past history of hypertension, hyperlipidemia, MI x 3, CHF s/p AICD placement, and COPD.

Chief complaint: fatigue, loss of appetite, and a 40 lb weight loss /1 year. Also reports progressive dyspnea and dry cough.

Mr. M’s Work Up

3-5/13: GI, EGD shows esophageal candidiasis

2/14: Hematology BM biopsy for pancytopenia

5/14: Pulmonary

5-6/14: Dermatology skin biopsy shows squamous cell carcinoma and CMV inclusions

7/14: Rheumatology (livido reticularis)
   HIV test positive,
   CD4 count 18 cels/dL,
   HIV-1 RNA 1.2 million copies/ml

It took 9 Months to diagnose HIV infection in one of the country’s leading tertiary care hospitals. WHY?

• Seen in Cardiology 11/13
HIV Manifestations

- CD4 lymphocyte count (x 10^3/l)
- Time (years)

- Seroconversion
- Skin disease
- Pulmonary tuberculosis
- Fatigue
- Oral thrush, night sweats
- Weight loss
- Non-Hodgkin's lymphoma
- Pneumocystis carinii pneumonia
- Kaposi's sarcoma
- Esophageal Candida
- Cryptococcosis
- Cryptosporidiosis
- Candidiasis
- Cytomegalovirus retinitis
- Mycobacterium avium complex
What do we know?
More People Are Living With HIV in the United States than Ever Before

- Living Patients
- Deaths
- New patients

Mortality per 100 patient-years

Number of patients (1000)
Percentage of Adults Living with HIV Aged 50+ By Year and Region

Source: UNAIDS 2012 estimates.
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 \(^5\)

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1. Lindau ST. NEJM 2007 357(8):762–774  
2. Ethno Med 2010;4:163–72  
Life Expectancy Not “Normal” in cART Era

<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 et al. [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 et al. [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>Mills et al. [11]</td>
<td>The AIDS Support Organization (TASO) cohort</td>
<td>Uganda</td>
<td>LE at age 20: 26.7 years. LE at age 35: 27.9 years</td>
<td>LE at age 20: 41 years</td>
</tr>
<tr>
<td>Losina et al. [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 et al. [17]</td>
<td></td>
<td>KwaZulu-Natal, South Africa</td>
<td>No specific estimates</td>
<td>LE at birth: 523 years in 2000; 49.2 years in 2003; 60.5 years in 2011</td>
</tr>
<tr>
<td>Lohse et al. [21]</td>
<td>Danish HIV Cohort Study</td>
<td>Denmark</td>
<td>LE at age 25: 8 years in 1995 to 1996; 23 years in 1997 to 1999; 33 years in 2000 to 2005</td>
<td>LE at age 25: 51 years</td>
</tr>
<tr>
<td>May et al. [23]</td>
<td>UK Collaborative HIV Cohort Study</td>
<td>UK</td>
<td>LE at age 20: 39.5 years in men; 502 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 et al. [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.

Veterans Aging Cohort Study (VACS)

• Large, characterized NIAAA cohort
  – >40,000 HIV+ matched to >80,000 HIV-
  – Nested in-depth cohort of >7,000 (half HIV+)
  – ~10 yrs. of longitudinal data on alcohol and MSU
  – Survey sites have new electronic baseline (~2700)
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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<th>Mean age</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>66,991</td>
<td>565</td>
<td>57.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV+</td>
<td>30,675</td>
<td>579</td>
<td>54.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Premature aging?

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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>2.15</td>
<td>(1.98, 2.33)</td>
<td>1.00</td>
<td>(1.00, 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>
<td></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?**

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<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
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.

Wada et al. The Effect of HAART-induced HIV suppression on Circulating Markers of Inflammation and Immune Activation. AIDS 2015 Feb 20; 463-471
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
How Can We Monitor Complexity?

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

eGFR = 186.3 \times CREAT^{-1.154} \times AGE^{-0.203} \times FEM\_VAL \times BLACK\_VAL \[2\]

FEM\_VAL = 0.742 if female, 1 if male
BLACK\_VAL = 1.21 if black, 1 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 1x10⁵</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>≥ 1x10⁵</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></td>
<td>5</td>
</tr>
</tbody>
</table>
Justice AC 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 Apr;54(7):984-94
### 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>Correlation (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VACS Index(^a)</td>
<td>Restricted index(^b)</td>
</tr>
<tr>
<td><strong>Endurance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic equivalents (METS)</td>
<td>6.0 (1.6)</td>
<td>-0.21 (0.1)</td>
</tr>
<tr>
<td>Exercise time, median (range), min</td>
<td>12.0 (4-15)</td>
<td>-0.20 (0.2)(^b)</td>
</tr>
<tr>
<td>6-min walk distance, m</td>
<td>533 (83)</td>
<td>-0.27 (0.05)</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quadriceps strength, N</td>
<td>596 (163)</td>
<td>-0.45 (&lt; 0.01)</td>
</tr>
<tr>
<td>Grip strength, kg</td>
<td>40.5 (7.9)</td>
<td>-0.28 (0.04)</td>
</tr>
<tr>
<td><strong>Body composition(^c)</strong></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>
</tr>
<tr>
<td>Total lean mass, kg</td>
<td>56.1 (7.4)</td>
<td>-0.51 (&lt; 0.001)</td>
</tr>
<tr>
<td>Leg lean mass, kg</td>
<td>18.7 (2.8)</td>
<td>-0.49 (&lt; 0.001)</td>
</tr>
<tr>
<td>Quadriceps cross-sectional area, cm(^2)</td>
<td>68.6 (13.3)</td>
<td>-0.37 (&lt; 0.01)</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)

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)

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

Justice AC et al. *Can the Veterans Aging Cohort Study (VACS) Index Improve Clinical Judgment?* CROI 2013 [Poster] Under Review
MICU Admission Over 6 Years

Kaplan-Meier Survival Estimates

**HIV Restricted Index**

**VACS Index**

Frailty$^{1,2}$

- 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


VACS Index Scores Higher in HIV+

HIV +

Median 23, IQR 12-39

Uninfected

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
**VACS Index Calculator**

- **Age:** 68
- **Sex:** Female
- **Race:** black
- **CD4:** ≥500
- **HIV-1 RNA:** <500
- **Hemoglobin:** ≥14
- **AST (SGOT):**
- **ALT (SGPT):**
- **Platelet count:**
- **FIB-4:** <1.45
- **Serum Creatinine:**
- **eGFR:** ≥60
- **Hepatitis C:** Yes
- **VACS index:** 73
  - 5 Year Mortality: 50%

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**Risk Factors**

- **Tobacco:**
- **Alcohol:** None, Modest, Moderate, Heavy
- **I sometimes miss my HIV meds.:**
- **Hepatitis C Treatment:** Fully, Partially, Never

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**HTTP://VACS.MED.YALE.EDU**

**Currently Active**

**Under Development**
How Do We Manage Complexity?

At ART Initiation

While Maintaining HIV-1 RNA Suppression

After Aging Takes Its Toll
Resting Energy Expenditure (kJ) per kg Fat-Free Mass in HIV-positives and Healthy Controls

**BATTERHAM**

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

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 (4.90, 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 (-0.41, 15.03)
-6.00 (-16.53, 4.53)
12.55 (0.85, 24.25)
21.63 (-0.81, 44.07)
13.32 (6.25, 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)

Am J Clin Nutr 2005; 81:702-713
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

<table>
<thead>
<tr>
<th></th>
<th>HIV-13</th>
<th>HIV-11</th>
<th>HIV-13</th>
<th>HIV+2</th>
<th>HIV+3</th>
<th>HIV+8</th>
<th>HIV+12</th>
<th>HIV+23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>+5-10l</td>
<td>+10-20l</td>
<td>&gt;20</td>
<td>+5-10l</td>
<td>+10-20l</td>
<td>&gt;20</td>
<td>+5-10l</td>
<td>+10-20l</td>
</tr>
<tr>
<td>events</td>
<td>13</td>
<td>11</td>
<td>13</td>
<td>38</td>
<td>43</td>
<td>23</td>
<td>73</td>
<td>82</td>
</tr>
<tr>
<td>per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PY</td>
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</tr>
</tbody>
</table>

Tate J et al. CROI [Poster] Atlanta, Georgia, March 3-6, 2013. Under Review
How Do We Manage Complexity?

At ART Initiation

While Maintaining HIV-1 RNA Suppression

After Aging Takes Its Toll
### Prescription Opioids/Benzodiazepines, Alcohol, MSU, Mortality

<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 receipt&lt;sup&gt;b&lt;/sup&gt;</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 count&lt;sup&gt;c&lt;/sup&gt;</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 pain&lt;sup&gt;d&lt;/sup&gt;</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 pain&lt;sup&gt;e&lt;/sup&gt;</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>

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

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.
How Do We Manage Complexity?

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
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*
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- **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 Koerbel, 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
- **Cross Cohort Collaborators**: Richard Moore (NA-ACCORD), Jonathan Sterne (ART-CC), Brian Agan (DoD)
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*Indicates individual is also the Chair of a Core or Workgroup
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Continued

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