Aging and HIV: The Next Challenge

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AIDS Events Increasingly Rare

ART-CC, Archives Int Med 2005: 165 416-423
>50% of Deaths Attributed to “Non-AIDS” Events

# Life Expectancy Estimates in the 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</td>
<td>Multi-country study (Europe and North America)</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: 22.66 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; 34.58 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: 52.3 years in 2000; 49.2 years in 2008; 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; 50.2 years in women. LE at age 35: 30.1 years in women; 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: 52.7 years in men; 57.8 years in women</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.*
Where Ever ART Is Available, People Are Aging with HIV

• Life expectancy at start of ART (35 y/o male, CD4>100):
  – US: 30-37 years (older data)¹
  – Uganda: 35-39 years (newer data)²

• More people are living (aging) with HIV now than ever and their numbers increase each year:
  – In US, ~38,000³
  – In SSA, ~333,000⁴

Percentage of Adults Living with HIV Aged 50+ By Year and Region

Source: UNAIDS 2012 estimates.
Key Questions

• Is aging with HIV different than aging without it?
• Should HIV infection change our approach to prevention and treatment of aging conditions?
• How can a risk index help us personalize health care for those aging with HIV infection?
### Strategies for Management of ART (SMART)

#### Table 2. Primary and Major Secondary End Points. *

<table>
<thead>
<tr>
<th>End Point</th>
<th>Drug Conservation Group (N = 2720)</th>
<th>Viral Suppression Group (N = 2752)</th>
<th>Hazard Ratio for Drug Conservation Group vs. Viral Suppression Group (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Participants with Event</td>
<td>Event Rate (per 100 Person-Yr)</td>
<td>No. of Participants with Event</td>
<td>Event Rate (per 100 Person-Yr)</td>
</tr>
<tr>
<td>Primary end point</td>
<td>120</td>
<td>3.3</td>
<td>47</td>
<td>1.3</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>55</td>
<td>1.5</td>
<td>30</td>
<td>0.8</td>
</tr>
<tr>
<td>Opportunistic disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>13</td>
<td>0.4</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Nonserious</td>
<td>63</td>
<td>1.7</td>
<td>18</td>
<td>0.5</td>
</tr>
<tr>
<td>Major cardiovascular, renal, or hepatic disease</td>
<td>65</td>
<td>1.8</td>
<td>39</td>
<td>1.1</td>
</tr>
<tr>
<td>Fatal or nonfatal cardiovascular disease</td>
<td>48</td>
<td>1.3</td>
<td>31</td>
<td>0.8</td>
</tr>
<tr>
<td>Fatal or nonfatal renal disease</td>
<td>9</td>
<td>0.2</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Fatal or nonfatal liver disease</td>
<td>10</td>
<td>0.3</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>Grade 4 event</td>
<td>173</td>
<td>5.0</td>
<td>148</td>
<td>4.2</td>
</tr>
<tr>
<td>Grade 4 event or death from any cause</td>
<td>205</td>
<td>5.9</td>
<td>164</td>
<td>4.7</td>
</tr>
</tbody>
</table>

* Numbers of individual events of each type do not sum to the total number because some participants had more than one event. End-point definitions are listed in the Supplementary Appendix. Grade 4 events were determined on the basis of toxicity grades developed by the Division of AIDS of the NIAID. CI denotes confidence interval.

*More AIDS and “Non-AIDS” Events Among Rx. Sparing Arm (HR 1.7 in SMART) NEJM 2006;355:2283-96
Stories From an Aging Epidemic

Robert, age 75

Sue, age 73

Bill, age 77

Anna, age 64

The Graying of AIDS

www.grayingofAIDS.org
Demography Matters: Deaths Among HIV+/- in NYC 2004-2008

Death Rates by Age and Race/Ethnicity

- Black Non-HIV-related
- Black HIV-related
- Hispanic Non-HIV-related
- Hispanic HIV-related
- White Non-HIV-related
- White HIV-related
- NYC all-cause

Age Group: 13-29, 30-49, 50-69

Death Rates per 1,000
Behavior Matters: Compared with Demographically Similar HIV-, Aging HIV+

- More likely to drink alcohol
- More likely to smoke
- Continue to use drugs
- Less likely to be overweight/obese (at ART initiation)
- (More likely to have HCV co-infection)
Timing of Treatment Matters: Delayed Presentation By Age

Sex- and age-specific incidence rates of type 2 diabetes mellitus between the Swiss Cohort (HIV-infected persons), and MONICA Augsburg Cohort (German study, not infected with HIV), and US population in 2004. Whiskers indicate standard error.

Ledergerber B et al., Clin Infect Dis 2007; 45(1):111-119
Biomarkers Seldom Tell The Whole Story

AIDS Events by CD4 and Risk of Death

By Median (IQR) CD4

By Relative Hazard of Death

ART-CC, CID 2009;48:1138-51
Biomarkers Seldom Tell The Whole Story
Fracture by Age and T-score (HIV- Women)

Kanis JA. Osteo Inter 2001, 12: 989.
Underlying Age Distribution Matters

Premature or Accentuated Cancer?

A. **Premature cancer**: cancer occurs earlier among those with HIV than uninfected comparators.

B. **Accentuated risk**: cancer could occur at the same ages but more often than among comparators.

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
**HIV and “Associated” Cancers**

*Anal, Hodgkin's, Lung, Liver, Oral Cavity and Pharynx*

<table>
<thead>
<tr>
<th></th>
<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>

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.

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>

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.
HIV and Myocardial Infarction Risk by BP

Figure 1. Unadjusted rate of incident acute myocardial infarction by systolic and diastolic blood pressure increments stratified by antihypertensive therapy (A), human immunodeficiency virus (HIV) infection status (B), and both HIV and antihypertensive therapy (C). Vertical bars represent 95% confidence intervals for rates. Abbreviations: AMI, acute myocardial infarction; BP, blood pressure; HIV, human immunodeficiency virus; py, person-years.

Armah KA et al, *Clinical Infectious Diseases* 2013; 58(1):121-129
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>

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 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.

### Table 4. Hazard Ratios for Hepatic Decompensation by Antiretroviral Therapy Initiation Status and Time Since Initiation From Marginal Structural Models\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Person-Years</th>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>46,444</td>
<td>645</td>
<td>...</td>
</tr>
<tr>
<td>No initiation</td>
<td>10,891</td>
<td>188</td>
<td>Referent</td>
</tr>
<tr>
<td>ART initiation</td>
<td>35,553</td>
<td>457</td>
<td>0.72 (.54–.94)</td>
</tr>
<tr>
<td>No initiation</td>
<td>10,891</td>
<td>188</td>
<td>Referent</td>
</tr>
<tr>
<td>&lt;2 y since initiation</td>
<td>10,727</td>
<td>154</td>
<td>0.75 (.56–1.01)</td>
</tr>
<tr>
<td>2 to &lt;4 y since initiation</td>
<td>8,560</td>
<td>109</td>
<td>0.69 (.46–1.03)</td>
</tr>
<tr>
<td>≥4 y since initiation</td>
<td>16,266</td>
<td>194</td>
<td>0.53 (.34–.83)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio.

\(^a\) Stabilized inverse probability of treatment/death/censoring weights, based on covariate history at each time point, were applied to models. Estimates are adjusted for the following baseline covariates: year (<2001, ≥2001); race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, other/unknown); history of drug abuse (yes, no); CD4 count (<50, 50–199, 200–349, 350–499, ≥500 cells/μL); HIV RNA load (≤400, 401–10,000, 10,001–100,000, >100,000 copies/mL); FIB-4 score (<1.45 [mild fibrosis], 1.45–3.25 [moderate fibrosis], >3.25 [advanced fibrosis]); history of AIDS-defining diagnoses (yes, no); age (<40, 40–49, 50–59, ≥60 years); history of diabetes (yes, no); and history of pegylated interferon therapy (yes, no).
Figure 2b. Standardized cumulative incidences of hepatic decompensation between antiretroviral-treated HIV/hepatitis C virus-coinfected patients with HIV RNA levels $\geq 1,000$ copies/mL on any result during follow-up (denoted by dashed line), antiretroviral-treated HIV/hepatitis C virus-coinfected patients with HIV RNA $<1,000$ copies/mL on all HIV RNA results during follow-up (denoted by solid line), and hepatitis C virus-monoinfected patients (denoted by dotted line).

Lo Re V et al, *Annals of Internal Medicine*; in press
Hepatic Fibrosis (FIB-4 >3.25), HIV, HCV, and Level of Alcohol Consumption (n=3,565)

Chi-square test for trend over categories of alcohol use
* HIV/HCV-uninfected, p=0.019
^ HCV-monoinfected, p<0.001
† HIV-monoinfected, p=0.0025
‡ HIV/HCV-coinfected, p=0.060

Lim JK et al, *Clinical Infectious Diseases*; in press
Resting Energy Expenditure (kJ) per kg Fat-Free Mass in HIV-positives and Healthy Controls

BATTERHAM

Study
Kotler(3)
Hommes(4)
Hommes(49)
Melchior(47)
Mulligan(52)
Melchior(50)
Salehian(92)
Macallan(53)
Godfied(54)
Sharpstone(45)
Schwenk(58)
Sharpstone(46)
McNurlan(88)
Heijligenberg(60)
Jimenez-Exposito(66,94)
Lane(75)
Coors(79)
Korach(82)
Hadigan(61)
Sekhar(83)
Batterham(87)
Luzi(86)
Kosmiski(8,85)
Crellin(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 (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 (-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)

**HIV, Comorbidity, and Inflammation (IL-6)**

<table>
<thead>
<tr>
<th>Model</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong> (Full sample)</td>
<td>HIV(-): REF 0.6* 1.4* 2.3* 4.0*</td>
</tr>
<tr>
<td></td>
<td>HIV(+) CD4≥500: REF 1.610</td>
</tr>
<tr>
<td></td>
<td>HIV(+) CD4 200-499: REF 2.8*</td>
</tr>
<tr>
<td></td>
<td>HIV(+) CD4&lt;200: REF 1.260</td>
</tr>
</tbody>
</table>

**Model 2** (Limited smoking & alcohol) (Limited comorbid disease)

**Model 3** (Limited comorbid disease)

**Comorbidities**: CVD, hypertension, diabetes, BMI≥30, hepatitis C, renal disease.

All models otherwise adjusted for age, race, CVD, blood pressure, diabetes, smoking, BMI, HDL, LDL, triglycerides, cocaine/alcohol abuse, hepatitis C, renal disease.

CID 2012 Armah K. et al.
Is Aging with HIV Different?
—Yes and No

• HIV + are more likely to have some established risk factors and less likely to have others

• Accounting for established risk factors, HIV increases risk for selected cancers, CVD, liver disease, and renal disease

• Modifiable contributing causes likely include:
  – Chronic inflammation and hypercoagulability from HIV leading to immune dysfunction and senescence
  – Long term toxicity from ART
  – *Interactions with ongoing alcohol, tobacco, and drug use; other viral infections; obesity; and non ART medications*

• On average, HIV associated risk akin to other risk factors
Key Questions

• Is aging with HIV different than aging without it?
• **Should HIV infection change our approach to prevention and treatment of other conditions?**
• How can a risk index help us personalize health care for those aging with HIV infection?
Three Unifying Concepts

- Multimorbidity
- Polypharmacy
- Frailty
Multimorbidity is the norm in aging and in HIV.
Figure 1.2a Percentage of Medicare FFS Beneficiaries by Number of Chronic Conditions: 2010

Figure 4.1 Co-morbidity among Chronic Conditions for Medicare FFS Beneficiaries: 2010

DATA HIGHLIGHTS:
Six percent of beneficiaries with high blood pressure had no other condition present, while 23% had 5 or more additional conditions.
Stroke and heart failure were highly co-morbid conditions with about 55% of beneficiaries with these conditions having 5 or more additional chronic health conditions.
This pattern of co-morbidity held for men and women, with beneficiaries 65 years and older and dual-eligibles having greater co-morbidity.

Swiss HIV Cohort 2008-10: Incident Disease

Of 1,189 events in 8,444 patients, only 16% were HIV events, 84% were Non HIV:

- Bacterial Pneumonia: 17%
- Fracture: 13%
- MI or PTCA: 11%
- Cancer: 10%
- Peripheral Vasc. Dz: 7%
- Diabetes: 6%
- Osteoporosis: 5%
- Liver disease: 5%
- Kidney disease: 3%
- Pancreatitis: 2%

Hasse B. et al. Morbidity and Aging in HIV-Infected Persons: Swiss HIV Cohort Study CID 2011 53:1130-1139
Multimorbidity by HIV Status: ALIVE Cohort

Diabetes, obstructive lung disease, liver disease, anemia, obesity, kidney dysfunction, and hypertension

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

Polypharmacy follows multimorbidity.
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

Daily Pill Count By Age and Purpose 1990-2010 (Southern Alberta Cohort, Canada)

ARV Pill Count Decreasing For <45 and 45+ Years of Age

Non ARV Pill Count Differentially Increasing For 45+ Years of Age

### Adverse Drug Events Associated with Common Medications (General Population)

#### Table 5. Most Common ADEs That Were Classified as Causal or Contributory to Admission and Possibly or Definitely Avoidable as per Hallas Criteria

<table>
<thead>
<tr>
<th>ADE</th>
<th>No. (%)</th>
<th>Attributed to STOPP Criteria PIMs</th>
<th>Attributed to Beers Criteria PIMs</th>
<th>ADEs Appearing Both in STOPP and Beers Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall(s) while receiving benzodiazepines</td>
<td>24 (15.9)</td>
<td>24 (100)</td>
<td>22 (91.7)</td>
<td>22 (91.7)</td>
</tr>
<tr>
<td>Symptomatic orthostasis while receiving antihypertensives</td>
<td>17 (11.3)</td>
<td>15 (88.2)</td>
<td>1 (5.9)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Falls while receiving opiates</td>
<td>10 (6.6)</td>
<td>10 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyponatremia while receiving diuretics</td>
<td>10 (6.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation while receiving opiates</td>
<td>6 (4.0)</td>
<td>6 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Falls while receiving sedative hypnotics</td>
<td>6 (4.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acute kidney injury while receiving diuretics</td>
<td>6 (4.0)</td>
<td>3 (50)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Symptomatic orthostasis while receiving diuretics</td>
<td>5 (3.3)</td>
<td>5 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Falls on neuroleptics</td>
<td>5 (3.3)</td>
<td>5 (100)</td>
<td>1 (20)</td>
<td>0</td>
</tr>
<tr>
<td>NSAID-related gastritis/peptic ulcer disease</td>
<td>5 (3.3)</td>
<td>3 (75)</td>
<td>1 (25)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Bradycardia while receiving β-blockers</td>
<td>4 (2.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: ADEs, adverse drug events; NSAID, nonsteroidal anti-inflammatory drug; PIMs, potentially inappropriate medicines; STOPP, Screening Tool of Older Persons’ potentially inappropriate Prescriptions.

## Non-ART Medications by Age

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total n (%)</th>
<th>&lt;50</th>
<th>50-64</th>
<th>≥65</th>
<th>P¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensives (not ACE inhibitors)</td>
<td>831 (9.8)</td>
<td>323</td>
<td>367</td>
<td>141</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensives (ACE inhibitors)</td>
<td>935 (11.1)</td>
<td>355</td>
<td>432</td>
<td>148</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>1071 (12.7)</td>
<td>356</td>
<td>527</td>
<td>188</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral antidiabetics</td>
<td>179 (2.1)</td>
<td>51</td>
<td>87</td>
<td>41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin</td>
<td>116 (1.4)</td>
<td>40</td>
<td>50</td>
<td>26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>488 (5.8)</td>
<td>121</td>
<td>237</td>
<td>130</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>846 (10.0)</td>
<td>560</td>
<td>251</td>
<td>35</td>
<td>0.659</td>
</tr>
</tbody>
</table>

¹ Test for trend across age-groups

Abbreviations: ART, antiretroviral therapy; ACE, Angiotensin converting enzyme

Chronic Medication Count by Age and HIV Status (VACS)

Edelman EJ et al. IDSA [oral], San Francisco, California, October 2-6, 2013.
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.
Frailty results from multimorbidity (and polypharmacy).
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


Pathophysiology of Frailty

Genetic factors

Epigenetic mechanisms

Environmental factors

Cumulative molecular and cellular damage

Reduced physiological reserve
- Brain
- Endocrine
- Immune
- Skeletal muscle
- Cardiovascular
- Respiratory
- Renal

Physical activity

Nutritional factors

Frailty

Stressor event

Falls
Delirium
Fluctuating disability

Increased care needs
Admission to hospital
Admission to long-term care

Is Frailty Expressed the Same Way Among those Aging with HIV?

• Fried phenotype uncommon (<7%), doesn’t include cognition, and may be confounded by depression

• Rockwood Index is complex and requires measures not routinely collected in HIV

• Can routine laboratory markers be combined to measure frailty among those with HIV?
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 FEM\_VAL \times BLACK\_VAL \quad [2]

FEM\_VAL = 0.742 \text{ if female, 1 if male}

BLACK\_VAL = 1.21 \text{ if black, 1 otherwise}

<table>
<thead>
<tr>
<th>Biomarkers of General Organ System Injury</th>
<th>HIV Specific Biomarkers</th>
<th>Restricted</th>
<th>VACS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&lt;50</td>
<td></td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>50 to 64</td>
<td></td>
<td>44</td>
<td>27</td>
</tr>
<tr>
<td>≥ 65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CD4 cells/mm³</strong></td>
<td>≥ 500</td>
<td>0</td>
<td>0</td>
</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>&lt; 500</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>500 to 1x10⁵</td>
<td>11</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>≥ 1x10⁵</td>
<td>25</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td><strong>Hemoglobin g/dL</strong></td>
<td>≥ 14</td>
<td>0</td>
<td>0</td>
</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>
<td>38</td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FIB-4</strong></td>
<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>
<td></td>
</tr>
<tr>
<td>&gt; 3.25</td>
<td>25</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td><strong>eGFR mL/min</strong></td>
<td>≥ 60</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>45 to 59.9</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>30 to 44.9</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>26</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis C Infection</strong></td>
<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>
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)  

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>

Kaplan-Meier Survival Estimates

VACS Index Predicts Fragility Fractures

VACS Index Correlated with Biomarkers of Inflammation

### 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&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Restricted index&lt;sup&gt;b&lt;/sup&gt;</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)&lt;sup&gt;b&lt;/sup&gt;</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&lt;sup&gt;c&lt;/sup&gt;</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, cm²</td>
<td>68.6 (13.3)</td>
<td>-0.37 (&lt;0.01)</td>
<td>-0.12 (0.4)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Pearson.

<sup>b</sup>Spearman.

<sup>c</sup>By DXA (n=50) and CT (n=48).
FIG. 1.  VACS index predicts quadriceps strength adjusted for muscle cross-sectional area (CSA).

\[ y = -57 \text{(Index-20 points)} + 4.8 \text{(CSA)} + 356 \]

Model: $p < 0.001$ adjusted $R^2 = 0.31$
The Veterans Aging Cohort Study Index is Associated With Concurrent Risk for Neurocognitive Impairment.

**Marquine MJ, Umlauf A, Rooney AS, Fazeli PL, Gouaux BD, Paul Woods S, Letendre SL, Ellis RJ, Grant I, Moore DJ; HIV Neurobehavioral Research Program (HNR) Group.**

**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.
VACS Index Measures Frailty in HIV

- Is associated with
  - Functional performance
  - Cognitive performance
  - Biomarkers of chronic inflammation

- Predicts
  - All cause and cause specific mortality
  - Hospitalization, MICU admission and 30 day mortality
  - Fragility fractures

- Is responsive to changes in care and behavior
  - ART interruption and intensification
  - Varying levels of ART adherence
Should HIV Infection Change Our Approach...Yes

• To the extent that it alters the balance between benefits and harms from additional screening and treatment, yes it should.

• How do we know? And how do we summarize risk?
Key Questions

• Is aging with HIV different than aging without it?
• Should HIV infection change our approach to prevention and treatment of other conditions?
• How can a risk index (frailty index) personalize health care for those aging with HIV infection?
VACS Index Calculator

Age: 68
Sex: Female
Race: black
CD4: $\geq 500$
HIV-1 RNA: $< 500$
Hemoglobin: $\geq 14$
AST (SGOT): 
ALT (SGPT): 
Platelet count: 
FIB-4: $< 1.45$
Serum Creatinine: 
eGFR: $\geq 60$
Hepatitis C: No
VACS index: 73
5 Year Mortality: 50%

Risk Factors
Tobacco: No
Alcohol: None
I sometimes miss my HIV meds. No
Hepatitis C Treatment: Fully

What it means?

Calculate Risk
**Proposed Changes**

**Things I Propose to Decrease my Risk**

**Smoking:**
- Continue
- Stop

**Alcohol:**
- Same
- Decrease
- Stop

**Adherence:**
- Non-good
- Good

**Hepatitis Treatment:**
- Non-good
- Good

**Risk**

<table>
<thead>
<tr>
<th>VACS Index</th>
<th>5 Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>73</td>
</tr>
<tr>
<td>After proposed change</td>
<td>73</td>
</tr>
<tr>
<td>Best available</td>
<td>55</td>
</tr>
</tbody>
</table>

**Close**
Things I Propose to Decrease my Risk

Smoking:
- Continue
- Stop

Alcohol:
- Same
- Decrease
- Stop

Adherence:
- Non-good
- Good

Hepatitis Treatment:
- Non-good
- Good

Risk

<table>
<thead>
<tr>
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<th>5 Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>73</td>
</tr>
<tr>
<td>After proposed change</td>
<td>70</td>
</tr>
<tr>
<td>Best available</td>
<td>55</td>
</tr>
</tbody>
</table>
**Things I Propose to Decrease my Risk**

**Smoking:**
- Continue
- Stop

**Alcohol:**
- Same
- Decrease
- Stop

**Adherence:**
- Non-good
- Good

**Hepatitis Treatment:**
- Non-good
- Good

---

**VACS Index Calculator**

<table>
<thead>
<tr>
<th>VACS Index</th>
<th>5 Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>73</td>
</tr>
<tr>
<td>After proposed change</td>
<td>55</td>
</tr>
<tr>
<td>Best available</td>
<td>55</td>
</tr>
</tbody>
</table>
Roles for Risk Index

- Patient counseling (as demonstrated)
- Stratification for, or outcome of, RCTs
- Means of prioritizing care
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 3.6 million patients annually. The VA is also the largest single provider of HIV care in the nation, serving 19,000 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.
National VACS Project Team
Acknowledgements

• **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 Køerbel, 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)

• **Major Funding by:** National Institutes of Health: AHRQ (R01-HS018372), NIAAA (U24-AA020794, U01-AA020790, U01-AA020795, U01-AA020799, U24-AA022001, U24 AA022007), NHLBI (R01-HL095136; R01-HL090342), NIAID (U01-A1069918), NIMH (P30-MH062294), NIDA (R01DA035616), NCI (R01 CA173754) 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
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Continued

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QR Codes

QR Code for VACS Homepage
QR Code for VACS INDEX CALCULATOR-
QR Code for VACS INDEX CALCULATOR-MOBILE APP