Aging and HIV: Unifying Concepts

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Chief General Internal Medicine, Veterans Administrative Connecticut Healthcare System
Three Eras of HIV Treatment

Opportunistic infection era
- Crisis management
- Treatment of opportunistic infections
- Palliative care
- Primary care

Antiretroviral era
- Focus on viral pathogenesis
- Specialization and medicalization of HIV care ("HIV specialist")

Chronic disease era
- HIV disease management
- Co-morbidities and aging
- Primary care

Chu and Selwyn, J Urb Health, 2011. 88:556-566
# Life Expectancy Estimates in the ART 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: 27.6 years in men; 36.8 years in women. LE at age 60: 10.1 years in men; 14.4 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 years: 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, \(~38,000\)^3
  - In SSA, \(~333,000\)^4

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

Source: UNAIDS 2012 estimates.
Demography Matters: Deaths Among HIV+/- in NYC 2004-2008

Death Rates by Age and Race/Ethnicity

- Orange: Black Non-HIV-related
- Yellow: Black HIV-related
- Light Blue: Hispanic Non-HIV-related
- Dark Blue: Hispanic HIV-related
- Pink: White Non-HIV-related
- Maroon: White HIV-related
- Gray: NYC all-cause

Age Groups:
- 13-29
- 30-49
- 50-69

HIV Epidemiology & Field Services Semiannual Report, NYCDOH. April 2010
Timing of Treatment Matters: Delayed Presentation By Age

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)
Overview

• How can we study aging with HIV?
• Unifying concepts
  – Return to Health Vs. Continued Effects of HIV
  – Multimorbidity
  – ART Toxicity and Polypharmacy
• Where do we go from here?
How can we study aging and HIV?
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 (Uninfected Women)

Kanis JA. Osteo Inter 2001, 12: 989.
Observation and Comparison

Levels of Evidence

1. Prevalence HIV+/-
   Are non AIDS conditions more common?

2. Incidence HIV+/-
   Are rates of non AIDS conditions higher?

3. Adjusted Incidence HIV+/-
   Are rates higher after adjustment for known risks?
Appropriate Uninfected Comparators

• Demographically similar
• Behaviorally similar
• Equally subject to disease detection
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
Common Mistakes in Comparators

• Biases that increase age difference
  – Comparator population older than HIV+
  – More risk factors among HIV+
  – Hepatitis C coinfection

• Biases that lower age difference
  – Competing risk of death
  – Requiring AIDS diagnosis (rather than HIV+ only)
  – Not accounting for risks more common among uninfected (e.g., obesity & metabolic syndrome)
The Veterans Aging Cohort Study (VACS)

- Large, well 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

- Focused on clinical outcomes (not biomarkers)

- Established collaboration
  - PIs have worked (and published) together
  - Extensive network of clinicians and experts
National VACS Project Team
Cross Cohort Collaborations

• Need to reproduce and extend findings

• Joined cross cohort collaborations (~30-60,000 subjects in each)
  – ART-CC: Largely European, 19 cohorts
  – HIV Causal: Largely European, 10 cohorts
  – NA-ACCORD: North American, 21 cohorts
Return to Health Vs. Residual Effects of HIV and ART
AIDS Events Increasingly Rare

ART-CC, Archives Int Med 2005: 165 416-423

1. *Mycobacterium avium* Disease
2. Kaposi Sarcoma
3. Cytomegalovirus Disease
4. *Pneumocystis carinii* Pneumonia
5. Tuberculosis
6. Esophageal Candidiasis
7. HIV-Related Encephalopathy
8. Toxoplasmosis of the Brain
9. Non-Hodgkin Lymphoma
10. Herpes Simplex Virus Disease
11. Wasting Syndrome
12. Progressive Multifocal Leukoencephalopathy
13. Cryptococcosis
14. Cryptosporidiosis
15. Bacterial Pneumonia
>50% of Deaths Attributed to “Non-AIDS” Events

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

BATTERHAM

Study

Mean difference
(95% CI)

Kotler(3)  
-34.31 (-57.11, -11.51)

Hommes(4)  
20.91 (10.57, 31.24)

Hommes(49)  
14.76 (7.19, 22.34)

Mellor(47)  
31.50 (21.15, 41.85)

Mulligan(52)  
13.00 (7.46, 18.54)

Mellor(50)  
21.00 (15.52, 26.48)

Salehian(92)  
15.90 (4.90, 26.90)

Macallan(53)  
15.06 (9.14, 20.99)

Godfried(54)  
13.00 (2.36, 23.64)

Sharpstone(45)  
8.42 (4.26, 12.59)

Schwenk(58)  
0.42 (-6.95, 7.79)

Sharpstone(46)  
0.84 (-12.98, 14.65)

McNurlan(88)  
9.71 (-0.62, 20.04)

Heijigenberg(60)  
6.30 (-2.87, 15.46)

Jimenez Exposito(66, 94)  
14.10 (7.61, 20.58)

Lane(75)  
6.28 (-0.57, 13.12)

Coors(79)  
4.31 (-6.41, 15.03)

Korach(82)  
-6.00 (-16.53, 4.53)

Hadigan(61)  
12.53 (-0.85, 24.25)

Sekhar(83)  
21.63 (-0.81, 44.07)

Batterham(87)  
13.32 (-6.26, 20.38)

Luzi(86)  
11.30 (-6.25, 28.85)

Kosmiski(8, 85)  
23.59 (12.78, 34.41)

Cenn(93)  
25.86 (14.61, 37.11)

Overall  
11.93 (8.44, 15.43)

Energy Expenditure in HIV

• 10-25% increased requirement among untreated HIV infected compared to uninfected
• Unclear among those on ART
• Even less clear once HIV-RNA is suppressed
• Is this an important clue to residual disease???
  – Viral reservoirs?
  – Ongoing inflammation?

Komiski L. Energy expenditure in HIV. Am J Clin Nutr 2011;94(suppl):1677S-82S.
Weight Change Over 12 Months by Baseline Weight Status

Uninfected

HIV Infected After ART Initiation

Baseline BMI

Underweight  Normal  Overweight  Obese

Uninfected

Underweight  Normal  Overweight  Obese

HIV Infected After ART Initiation

Weight change over 12 months following start date

- Lost > 5 lbs
- Remained within ± 5 lbs
- Gained > 5 lbs

Tate J et al.  CROI [Poster] Atlanta, Georgia, March 3-6, 2013.
% Undetectable HIV-1 RNA After 1 Year of ART By Weight and Weight Gained

Preliminary Data
Baseline (Blue) and 1 Year (Red) Values Among those Achieving VL Suppression

CD4

VACS Index

Preliminary Data
Incidence of Diabetes by Weight Status at Baseline and Weight Gain Over 12 Months

Tate J et al. CROI [Poster] Atlanta, Georgia, March 3-6, 2013.
Weight Change after ART And Mortality Among Normal (n=2226) Vs. Overweight/Obese (n=1842) Individuals

*Adjusted for VACS Index at ART Initiation
HIV Disease Intervals

- Pre-HIV
- Pre-ART
- Post-ART

HIV infection
ART initiation

HIV effect
Most Often Studied

HIV + ART effect
Study Population

- 60% African American
- 10-34% prevalence substance abuse
- 11-18% hepatitis C
- 2-6% prevalence CVD, diabetes, NM cancer
- 3.5 years median HIV duration
- 1.3 years median ART exposure

728 eligible

164 excluded (incomplete measurement pairs)

N=422 HIV effect

N=297 HIV+ART effect

Clinical Biomarkers

- **Lipids**: Total-, LDL-, HDL and non HDL-cholesterol, triglycerides
- **Hepatic**: Albumin, bilirubin, blood glucose, HbA1c, ALT, AST, FIB4
  \[ FIB4 = \frac{age \times AST}{platelets \times \sqrt{ALT}} \]
- **Renal**: BUN, creatinine, eGFR
- **CVD/hematologic**: SBP, DBP, heart rate, hemoglobin, platelets
- **No significant change in BMI**

Change in Lipids

** p<0.05

- Total cholesterol
- HDL cholesterol
- LDL cholesterol
- Triglycerides

% change in median biomarker level

** HIV effect
** HIV + ART effect

Change in Hepatic Markers

FIB4 = \frac{\text{age} \times \text{AST}}{\text{platelets} \times \sqrt{\text{ALT}}}

\[
\text{HIV effect} \quad \text{HIV + ART effect}
\]

Change in Hemoglobin

HIV effect
HIV + ART effect

** p<0.05

HIV Associated Non AIDS(HANA) Conditions

• After adjustment for established risk factors, association with HIV remains
  – Compare to demographically and behaviorally similar uninfected controls
  – Weaker (<2 fold) associations may be due to inadequate adjustment for risk factors

• May be due to HIV, ART, or both
Underlying Age Distribution Matters

Premature or Accentuated Events?

A. Premature events: 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.

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.

HIV and “Associated” Cancers

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

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<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>

**Premature aging?**

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 (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.

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
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
# HIV and Hepatic Decompensation by ART Exposure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Person-Years</th>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</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.

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*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).*
Conclusions

• HIV progression contributes more risk of non AIDS conditions than does ART toxicity
• “Return to health” mis-attributed to ART toxicity
• Clinical biomarkers do not “normalize” after ART
• Increased risk of HANA conditions does not automatically imply premature aging
Multimorbidity
HIV Does Not Occur in a Vacuum

• Before aging an issue, care complicated by:
  – Multi drug regimens susceptible to non adherence, resistance, and toxicity
  – Co infections (HCV, TB, MDR-TB)
  – Major socioeconomic issues: stigma, addiction, incarceration, homelessness, undernutrition

• Aging adds chronic non infectious disease to mix
“Two-thirds of Medicare beneficiaries had multiple chronic conditions”

Figure 1.2a Percentage of Medicare FFS Beneficiaries by Number of Chronic Conditions: 2010

- 32% for 0 to 1 chronic conditions
- 32% for 2 to 3 chronic conditions
- 23% for 4 to 5 chronic conditions
- 14% for 6+ chronic conditions

DATA HIGHLIGHTS:
Among the 15 chronic conditions examined, the prevalence of multiple chronic conditions was high, with over two-thirds of beneficiaries having two or more chronic conditions and 14% having 6 or more chronic conditions.
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.

“Co-morbidity among chronic conditions is very common”
Incident Disease: Swiss Cohort 2008-10

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 and HIV in the ALIVE Cohort

(N = 1262)

Number of Multimorbid Conditions

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

Salter et al., 2011. *CID.* 53:1256-64.
HIV, Comorbidity, and Inflammation (IL-6)

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.
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

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
<table>
<thead>
<tr>
<th>Biomarkers of General Organ System Injury</th>
<th>HIV Specific Biomarkers</th>
<th>Index Score</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>≥ 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></td>
</tr>
<tr>
<td>10 to 11.9</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>38</td>
<td></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></td>
</tr>
<tr>
<td>&gt; 3.25</td>
<td>25</td>
<td></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></td>
</tr>
<tr>
<td>30 to 44.9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C Infection</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)

Justice AC. et al. Predictive Accuracy of the Veterans Aging Cohort Study (VACS) Index for Mortality with HIV infection: A North American Cross Cohort Analysis. JAIDS in press Feb 1 201
MICU Admission Over 6 Years

Kaplan-Meier Survival Estimates

HIV Restricted Index

VACS Index

VACS Index Predicts Fragility Fractures

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>

VACS Index Correlated with Biomarkers of Inflammation

VACS Index Also Correlates With:

• Functional Performance
  – Erlandson KM et al. Prospective comparison of three functional assessments with the VACS Index in virologically suppressed HIV-infected adults. 2nd International Workshop on HIV and Aging 2011

• Cognitive Performance
  – Marquine MJ et al. Higher VACS Index Scores are associated with concurrent risk of neurocognitive impairment. 3rd International Workshop on HIV and Aging 2012
Conclusions

• Multimorbidity is a Game Changer
  – Increases risk of toxicity
  – Introduces competing concerns
  – Patients/providers must start to prioritize care

• Risk indices integrate diverse sources of injury and may help inform prioritization

• Multiple mechanisms likely the norm making biomarker outcomes even more problematic
Polypharmacy
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
### 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>4 (2.6)</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.

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

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total n (%)</th>
<th>&lt;50</th>
<th>50-64</th>
<th>≥65</th>
<th>P^1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensives (not ACE inhibitors)</td>
<td>831 (9.8)</td>
<td>323 (5.6)</td>
<td>367 (16.4)</td>
<td>141 (31.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensives (ACE inhibitors)</td>
<td>935 (11.1)</td>
<td>355 (6.2)</td>
<td>432 (19.4)</td>
<td>148 (32.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>1071 (12.7)</td>
<td>356 (6.2)</td>
<td>527 (23.6)</td>
<td>188 (41.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral antidiabetics</td>
<td>179 (2.1)</td>
<td>51 (0.9)</td>
<td>87 (3.9)</td>
<td>41 (9.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin</td>
<td>116 (1.4)</td>
<td>40 (0.7)</td>
<td>50 (2.2)</td>
<td>26 (5.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>488 (5.8)</td>
<td>121 (2.1)</td>
<td>237 (10.6)</td>
<td>130 (28.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>846 (10.0)</td>
<td>560 (9.7)</td>
<td>251 (11.2)</td>
<td>35 (7.8)</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\textsuperscript{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

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?
Conclusions

• In the context of aging and multimorbidity, individual prioritization of care is essential

• Prioritization should consider
  – Risk of short term mortality
  – Maximizing what is most important to patient
  – Minimizing risk of causing harm

• More medication, even if suggested by care guidelines, may cause harm
Future

• Adapt approach to tailoring treatment guidelines to incorporate multimorbidity

• Use large well characterized observational cohort study to
  – develop and validate risk index
  – Initially identify net absolute benefit to treatments

• Conduct strategy trials that individualize care based on estimated risk and benefit
Stories From an Aging Epidemic

Robert, age 75

Sue, age 73

Anna, age 64

Bill, age 77

www.grayingofAIDS.org
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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)
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*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
www.vacohort.org

Opened 6/1/11

Hits: 12,571

Unique Visitors: (3 months) 1,923

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-records 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.