HIV Progression, Alcohol, and Aging
Towards a combined prognostic index for survival in HIV infection – the role of Non-HIV Markers

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The value of cohort studies for measuring progression and aging in HIV?

How can you assess the impact of different systems of care or specific interventions (for alcohol) within these systems?
A few facts about alcohol and HIV

• In the U.S. 15-40% of HIV+ individuals have and a current alcohol use disorder

• International samples have exceeded 60%

• Physicians advise patients not to drink with cART treatment (per warning labels)

• 80% of patients continue drinking

• Heavy drinking will reduce expected life years by half (24 to 12)
People with HIV are Living Longer

Deaths/1000 PY

- **Denmark**: 124
  - HIV+<1999: 25
  - HIV+>1999: 11
  - HIV-: 11

- **New York IDU**: 114
  - HIV+<1999: 54
  - HIV+>1999: 15
  - HIV-: 15

- **Barcelona**: 45
  - HIV+<1999: 10
  - HIV+>1999: 5
  - HIV-: 5

Refs:
- Denmark: Ann Intern Med 2007:146:87-95
- Barcelona: HIV Medicine 2007;8:251-8
Life Expectancy is **Not** “Normal”

<table>
<thead>
<tr>
<th>At HAART Initiation</th>
<th>CD4 Cell Count (mm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;100</td>
</tr>
<tr>
<td>A 20 yr old will live to</td>
<td>52</td>
</tr>
<tr>
<td>A 35 yr old will live to</td>
<td>62</td>
</tr>
<tr>
<td>% Remaining Life Lost (all ages)</td>
<td>46%</td>
</tr>
</tbody>
</table>

Adapted from ART-CC, *Lancet* 2008;372:293-99 by adding additional expected survival to age at treatment initiation.
“By 2015, an estimated 50% of people living with HIV/AIDS [in the US] will be over 50 years of age.”

"Non AIDS" Deaths HIV+ More Common

<table>
<thead>
<tr>
<th>Source</th>
<th>Non AIDS</th>
<th>Leading Causes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NY Death Certificates</td>
<td>26%</td>
<td>Alcohol/drug abuse (31%), CVD (24%), Cancer (21%)</td>
<td>Ann Intern Med 2006;145:397-406</td>
</tr>
<tr>
<td>Barcelona Death Certificates</td>
<td>60%</td>
<td>Liver (23%), Infection (14%), Cancer (11%), CVD (6%)</td>
<td>HIV Med 2007:8;251-8</td>
</tr>
<tr>
<td>HOPS Chart Rev.</td>
<td>63%</td>
<td>Liver (18%), CVD (18%), Pulmonary (16%), Renal (12%), GL (11%), Infection (10%), Cancer (8%)</td>
<td>J Acquir Immune Defic Syndr 2006;43:27-34</td>
</tr>
<tr>
<td>Cascade Chart Rev.</td>
<td>63%</td>
<td>Liver (20%), Infections (24%), Unintentional (33%), Cancer (10%), CVD (9%)</td>
<td>AIDS 2006; 20;741-9</td>
</tr>
</tbody>
</table>
Goals Cohort Studies

To understand the roles of aging, comorbidity, treatment toxicity and substance use (Alcohol and Drugs) in determining morbidity and mortality with HIV infection and to use these insights to develop informatics based interventions to improve patient outcomes
Three Assumptions

• Aging, comorbidity, treatment toxicity, and substance use interact with HIV infection

• Many of these interactions are modifiable – alcohol use is one of the most modifiable

• Strategies which individually tailor and prioritize care will be most effective
VACS Virtual Cohort (VC)
Sources of Data for Indicators

- CURRENT DATA SOURCES: National administrative, laboratory, pharmacy, cancer registry, MI quality of care, and all cause mortality (requesting Medicare)

- SUBJECTS: 41,753 HIV infected; 83,506 uninfected
  - All individuals with HIV diagnoses
  - Age, race/ethnicity, region 2:1 matched controls
  - Last updated: September, 2008

- SITES: All VA sites

- BASELINE: 1998 (11 years of follow up)
  - HIV infected veterans at initiation of HIV care
  - Controls selected and followed in same calendar year
VACS 8

• CURRENT DATA SOURCES (VC sources plus)
  – Consented for all clinical data
  – Records for sentinel events requested outside VA
  – All VA Electronic medical records including text fields
  – DNA and tissue bank
  – Annual self completed surveys

• SUBJECTS:
  – 3,600 HIV infected (alcohol using); 3,600 uninfected
  – Group matched: age, race/ethnicity, and site

• SITES: Manhattan, Bronx, Washington DC, Baltimore, Pittsburgh, Atlanta, Houston, Los Angeles

• BASELINE: 2002 (8 years)
DNA and Tissue Bank
(Collection Completed 8/31/07)

<table>
<thead>
<tr>
<th></th>
<th>HIV+</th>
<th>HIV-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unique Pts</td>
<td>1656</td>
<td>892</td>
<td>2548</td>
</tr>
<tr>
<td>DNA Samples</td>
<td>1656</td>
<td>892</td>
<td>2548</td>
</tr>
<tr>
<td>Tissue Samples</td>
<td>1542</td>
<td>867</td>
<td>2409</td>
</tr>
</tbody>
</table>

To collect serial samples on those newly initiating antiretroviral treatment in the future.
Traditional Measures of Viral Replication and Immune Function

ARV Treatment Effectiveness
AIDS Events Are Deceased on cART

Figure 1. Incidences of 15 AIDS-defining events in 5 time periods after initiation of highly active antiretroviral therapy (HAART).

ART-CC Arch Intern Med 2005 165:416-423
AIDS Events are Variably Associated with CD4 and Survival

By Median (IQR) CD4

By Relative Hazard of Death

ART-CC, CID 2009;48:1138-51
Is This the Price of Success?

• No surprise that older people have an increased risk of mortality

• Younger people may now be living long to die from other causes

• Or, *is something more subtle going on?*
More AIDS and “Non-AIDS” Events Among Rx. Sparing Arm (HR 1.7 in SMART)

<table>
<thead>
<tr>
<th>Event</th>
<th>Rx. Sparing</th>
<th>Rx. Intensive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause Death</td>
<td>55</td>
<td>30</td>
<td>85</td>
</tr>
<tr>
<td>Serious OI</td>
<td>13</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Nonserious OI</td>
<td>63</td>
<td>18</td>
<td>81</td>
</tr>
<tr>
<td>Major CAD, Renal, or Liver Disease</td>
<td>65</td>
<td>39</td>
<td>104</td>
</tr>
</tbody>
</table>

Strategies for Management of Antiretrivoral Therapy NEJM 2006;355:2283-96
HIV Infection is a Complex Chronic Disease

- Many common ‘Non AIDS’ conditions are associated with HIV infection and disease progression
- AIDS defining conditions are increasingly rare and variably associated with mortality
Case History: Low Bone Mineral Density (BMD)

- 55 year old male with HIV
- Dexa scan shows BMD 1 SD below normal
- Body mass index of 30
- Long term alcohol abuse
- Long term smoker
Decreased Bone Mineral Density

- Amiel et al, 2004
- Brown et al, 2004
- Bruera et al, 2003
- Dolan et al, 2004
- Huang et al, 2002
- Knobel et al, 2001
- Madeddu et al, 2004
- Loiseau-Peres et al, 2002
- Teichman et al, 2003
- Tebas et al, 2000
- Yin et al, 2005
- Teichman et al, 2003
- Madeddu et al, 2004
- Loiseau-Peres et al, 2002
- Knobel et al, 2001
- Huang et al, 2002
- Dolan et al, 2004
- Bruera et al, 2003
- Brown et al, 2004
- Amiel et al, 2004

Brown TT & Qaqish RB. AIDS. 2006; 20:2165-2174
BMD Vs. Fragility Fracture

- Low BMD is a risk factor for vertebral, wrist, or hip fracture (fragility fracture)
- HIV and time on cART is associated with low BMD
- One age, race and gender, adjusted study has shown an increased risk of fragility fractures
  - 3.1 vs. 1.8 per 100 PY for HIV+/- men (72% increase)
  - 2.5 vs. 1.7 per 100 PY for HIV+/- women (47% increase)
  - But let's look at this more closely…

Triant et al J Clin Endo and Metabolism 2008 93:3499-504
‘Fragility Fracture’ Prevalence

Includes fractures caused by violent injury. Not adjusted for Body Mass Index, smoking, alcohol, prior fracture, functional status or BMD. Triant VA. J Clin Endocrinol Metab 93:3499-3504, 2008
VACS VC Prevalence in Men

Any  N=2152

Wrist  N= 1233

Vertebral  N= 297

Hip  N= 622

Fractures per 100 persons vs. Age (years)
### VC Incident Fragility Fractures in Men

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted model</th>
<th>Full model</th>
<th>HIV-infected only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>Hazard ratio (95% CI)</td>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td><strong>HIV</strong></td>
<td>1.53 (1.34, 1.75)</td>
<td>1.38 (1.18, 1.60)</td>
<td></td>
</tr>
<tr>
<td><strong>Cachexia</strong></td>
<td></td>
<td>2.83 (2.26, 3.54)</td>
<td>2.52 (1.82, 3.49)</td>
</tr>
<tr>
<td><strong>Cerebrovascular disease</strong></td>
<td></td>
<td>1.89 (1.34, 2.65)</td>
<td>1.70 (0.92, 3.14)</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>1.79 (1.57, 2.04)</td>
<td>1.81 (1.64, 1.99)</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol dependence</strong></td>
<td>1.73 (1.42, 2.10)</td>
<td>1.88 (1.37, 2.58)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (10 year increments)</strong></td>
<td>1.53 (1.44, 1.63)</td>
<td>1.81 (1.47, 2.23)</td>
<td></td>
</tr>
<tr>
<td><strong>Enrollment year before 1999</strong></td>
<td>0.75 (0.64, 0.87)</td>
<td>0.89 (0.69, 1.14)</td>
<td></td>
</tr>
<tr>
<td><strong>CD4 (per 100 cells/mm³)</strong></td>
<td></td>
<td>0.96 (0.91, 0.99)</td>
<td></td>
</tr>
<tr>
<td><strong>Tenofovir use at baseline</strong></td>
<td></td>
<td>1.22 (0.72, 2.05)</td>
<td></td>
</tr>
<tr>
<td><strong>NNRTI use at baseline</strong></td>
<td></td>
<td>0.68 (0.45, 1.04)</td>
<td></td>
</tr>
<tr>
<td><strong>PI use at baseline</strong></td>
<td></td>
<td>1.22 (0.97, 1.53)</td>
<td></td>
</tr>
</tbody>
</table>

Also controlled for: congestive heart failure, pulmonary disease, peripheral vascular disease, drug abuse, major depressive disorder, CAD, diabetes, liver disease, renal insufficiency, osteonecrosis, steroid use at baseline. Adjustment for non-proportionality: HIV*\log\text{(time)} HR: 1.09 (95% CI: 1.01, 1.18)
Prevention of Fragility Fractures

• Behavior
  – Smoking and alcohol cessation
  – Exercise and weight maintenance

• Nutrition
  – Calcium, Vitamin D

• Bisphosphonates (Alendronate, Risedronate, etc.)
  – Toxicities: GI reflux, ulcers, esophageal cancer and jaw osteonecrosis
  – Unknown efficacy in HIV
Also Under Study in VACS

- Liver Cirrhosis
- Non AIDS Cancers
- Anemia of Chronic Inflammation
- COPD and Bacterial Pneumonia
- Stroke
- Cardiovascular Disease
- Renal Disease
Implications For An Aging Epidemic

• HIV infection increases risk of common ‘non AIDS’ conditions but not as much as many established risk factors

• Primary care guidelines for non-AIDS condition must be adapted for those with HIV
  – Some non-AIDS conditions may justify earlier ARV treatment
  – Selected ARV treatments likely cause some non-AIDS conditions, but effects are often less than those of HIV itself

• We need a comprehensive index to chart changes in total risk of morbidity and mortality
<table>
<thead>
<tr>
<th>Points</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>0</td>
</tr>
<tr>
<td>50 to 64</td>
<td>9</td>
</tr>
<tr>
<td>≥ 65</td>
<td>27</td>
</tr>
<tr>
<td>CD4</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>17</td>
</tr>
<tr>
<td>50 to 99</td>
<td>14</td>
</tr>
<tr>
<td>100 to 199</td>
<td>11</td>
</tr>
<tr>
<td>200 to 349</td>
<td>8</td>
</tr>
<tr>
<td>≥350</td>
<td>0</td>
</tr>
<tr>
<td>AIDS defining condition</td>
<td>7</td>
</tr>
<tr>
<td>Log Viral load &gt; 5</td>
<td>3</td>
</tr>
<tr>
<td>Hemoglobin &gt; 12</td>
<td>0</td>
</tr>
<tr>
<td>10-12</td>
<td>9</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>13</td>
</tr>
<tr>
<td>FIB4 &lt;1.45</td>
<td>0</td>
</tr>
<tr>
<td>1.45 to 3.24</td>
<td>10</td>
</tr>
<tr>
<td>&gt; 3.25</td>
<td>18</td>
</tr>
<tr>
<td>Estimated GFR &lt; 30</td>
<td>12</td>
</tr>
<tr>
<td>Alcohol or Drug Abuse</td>
<td>8</td>
</tr>
<tr>
<td>Hepatitis B or C</td>
<td>9</td>
</tr>
</tbody>
</table>

Veterans Aging Cohort (VACS) Risk Index

Justice 2009 HIV Medicine published electronically
Individual Score Pre cART

\[ R^2 = 0.99 \]
Survival by VACS Index Score (6 years)
Median VACS Index Score and Self Reported Function

- No problem
  - Sprint: 17
  - Light Housework: 17
  - Walk Uphill: 24
  - Lineal (Walk Uphill): 24

- Yes, slowly
  - Sprint: 24
  - Light Housework: 24
  - Walk Uphill: 27
  - Lineal (Walk Uphill): 27

- Not able to
  - Sprint: 27
  - Light Housework: 27
  - Walk Uphill: 27
  - Lineal (Walk Uphill): 27
Patient Normative Feedback Imagine!

- Welcome to the Latin American Cohort Study (LACS) Risk Index Calculator. If you have HIV infection, this calculator will determine your risk score. It does this using your age, whether or not you have started antiretroviral therapy, how long you have taken antiretroviral therapy, and your most recent routine laboratory values score and a few lifestyle questions.
What is needed

- CD4 cell count, HIV viral load, creatinine, hemoglobin, Aspartate Transaminase (AST), Alanine Transaminase (ALT), platelet count, and hepatitis C test, and use of alcohol.

- In most healthcare settings, you can request these laboratory values from your provider or ask for a copy to be sent to you when your blood is drawn.

- After you enter this information at the prompts, the calculator will give you or your care provider a risk score.
The Best Index

• Demonstrate
  – Generalizability and Cultural Specificity
  – Responsiveness to interventions (adherence, cART, alcohol cessation, HCV treatment)

• Determine whether additional biomarkers improve Index and lifestyle questions to target brief interventions

• Create medical decision support tools to optimize care and motivate behavior change

• Use as surrogate outcome in health services strategy trials
Thank You
Website

Veterans Aging Cohort Study

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.
Veterans Aging Cohort Study

- **PI and Co-PI**: AC Justice, DA Fiellin

- **Scientific Officer (NIAAA)**: K Bryant

- **Participating VA Medical Centers**: Atlanta (D. Rimland), Baltimore (KA Oursler, R Titanji), Bronx (S Brown, S Garrison), Houston (M Rodriguez-Barradas, N Masozera), Los Angeles (M Goetz, D Leaf), Manhattan-Brooklyn (M Simberkoff, D Blumenthal, J Leung), Pittsburgh (A Butt, E Hoffman), and Washington DC (C Gibert, R Peck)

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- **Staff**: D Cohen, A Consorte, K Gordon, F Kidwai, F Levin, K McGinnis, J Rogers, M Skanderson, J Tate, Harini, T Boran

- **Major Collaborators**: VA Public Health Strategic Healthcare Group, VA Pharmacy Benefits Management, Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), Yale Center for Interdisciplinary Research on AIDS (CIRA), Center for Health Equity Research and Promotion (CHERP), ART-CC, NA-ACCORD, HIV-Causal

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