Aging and HIV: Insights from the Veterans Aging Cohort Study (VACS)

Amy C. Justice, MD, PhD
Professor of Medicine and Public Health
Yale University
Outline

• What is the Veterans Aging Cohort Study?

• How does aging with HIV differ from aging without HIV?

• Where is VACS going?
Outline

• What is the Veterans Aging Cohort Study?

• How does aging with HIV differ from aging without HIV?

• Where is VACS going?
VACS is Based in the VA Healthcare System
VA an Amazing Laboratory

- >6 million veterans in care each year
- National coordination and leadership
- Largely captured, aging, diverse population
- National, paperless, EHR
- Pharmacy fill data
- Culture of evidence based medicine
- Long term time horizon
Veterans Aging Cohort Study (VACS)

• Cohort
  – All individuals with HIV diagnoses
  – Age, race/ethnicity, region 2:1 matched controls
  – Last updated: June 2016

• 168 VA Medical Centers across US

• BASELINE: 1998 (18 years of follow up)
  – HIV infected veterans at initiation of HIV care
  – Controls selected and followed in same year
Current cohort consists of ~50K HIV+ demographically matched to ~100K uninfected veterans. VACS is predominantly male but includes ~3,500 (1000 HIV+) women. We have 3 times the national proportion of 65+ year old individuals.
VACS Survey Substudy

• Group matched (1:1)
• Consented Subset of VACS (~9,000)
• 8 survey waves from 2003-Present
• 8 sites:
  - Los Angeles CA
  - Manhattan/Brooklyn NY
  - Bronx NY
  - Atlanta GA
  - Washington DC
  - Nashville TN
  - Houston TX
  - Dallas TX
Biomarker Cohort (VAC-BC)

- 1525 HIV+ and 853 Uninfected (Subset of VACS Survey)
- Linked to longitudinal EHR and surveys
- Blood and DNA 2005-2006, As of 1/2017:
  - 303 incident (422 prevalent) cancers
  - 63 incident (66 prevalent) MIs
  - >400 deaths
- Assays completed:
  - IL-6, D-dimer, and sCD14
  - Phosphatidalethanol (PEth)
  - Th1, Th2, Th17, Treg, naïve, memory, natural killer and delta gamma cells, B cells, monocytes
  - GWA (illumine HumanOmniExpress Beadchip 980K)
- SOMAlogic to run SOMAscan (4000 protein assay)
Site PIs

Vincent Marconi, MD
Atlanta

Sheldon Brown, MD
Bronx

Michael Simberkoff, MD
Brooklyn/Manhattan

Roger Bedimo, MD
Dallas

Maria Rodriguez-Barradas, MD
Houston

Matthew Goetz, MD
Los Angeles

Todd Hulgan, MD
Nashville

Cynthia Gibert, MD
Washington, DC
CURRENT FUNDING EXTENDS VACS THROUGH 2021
Guiding Principals

• Aging, alcohol & substance use, comorbidity, and treatment toxicity interact with HIV & ART

• Most of these interactions are modifiable

• Tailoring and prioritizing care accounting for these conditions can improve outcomes
Long Term Goals

1. Understand roles of aging, comorbidity, toxicity, and multisubstance use (alcohol, tobacco, and drugs) in patient outcomes among HIV+/-

2. To apply these insights to the development and implementation of interventions to improve outcomes
To Propose Analyses...

You:
1. Go to website (vacohort.org) to understand data/samples (Brainstorm with relevant Core and/or Workgroup Chairs)
2. Write brief (1 page) concept sheet (CS, form on website)
3. Submit to Teresa Bohan (Teresanne.Bohan@va.gov)

We:
1. Assign to a Core/Workgroup for initial review. Chair recommends approval/disapproval and priority
2. Executive committee determines final decision and priority
3. If approved, CS returned to Core/Wkgp. Call set up with investigator/writing group to specify request/monitor progress

NB: 40% of our projects are initiated by outside collaborators!
• >300 publications
• >13,000 citations
• >150 trainees
• Largest cohort of HIV+ in North America
• VACS has helped shape the discussion of HIV and aging
2017 CROI Abstracts - VACS

**ORAL:** Marconi VC et al. Hyperbilirubinemia prevents Cardiovascular Disease for HIV+ and HIV- Individuals

**Posters:**
- Farhadian S et al. Age and HIV Do Not Synergistically Impact T Cell Maturation or Activation
- Sigel K et al. Treatment and Outcomes of Non-Small Cell Lung Cancer in Later ART-Era HIV Infection
- McClintic H et al. Physical Function and Inflammation in Older HIV-Infected Men.
- Rentsch C et al. VACS Index is superior to nadir CD4 count for predicting AMI and mortality
- Torgersen J. et al. Prevalence and risk factors for hepatic steatosis in HIV+ persons
- Triplette M et al. Chronic Obstructive Pulmonary Disease with Mortality in HIV.
- Womack JA. et al. Longitudinal Association between HIV Status and Occurrence of Medically Significant Falls.
• NA-ACCORD (Althoff K.). The Large Gap Between Statin Eligibility and Prescription among HIV+ in North America/ Statin Treatment Gap and Effect on Myocardial Infarction in North America.

• NA-ACCORD (Wong C.). Trend in Multimorbidity among HIV+ Adults in Clinical Care in the US.
Outline

• What is the Veterans Aging Cohort Study?

• How does aging with HIV differ from aging without HIV?

• Where is VACS going in the future?
Percentage of Adults Living with HIV Aged 50+ By Year and Region

- Western and Central Europe and North America
- Eastern Europe and Central Asia
- Latin America
- Caribbean
- Sub-Saharan Africa
- Asia and the Pacific
- Middle East and North Africa

10-year Decreased Life Expectancy in Older HIV+ Adults in Modern ART Era

Why Isn’t HIV-1 Suppression Enough?
Does HIV Accelerate Aging? An Important Clue from Nature

Sooty Mangabey
- Infect with SIV
- High levels of viral replication
- No AIDS, normal lifespan
- Minimal immune activation

Rhesus Macaque
- Infect with SIV
- High levels of viral replication
- AIDS and death
- Massive immune activation

SIV = simian immunodeficiency virus.
Inflammation and Immune Activation
Pre- and Post-ART (MACS 1984–2009)

- Generalized gamma models adjusted for age, race, smoking, HCV, obesity, diabetes, and site
- Median ages (years): 42 uninfected, 38 ART-naïve, and 48 suppressed
- 13 biomarkers “normalized” in 1 year, 12 remained distinct from uninfected
- After 1 year, values stabilized

Lower But Persistently Abnormal Immune Activation with Very Early ART (RV254)

- Thai study of HIV+ individuals diagnosed very early during acute HIV infection
- Compared to high-risk HIV- controls and ART-suppressed HIV+ who initiated during chronic HIV infection

Utay NS, et al. CROI 2015; Poster 47.
Inflammation Predicts Disease in Treated HIV Infection

- Mortality (Kuller, 2008; Tien, 2010; Justice, 2012; Hunt, 2014)
- Cardiovascular Disease (Duprez, 2009)
- Cancer (Breen, 2010; Borges, 2013)
- Venous Thromboembolism (Musselwhite, 2011)
- Type II Diabetes Mellitus (Brown, 2010)
- COPD (Attia, 2014)
- Renal Disease (Gupta, 2015)
- Bacterial Pneumonia (Bjerk, 2013)
- Cognitive Dysfunction (Burdo, 2013; Letendre, 2012)
- Depression (Martinez, 2014)
- Frailty (Erlandson, 2013)

How Can We Monitor Disease Progression?
Many Interacting Factors Play A Role

HIV
Viral Hepatitis
Substance Use

Immune Dysfunction + Senescence
Microbial Translocation “Leaky Gut”
Chronic Inflammation and Platelet Hypercoagulability
HIV + Non HIV Treatment Toxicity
Oxidative Stress
Associated Comorbid Disease

Incremental Depletion in Organ System Reserve

Functional Decline
Organ System Failure
Repeated Hospitalization / Nursing Home Placement

Death

PRESENTING CONDITIONS

Overlapping + Interacting Pathophysiologic Processes

Preclinical + Clinical Organ System Injury

Advanced Clinical Disease

AGING

VACS Risk Index

Health Care Outcomes
# VACS Index Components

<table>
<thead>
<tr>
<th>Biomarkers of General Organ System Injury</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Specific Biomarkers</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>0</td>
</tr>
<tr>
<td>50–64</td>
<td>12</td>
</tr>
<tr>
<td>≥ 65</td>
<td>27</td>
</tr>
<tr>
<td>CD4 cells/mm³</td>
<td></td>
</tr>
<tr>
<td>≥ 500</td>
<td>0</td>
</tr>
<tr>
<td>350–499</td>
<td>6</td>
</tr>
<tr>
<td>200–349</td>
<td>6</td>
</tr>
<tr>
<td>100–199</td>
<td>10</td>
</tr>
<tr>
<td>50–99</td>
<td>28</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>29</td>
</tr>
<tr>
<td>HIV-1 RNA copies/mL</td>
<td></td>
</tr>
<tr>
<td>&lt; 500</td>
<td>0</td>
</tr>
<tr>
<td>500 to 1 x 10^5</td>
<td>7</td>
</tr>
<tr>
<td>≥ 1 x 10^5</td>
<td>14</td>
</tr>
<tr>
<td>Hemoglobin g/dL</td>
<td></td>
</tr>
<tr>
<td>≥ 14</td>
<td>0</td>
</tr>
<tr>
<td>12–13.9</td>
<td>10</td>
</tr>
<tr>
<td>10–11.9</td>
<td>22</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>38</td>
</tr>
<tr>
<td>FIB-4</td>
<td></td>
</tr>
<tr>
<td>&lt; 1.45</td>
<td>0</td>
</tr>
<tr>
<td>1.45–3.25</td>
<td>6</td>
</tr>
<tr>
<td>&gt; 3.25</td>
<td>25</td>
</tr>
<tr>
<td>eGFR mL/min</td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>0</td>
</tr>
<tr>
<td>45–59.9</td>
<td>6</td>
</tr>
<tr>
<td>30–44.9</td>
<td>8</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>26</td>
</tr>
<tr>
<td>Hepatitis C Infection</td>
<td>5</td>
</tr>
</tbody>
</table>
Biomarkers of Inflammation Correlated with VACS Index (overall and components)

VACs Index is Accurate in Subgroups

NA-ACCORD (N=10,835)

VACs (N=5,066)

Age < 50 years (N = 11,191)

Age > 50 years (N = 4,710)

Men (N=12,785)

Women (N=3,116)

Black (N = 5,878)

White (N = 6,079)

Undetectable VL (N = 8,715)

Detectable VL (N = 7,186)

NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design.
VACS Index Reflects Frailty Indicated By:

- Functional Performance (Erlandson, 2012)
- Sarcopenia (Oursler, 2013)
- Neurocognitive Performance (Marquine, 2014)
- Autonomic Neuropathy (Robinson-Papp, 2013)
- Fragility Fractures (Womack, 2013; Yin, 2016)
- Hospitalizations and ICU Admissions (Akgun, 2013)

ICU = intensive care unit.

Time-updated VACS Index provided better AMI prediction than CD4 count and HIV-1 RNA suggesting that current health determines risk more than prior history and that risk assessment can be improved by biomarkers of organ injury.

**Table:**

<table>
<thead>
<tr>
<th>HIV Viral Load (copies/mL)</th>
<th>Baseline</th>
<th>&lt;100,000</th>
<th>&lt;100,000+</th>
<th>201-999</th>
<th>1,000-9,999</th>
<th>1,000+</th>
<th>1,000-14,999</th>
<th>&lt;1,000</th>
<th>1,000-14,999</th>
<th>15,000-99,999</th>
<th>100,000+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-updated</td>
<td>≤200</td>
<td></td>
<td></td>
<td>200</td>
<td>200-349</td>
<td>350-499</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative time-updated</td>
<td>&lt;1,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD4 (cells/mm³)</th>
<th>Baseline</th>
<th>≥200</th>
<th>&lt;200</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-updated</td>
<td>≥500</td>
<td></td>
<td>&lt;200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative time-updated</td>
<td>≥2,700</td>
<td></td>
<td>&lt;815</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VACS Score</th>
<th>Baseline</th>
<th>&lt;50</th>
<th>50+</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-updated</td>
<td>&lt;20</td>
<td></td>
<td>20-34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative time-updated</td>
<td>&lt;85</td>
<td></td>
<td>85-149</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*lowest AIC (best model fit)

AMI = acute myocardial infection.
Time-updated VACS Index for Predicting All-Cause Mortality

Time-updated VACS Index provided better mortality prediction than CD4 count and HIV-1 RNA suggesting that current health determines risk more than prior history and that risk assessment can be improved by biomarkers of organ injury.

What Can We Do?
Delayed Treatment by Age

*Among individuals in NA-ACCORD.
HIV-1 RNA Suppression and Cancer

HCV Infection Harms Are Widespread

**Liver**
- Inflammation
- Steatosis
- Fibrosis/Cirrhosis
- Hepatocellular Carcinoma
- Cholangiocarcinoma

**Hematologic and Autoimmune Diseases**
- Mixed Cryoglobulinemia
- B-cell Lymphoma
- Autoimmune Thyroiditis
- Membrano-Proliferative Glomerulonephritis
- Sicca Syndrome

**CVD/Metabolic Disease**
- Atherosclerosis
- Insulin Resistance/Diabetes
- Myocardial Dysfunction

**Neurocognitive Diseases**
- Cognitive Impairment
- Fibromyalgia

Lifestyle Contributes to Immune Activation in Treated HIV

- Smoking increases monocyte activation (Valiathan, 2014)
- Hazardous EtOH associated with ↑ sCD14 / microbial translocation (Carrico, 2015)
- Methamphetamine use increases immune activation and suppresses T-cell function (Massanella, 2015)
- Obesity associated with increased inflammation (Koethe, 2013)
- Moderate exercise decreases inflammation in pilot trials (Longo, 2014)

EtOH = ethyl alcohol; sCD14 = soluble CD14.
Weight Change After ART and Mortality
(Normal [N = 2,226] vs Overweight/Obese [N = 1,842])

*Adjusted for VACS Index at ART initiation.
BMI = body mass index.
Alcohol use more harmful for HIV+

Mortality

Physiologic Frailty

Polypharmacy

• Typically defined as > 5 chronic drugs
• Associated with diminished marginal benefit from additional medication due to:
  • Nonadherence
  • Drug-drug interactions
  • Cumulative toxicity
• Risk of adverse events increases approximately 10% with each additional medication
• Interacts with alcohol, tobacco, or other substances

Chronic Medication Count by Age and HIV Status (VACS)

Daily Long-term Medications

- Uninfected (n=47,613)
- HIV-Infected (n=16,324)

Age (years)

< 40
40 - 50
51 - 60

Opioid Prescribing Trends by HIV status

- Increasing prescribing of opioids to patients +/-HIV
- HIV status associated with receiving any and high dose opioids
- Opioid receipt common among older age groups, greater differences by HIV status among age >45 years

Becker WC et al. *AIDS Behav* 2016
Prescription Opioids Co-prescribed with Benzodiazepines and Mortality among HIV+ (propensity-matched)

- Long-term opioid: 46% increased risk of all-cause mortality
- With long-term benzodiazepine: 65% increased risk of all-cause mortality
- Increasing risk with higher doses

Weisberg DF et al JAIDS 2015
<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (N = 64,441)</th>
<th>Uninfected (n = 47,452)</th>
<th>HIV-infected (n = 16,989)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Long-term opioid receipt</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</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</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</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>&lt; 0.001</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>

PTSD = post-traumatic stress disorder.
Polypharmacy and Substance Use

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

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

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

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

Exercise

• Compared to less active adults, greater activity:
  • Lowers mortality, CAD/CVD, HTN, diabetes, colon/breast cancer, and depression
  • Decreases hip and vertebral fracture
  • Improves weight maintenance

• WHO recommendations for adults:
  • Perform 150 mins of moderate (75 mins of vigorous) aerobic/wk:
    • In bouts of 10+ mins each
    • Increase to 300 mins of moderate (150 mins of vigorous)/wk
  • Muscle strengthening (resistance) 2+ days/wk

• Inactive people: start small and increase over time

• Exercise prescriptions, apps, and partnering with a friend help

CAD = coronary artery disease; HTN = hypertension; WHO = World Health Organization.
Outline

• What is the Veterans Aging Cohort Study?

• How does aging with HIV differ from aging without HIV?

• Where is VACS going?
### VACS Methods Generalize

<table>
<thead>
<tr>
<th>Title</th>
<th>PI</th>
<th>Funding</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ERCHIVES</strong> (Electronic Retrieved Cohort of HCV Infected Veterans)</td>
<td>A. Butt</td>
<td>NIH/Industry</td>
<td>600,000</td>
</tr>
<tr>
<td><strong>WVCS</strong> (Women Veterans Cohort Study)</td>
<td>C. Brandt/S. Haskell</td>
<td>VA Merit</td>
<td>&gt;1 million</td>
</tr>
<tr>
<td><strong>MSD</strong> (Musculoskeletal Disorders Cohort)</td>
<td>R. Kerns/C. Brandt/J. Goulet</td>
<td>VA Center Grant</td>
<td>4.4 million</td>
</tr>
<tr>
<td><strong>VOCAL</strong> (Veterans Outcomes and Costs Associated with Liver Disease)</td>
<td>T. Taddei/D. Kaplan</td>
<td>Industry</td>
<td>55,000 cirrhotics &amp; 7,000 HCC</td>
</tr>
<tr>
<td><strong>1945-65 Birth Cohort</strong></td>
<td>A. Justice</td>
<td>Rural/Urban COE</td>
<td>5.5 million</td>
</tr>
</tbody>
</table>
Sustaining Themes:

• Alcohol and related substance use
  – Role in patient outcomes overall and via interactions with medication & chronic disease?

• Multimorbidity and viral infections
  – How does suppression of virus and/or cure alter overall level of frailty and risk of adverse events?

• Medication safety, effectiveness & alternatives
  – Which medications make sense, does it depend on genes?
  – How do we use information to change health behaviors?
New Initiatives

• VACS Cancer and Pre Cancer Tissue Repository

• US Veteran Birth Cohort (1945-65)

• Phenotyping for Genetic and Omic Discovery
Hepatocellular Cancer (HCC) in HIV+/-

- In uninfected, HCC occurs in the context of:
  - Multimorbidity
    - Viral hepatitis (B and C)
    - Heavy alcohol use
    - Obesity/diabetes
  - Liver cirrhosis (90%)
- Less is known among HIV+
  - 2-4 times the risk overall
  - HIV+/HCV+ have twice the risk of HCV+
  - Many cases are HIV+ alone
Figure 3. Interplay of the Biology of Aging, Long Term HIV and ART, and Hepatocellular Cancer: A Conceptual Model

**Patient Characteristics of HIV+ on ART Compared with Uninfected:**
- Immune dysfunction
- Immune activation
- Hepatitis C
- Hepatitis B
- Harmful alcohol
- Tobacco Use
- Multimorbidity
- Polypharmacy
- Obesity
- Diabetes

**HCC Among HIV+ on ART Compared with Uninfected:**

- **Liver Parenchymal Characteristics:**
  - Inflammation and Fibrosis
  - NAFLD activity, Small and Large Cell Changes
- **Tumor Characteristics:**
  - Differentiation, Mitotic Index, Stage, Growth Pattern, Architecture, Morphology, Stem Cell Markers, Inflammatory Cells

**Continued Aging of HIV+ on ART and uninfected:**
- HIV, HCV, HBV, alcohol, liver toxic medications, polypharmacy, obesity, diabetes, & multimorbidity.
HCC in VACS as of 2015

- 832 Confirmed HCC (375 HIV+)
- ~50% confirmed by liver biopsy
- Among HIV+
  - 58% HCV+
  - 27% HBV+
  - 21% alcohol use disorder
  - 6% diabetes
- 33% HIV+ Vs. 20% HIV- **DO NOT** have cirrhosis
VACS Validated EHR Phenotypes

- **Substance use and psychiatric disease (A. Justice Chairs MVP Workgroup)**
  - Mental illness: PTSD, schizophrenia, bipolar, depression
  - Substance use: Harmful alcohol use, smoking

- **Medical diseases**
  - HIV, HCV, and HBV infection
  - Metabolic syndrome: myocardial infarction, congestive heart failure, and diabetes
  - Bacterial pneumonia
  - Decompensated liver cirrhosis
  - SEER reportable cancers

- **Severity of illness/Frailty**
  - Fragility fractures, medically significant falls
  - VACS Index for mortality, hospitalization, and other clinical outcomes

- **Prescription drug exposures**
  - Current and total medications, fill/refill adherence
  - Antiretroviral regimens
  - Opioids with conversion to morphine equivalents
  - Total medication counts
How Can We Make the Biggest Difference in the Future?

• Clinical Research in HIV+ and others:
  – Generalizability to other health systems/ countries
  – Leverage methods, learn from others
  – Continue policy work with operations research
  – Conduct large scale clinical trials

• Adapt phenotypes and repositories to genetic and omic discovery
Acknowledgements

- **Consortium PI**: AC Justice*

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

- **Affiliated PIs**: S Braithwaite, K Crothers*, R Dubrow *, DA Fiellin*, M Freiberg*, V LoRe*

- **Participating VA Medical Centers**: Atlanta (D. Rimland*, V Marconi), Baltimore (M Sajadi, R Titanji), Bronx (S Brown, Y Ponomarenko), Dallas (R Bedimo), Houston (M Rodriguez-Barradas, N Másozera), Los Angeles (M Goetz, D Leaf), Manhattan-Brooklyn (M Simberkoff, D Blumenthal, H Leaf, J Leung), Pittsburgh (A Butt, K Kraemer, M Freiberg, E Hoffman), and Washington DC (C Gibert, R Peck)

- **Core and Workgroup Chairs**: C Brandt, J Edelman, N Gandhi, J Lim, K McGinnis, KA Oursler, C Parikh, J Tate, E Wang, J Womack

- **Staff**: H Bathulapalli, T Bohan, J Ciarleglio, A Consorte, P Cunningham, L Erickson, C Frank, K Gordon, J Huston, F Kidwai-Khan, G 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)

- **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), NÍDA (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
Acknowledgements

Continued

• COMpAAAS/Veterans Aging Cohort Study, a CHAART Cooperative Agreement, supported by the National Institutes of Health: National Institute on Alcohol Abuse and Alcoholism (U24-AA020794, U01-AA020790, U01-AA020795, U01-AA020799) and in kind by the US Department of Veterans Affairs. In addition to grant support from NIAAA, we gratefully acknowledge the scientific contributions of Dr. Kendall Bryant, our scientific collaborator.

QR Codes

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