ACTHIV 2016: A State-of-the-Science Conference for Frontline Health Professionals
Aging and Frailty

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Professor of Geriatric Medicine
UCSF Department of Neurology
Learning objectives

• Incorporate into practice geriatric principles as they apply to mental health
• Consider functional life expectancy as a meaningful outcome in the care of patients
• Overall goal: Geriatric Medicine 101 for HIV providers
  – Aging HIV epidemiology
  – Geriatric Syndromes: Polypharmacy, Frailty, Multimorbidity, Dementia, Depression
  – Compression of morbidity & functional life expectancy
Regarding medications for older HIV+ patients, which of the following is true?

A. The number of antiretroviral pill taken daily (antiretroviral pill burden) has increased over the years

B. Polypharmacy is less common in older age than in younger age

C. Over all pill burden is linked to falls

D. Antidepressants are the most common non-antiretroviral medication class used in age over 65
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/sp-6haej3
Cognitive impairment among patients who adhere to antiretroviral therapy and maintain suppression of plasma viral load is due to comorbidity (e.g. other diseases instead of HIV)

A. True
B. False
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/sp-44l7x
Aging Worldwide
HIV Prevalence in age > 50

HIV and aging – Preparing for the Challenges Ahead, NEJM 2012
So what?
Aging with HIV is Heterogeneous

The variability in old age is greater than the variability across ages
Polypharmacy
Polypharmacy

A total of 1,198 medications prescribed to 89 participants

Greene et al. 2014 J Am Geriatr Soc
Polypharmacy

Inappropriate Anticholinergic Drug Medication Score
≥3

Greene et al. 2014 J Am Geriatr Soc
Daily Pill Count By Age
1990-2010 (Southern Alberta Cohort, Canada)

Antiretroviral pill count DECREASED

Total pill count INCREASED in older HIV+

Krentz HB et al. 2012 Antiviral Therapy
## 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>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>

<sup>Hasse B. et al. CID 2011</sup>
Polypharmacy increases fall risk

Erlandson, 2011, 2ND Annual HIV and Aging Workshop
Regarding medications for older HIV+ patients, which of the following is true?

A. The number of antiretroviral pill taken daily (antiretroviral pill burden) has increased over the years
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Frailty, a Geriatric Syndrome

- A geriatric syndrome of:
  - weakness
  - weight loss
  - low activity
- Not associated with any specific disease but associated with adverse health outcomes
- A biological vulnerability to adverse outcomes that stems from alterations in multiple physiological systems
How is frailty helpful?

• In clinical practice
  – Identifies patients at highest risk for adverse clinical outcomes
  – Provides a measure for the development and testing of interventions to decrease risk

• Applicability in HIV? - undetermined
The Multicenter AIDS Cohort Study (MACS): Frailty (modeled) associated with CD4 count and cART cohort

Desquilbet et al. 2009 J Acquir Immune Defic Syndr
Limitations of Frailty in HIV

• Multiple studies identify low frequency of frailty using traditional measures (3-10%)
• Traditional measures do not include cognitive impairment, occurring in 50% of HIV patients
  – Dementia is a leading cause of vulnerability
• The frailty concept may not be suited for a population with high numbers of comorbidities
### Other Geriatric Syndromes

<table>
<thead>
<tr>
<th>Geriatric Syndrome</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls</td>
<td>40 (26%)</td>
</tr>
<tr>
<td>Urinary Incontinence</td>
<td>39 (25%)</td>
</tr>
<tr>
<td>Pre-frailty</td>
<td>87 (56%)</td>
</tr>
<tr>
<td>Frailty</td>
<td>9 (14%)</td>
</tr>
<tr>
<td>Difficulty with ≥1 ADL</td>
<td>39 (25%)</td>
</tr>
<tr>
<td>Difficulty with ≥1 IADL</td>
<td>72 (47%)</td>
</tr>
</tbody>
</table>

Predictors of geriatric syndromes:
female gender, on-white race, number of comorbidities, lower CD4 nadir

Greene et al, CROI 2014
Multimorbidity

- Multiple, clinically significant, conditions that interact
- Considers cumulative injury on major organ systems & overall functional compromise
- Not just a subset or count of diagnoses
  - Liver disease
  - Cardiovascular disease
  - Kidney impairment
  - Cognitive decline
  - Non-AIDS cancers
  - Osteoporosis
Veteran Aging Cohort Study (VACS) Index

**Concept:**

As plasma HIV RNA level and CD4 count predicted outcomes in the pre-cART era, adding the quantified burden of major comorbidities may improve performance in the post-cART era.

Amy Justice HIV Medicine 2010
5-Year Mortality in NA-ACCORD

VACS Index

Y = 0.57 + 0.38 score + 0.005 score^2
R^2 = 0.96

Age, CD4 and VL alone

Y = 2.77 + 0.70 x score
R^2 = 0.88

Justice AC. et al. CROI 2011 Poster # 793
The Veterans Aging Cohort Study Index is Associated With Concurrent Risk for Neurocognitive Impairment

Maria J. Marquine, PhD,* Anya Umlauf, MS,* Alexandra S. Rooney, BA,* Pariya L. Fazeli, PhD,* Ben D. Gouaux, BA,* Steven Paul Woods, PsyD,* Scott L. Letendre, MD,† Ronald J. Ellis, MD, PhD,‡ Igor Grant, MD,* David J. Moore, PhD,* and the HIV Neurobehavioral Research Program (HNRP) Group

VACS associated with Cognitive impairment
• Independent of CD4 nadir and duration of HIV

Marquine et al. J Acquir Immune Defic Syndr 2014
Cognitive Diagnoses

**Pre-cART vs. Post-cART**

**Pre-cART**
- 50 total
  - HIV-associated dementia (HAD): 18
  - Minor Neurocognitive disorder (MND): 12
  - Asymptomatic Neurocognitive Impairment (ANI): 20

**Post-cART**
- 50 total
  - HAD: 5
  - MND: 17
  - ANI: 28
  - Normal (NL): 12

n=1555, US participants attending academic centers
~50% suppressed

Modified from Ellis et al, 2007 Nat Rev Neurosci & Grant et al.
Stroke and White Matter Disease

Valcour et al, ISNV 2013

$r = -0.240, p = 0.032$
Increasing Frequency of Ischemic Stroke in HIV

Ovbagle and Nath 2011 Neurology & Chow et al 2011 JAIDS
HIV protease inhibitor exposure predicts cerebral small vessel disease

Virawudh Soontornniyomkij\textsuperscript{a,b}, Anya Umlauf\textsuperscript{a}, Sandra A. Chung\textsuperscript{a}, Megan L. Cochran\textsuperscript{a}, Benchawanna Soontornniyomkij\textsuperscript{b}, Ben Gouaux\textsuperscript{a}, Will Toperoff\textsuperscript{a}, David J. Moore\textsuperscript{a,b}, Eliezer Masliah\textsuperscript{a,c,d}, Ronald J. Ellis\textsuperscript{a,d}, Igor Grant\textsuperscript{a,b} and Cristian L. Achim\textsuperscript{a,b,c}

50\% of cases

Soontornniyomkij et al AIDS 2014
IS ALL OF THE COGNITIVE IMPAIRMENT IN TREATED PATIENTS DUE TO COMORBIDITY?
Increased microglia activation in neurologically asymptomatic HIV-infected patients receiving effective ART

Lucy J. Garvey\textsuperscript{a,b}, Nicola Pavese\textsuperscript{c}, Marios Politis\textsuperscript{c}, Anil Ramlackhansingh\textsuperscript{c}, David J. Brooks\textsuperscript{c}, Simon D. Taylor-Robinson\textsuperscript{a} and Alan Winston\textsuperscript{a,b}

- 7 asymptomatic subjects (9 years (3-22) of infection, on cART > 3 years, UD plasma HIV RNA
- \textsuperscript{11}\textsuperscript{c}-PK1116 PET ligand signal in corpus callosum, anterior cingulate, posterior cingulate, temporal and frontal lobes
- Correlated to poorer executive function

Garvey et al AIDS 2014
Increased Macrophage Staining Despite cART

n=10 cART vs. 9 NL

Anthony et al. J Neuropath Exp Neuro 2005
Elevated sCD163 Associated with Cognitive Impairment

N=34, suppressed plasma HIV RNA, on cART > 1 year; CD4 > 500

Burdo et al AIDS 2013
Cognitive impairment among patients who adhere to antiretroviral therapy and maintain suppression of plasma viral load is due to comorbidity (e.g. other diseases instead of HIV)

A. True
B. False
Brain injury in the Setting of HIV

**Cognition**
- Memory loss
- Concentration
- Mental slowing
- Comprehension

**Behavior**
- Apathy
- Depression
- Agitation, Mania

**Motor**
- Unsteady gait
- Poor coordination
- Tremor
Parkinsonism

UPDRS scores of Controls, HIV, AD

Lau et al. 2015 Hawaii J Med Public Health
Neuropsychiatry Findings in age > 60

Mood

Agitation

Restlessness

Milanini, et al. Psychiatric symptom burden in older people with HIV. under review
Potential Causes of Depression and Apathy in HIV

• Psychosocial factors
• Medications
• Opportunistic infections and tumors
• Illicit drug use
• Direct and indirect effects of the HIV virus
Common Barriers to Missed Diagnosis of Depression in patients with HIV

- Stigma for psychiatric disorders
- Somatization
- Limited time for patient follow-up
- Perceived lack of resources for referral and treatment
- Perception that there are more important issues to address
Anatomic Correlates to Depression

• Smaller orbitofrontal cortex volume seen by MRI in patients with depression in remission compared to controls
  
• Autopsy data also confirm smaller orbitofrontal cortex in depression

• Functional imaging identifies hypometabolism in the frontal cortex among patients with depression

• White matter hyperintensities correlate to depression

1 Bremner et al, Biol Psych 2002; 2 Barber et al, J Neuropsych 1999
Apathy

- Syndrome of decreased motivation, psychomotor retardation, and anergia
- Common in elders without HIV and HIV patients of all ages
- Often co-exists with depression; both associated with neuroanatomic abnormalities in the pre-frontal cortex\(^1\)
- Apathy is associated with volume of the nucleus accumbens inpatients infected with HIV\(^2\)

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\(^1\) Lavretsky et al. Am J Geriatr Psychiatry 2007
\(^2\) Paul et al. J Neuropsych Clin Neurosci 2005
Compression of Morbidity

J. Fries NEJM 1980
Heterogeneity in Old Age

- Independent
  - Few health problems, active and robust
  - Some health problems
  - Multiple medical problems

- Dependent
  - Frail, vulnerable

HIV OUR GOAL

- ACTHIV
  - The American Conference for the Treatment of HIV
Conclusions

• Aging is a heterogeneous process
  – HIV related and unrelated factors contribute to this heterogeneity
• HIV infection is associated with higher frequency of geriatric syndromes
  – Cognitive and psychiatric complications are common
  – Polypharmacy is an urgent issue
• Multimorbidity is a potentially useful tool to frame care
• Compression of morbidity is an important goal
Thank you

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