The Impact of HIV and Aging on the Brain

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Disclosures

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• Merck & Co., Inc.
• ViiV Healthcare

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Adults with HIV are Aging but May Not Age Successfully

In HIV- Adults: Most common correlates of Successful Aging are non-smoking and absence of disability, arthritis, and diabetes

In HIV+ Adults: Successful Aging associated with better physical and emotional functioning but not HIV disease indicators or negative life events

Smit, Lancet Inf Dis 2015, 15(7):810-8

Depp & Jeste, Am J Geriatric Psychiatry. 2006; 14: 6-20
Moore et al, J Clinical Psychiatry 2013, 74: e417-23
Unsuccessful Aging Can Affect Every Organ System in HIV+ Adults

- **Nervous System**
  - Cognitive Disorders
  - Depression
  - Neuropathy
  - Sleep Disorders

- **Vascular System**
  - Cardiovascular
  - Cerebrovascular

- **Endocrine/Metabolic**
  - Diabetes
  - Hypogonadism

- **Liver**
  - ↓ Drug Metabolism
  - ↓ Synthetic Function

- **Kidney**
  - ↓ Drug Elimination

- **Musculoskeletal**
  - Osteoporosis
  - Frailty

- **Pulmonary System**

- **Cancer**

HIV May Cause Premature Neurocognitive Decline

Modified from Valcour et al, Neurology 2004;63:822–827

Some Studies Do Not Clearly Support Premature CNS Aging

Ciccarelli et al, JAGS 2012, 60:2048–2055

HIV May Accelerate White Matter Injury in the Brain

Unpublished CHARTER Data

HIV x Age Interaction $p = 0.003$

HIV May Accelerate White Matter Injury in the Brain


HIV is Associated with Lower Subcortical Gray Matter Volumes and Cerebral Blood Flow

Ances et al, J Acquir Immune Defic Syndr 2012; 59: 469-77

Ances et al, Journal of Infectious Diseases 2010; 201:336–40
HIV and Age May Alter the Shape of Subcortical Gray Matter

HIV x Age Interaction, p < 0.001
(bilateral nucleus accumbens, amygdala, caudate, and thalamus)

Kuhn et al, Human Brain Mapping, 2016, DOI: 10.1002/hbm.23436
If Premature Aging Occurs, Multiple Mechanisms May Contribute

- **Cellular senescence**
  - Shortened telomeres
  - Immune senescence
  - Mitochondrial damage & oxidative stress
  - Altered autophagy

- **Comorbidities**
  - Vascular disease
  - Metabolic syndrome
  - Frailty & sarcopenia
  - Anemia & iron metabolism
  - Other neurodegenerative diseases (e.g., Alzheimer’s)

- **Viral**
  - Compartmentalization and neurotoxic proteins

- **Polypharmacy, Drug interactions, & Altered drug metabolism & distribution**
  - Reduced elimination & drug binding
  - Altered blood-brain barrier permeability & molecular drug transporter functioning
Biomarkers of HAND May Differ in Younger and Older HIV+ Adults

- **Similar in older and younger adults**
  - HIV RNA (SCA)
  - Neurofilament light
  - sCD163
  - Neopterin
  - D-dimer, hsCRP

- **Stronger in older adults**
  - HIV DNA
  - Telomere length and other aging biomarkers
  - IL-6, MCP-1, sCD40L
  - Amyloid β1-42, p-Tau

<table>
<thead>
<tr>
<th></th>
<th>Correlation</th>
<th>Interaction</th>
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<tbody>
<tr>
<td></td>
<td>Age</td>
<td>GDS</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA (SCA)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV DNA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Neuronal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phospho-Tau (181)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Total tau</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neurofilament Light</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td><strong>Aging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telomere Length</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Mitochondrial Common Deletion</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Free Mitochondrial DNA</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>8-OHdG</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Protein Carbonyls</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>F2-isoprostanes</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td><strong>Macrophage/Glial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>sCD163</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neopterin</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>GFAP</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td><strong>Metabolic/Vascular/Inflammation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>sCD40L</td>
<td>X</td>
<td>-</td>
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<tr>
<td>D-dimer</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>hsCRP</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Amyloid β1-42</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Higher HIV DNA Levels are Associated with Older Age and HAND


Graph Courtesy Jean-Pierre Routy, McGill University
Shorter **Lymphocyte Telomere Length** is Associated with HIV and Inflammation

Leeansyah et al, JID 2013; 207:1157

Srinivasa et al, JAIDS 2014; 67: 414

**Graphs:**
- **Left Panel:**
  - HIV-: $r = -0.12$, $p = 0.430$
  - HIV+: $r = -0.41$, $p = 0.009$

- **Right Panel:**
  - $r = 0.31$, $P = 0.0002$
Correlates of Shorter Telomere Length at UCSD

<table>
<thead>
<tr>
<th>Risk</th>
<th>Effect size</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>d = 1.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>d = 1.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td>r = -0.32</td>
<td>0.03</td>
</tr>
<tr>
<td>Duration of HIV</td>
<td>r = -0.31</td>
<td>0.06</td>
</tr>
<tr>
<td>Duration of Current ART</td>
<td>r = -0.27</td>
<td>0.08</td>
</tr>
<tr>
<td>Plasma HIV RNA</td>
<td>d = 1.0</td>
<td>0.07</td>
</tr>
<tr>
<td>Global Deficit Score</td>
<td>r = 0.04</td>
<td>0.80</td>
</tr>
<tr>
<td>GDS Impairment</td>
<td>X² = 0.09</td>
<td>0.76</td>
</tr>
</tbody>
</table>

n = 47

Unpublished UCSD Data
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Aging-Related Biomarkers Vary by HIV & Methamphetamine Use

Cohen's d

Telomere Length | mtDNA | CD/mtDNA
---|---|---
All Participants: 

**H-M+** | **H+M-** | **H+M+**
---|---|---

Younger than Median (47):

**H-M+** | **H+M-** | **H+M+**
---|---|---

**CD = Common Deletion**
Accelerated Aging in Blood and Brain Cells by DNA Methylation

Horvath & Levine, J Infect Dis 2015, 212:1563–73

Levine et al, J Neurovirol 2016; 22(3):366-75
Other Age and Lower Nadir CD4+ T-Cell Counts Correlate with Higher Anti-CMV IgG Levels

- **Other correlates of higher anti-CMV IgG**: AIDS diagnosis, ART use (p=0.005), and higher serum globulins (p=0.04). Trend with sCD163 (p=0.069).
- Among those with detectable HIV RNA in CSF, higher anti-CMV IgG in serum correlated with higher HIV RNA in CSF and higher CSF WBC counts (p=0.006)
Anti-CMV IgG is Associated with Worse Neurocognitive Performance

Correlation for Entire Group:
\[ r = -0.20, \ p = 0.02 \]

Letendre, et al, J Infect Dis, 2016, Submitted
HIV+ Adults Have Higher Risk of Vascular Disease

- HIV+ adults have greater 10-year risk of cardiovascular events (CVEs) and higher rates of atherosclerosis than HIV-adults
- HIV disease is associated with greater risk of atherosclerosis independent of viral load, type of ART, or severity of immunodeficiency

Higher Risk of Acute Myocardial Infarction & Stroke in HIV+ Adults

- Hazard ratio for acute MI: 1.5 after adjusting for Framingham risk factors, comorbidities, and substance use


Chow et al, CROI 2016, Abstract 638
Vascular and Metabolic Disease Increase Risk for Neurocognitive Impairment

- 292 HIV+ adults in the START study
- Prior CVD was associated with NCI

Wright et al. Neurology 2010; 75: 864

- 130 HIV+ adults in the CHARTER study
- Diabetes and waist circumference were associated with NCI

McCutchan et al. Neurology 2012. 78: 485

<table>
<thead>
<tr>
<th></th>
<th>Risk</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior CVD</td>
<td>Yes</td>
<td>6.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Higher</td>
<td>1.1</td>
<td>0.06</td>
</tr>
<tr>
<td>AIDS</td>
<td>No</td>
<td>0.41</td>
<td>0.08</td>
</tr>
<tr>
<td>Race</td>
<td>Black</td>
<td>2.2</td>
<td>0.08</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Risk</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Yes</td>
<td>49.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>17.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>Larger</td>
<td>1.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Lower</td>
<td>0.32</td>
<td>0.09</td>
</tr>
<tr>
<td>BMI</td>
<td>Smaller</td>
<td>0.69</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Persistent Inflammation

Dyslipidemia
Visceral Fat

Insulin Resistance

Steatohepatitis
Liver Fibrosis

Brain Disease
Vascular Disease
Blood-Brain Barrier Permeability Increases with Age and may Increase Drug Distribution into the CNS

Letendre et al, 18th CROI, 2011, Abstract 408

Croteau et al, 19th CROI, 2012, Abstract 592
Higher Concentrations of ART Drugs Can Injure Neurons in the Lab

- Fetal rat cortical neuron cultures exposed to increasing ARV concentrations
- At least mild injury was seen with all drugs
- Constructed dose-effect curves and calculated toxicity indices

Robertson et al, J Neurovirol 2012, 18: 388-299
Other Signs of CNS-Relevant ART Toxicity Have Been Accumulating

- Longer Duration of Protease inhibitors Associated with Thicker Carotid Wall
- Protease Inhibitors Associated with Cerebral Small Vessel Disease

LaBounty et al, HIV Medicine 2016, 17(7):516-23
Soontornniyomkij et al, AIDS 2014, 28:1297–1306
Higher NRTI Levels in CNS May Increase Mitochondrial and Telomere Toxicity


Tenofovir was the most potent inhibitor of telomerase activity

Leeansyah et al, JID 2013; 207:1157
How can HAND be differentiated from other neurodegenerative diseases in older adults?

• In patients with HAND who are not on ART, CSF HIV viral load and markers of immune activation may be elevated (CEBM 2b; GOR B)

• Other biomarkers such as amyloid β1-42 and total tau can be abnormal in both HAND and Alzheimer’s disease (CEBM 2b; GOR B). Soluble amyloid precursor protein may be able to differentiate the conditions (CEBM 2b; GOR B)

• Imaging is helpful in excluding other disorders
  – Magnetic resonance spectroscopy of the basal ganglia may be useful, since it is abnormal in HAND and rarely in other degenerative disorders (CEBM 2b; GOR B)

Older HIV+ APOE ε4 Carriers May be at Increased Risk for Brain Injury


Wendelken et al, J Acquir Immune Defic Syndr 2016;73:426–432
Aerobic Fitness & Exercise are Associated with Neurocognitive Performance

- Assessed 37 HIV+ adults older than 50 on a treadmill
- Peak VO2 (oxygen consumption) related to verbal and visual memory, visual perception, and language
- Lower peak VO2 associated with more HAND ($p = 0.01$)

Mapstone et al, Aging and Disease 2013, 4(6): 311-9

- 335 HIV+ adults with self-reported activity within 72 hours
- Exercisers had lower odds of global neurocognitive impairment (odds ratio = 0.38, $p < 0.05$)

Dufour et al, J Neurovirol 2013, 19(5):410-7
Stopping Smoking Reduces Risk for Cardiovascular Events

- More than 27,000 HIV+ patients had a total of 3,680 cardiovascular events or mortality.
- Adjusted incidence rate ratio in patients who stopped smoking decreased from 2.3 within the first year to 1.5 after >3 years compared with those who never smoked.

Summary

• Premature aging of the brain in HIV+ adults is supported by most – but not all – reports
• Mechanisms of premature aging are being explored but may include cellular senescence with possible contributions by CMV, systemic vascular and metabolic disease, and perhaps the gut microbiome
• ART distribution into the CNS may increase with aging and could lead to greater neurotoxicity, which could in turn necessitate shifts in treatment regimens in older patients
• Interventions have not been identified but, in the short term, could include exercise and smoking cessation
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