Management of Neurocognitive Impairment in HIV+ Adults

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Disclosures

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- Gilead Sciences
- Merck & Co., Inc.
- ViiV Healthcare

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- Merck & Co., Inc.
- ViiV Healthcare

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- Janssen
And Now for Something Completely Different...
HIV May Accelerate Neurocognitive Decline

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

HIV May Accelerate White Matter Injury in the Brain

Unpublished CHARTER Data

HIV May Accelerate Subcortical Gray Matter Changes

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
HIV May Accelerate Neuronal Injury in the Frontal Lobe

Chang et al, Neurology 2014; 82:2213–2222

Not All Neurocognitive and Imaging Studies Support Accelerated Aging

Ciccarelli et al, JAGS 2012, 60:2048–2055
Ances et al, J Infect Dis, 2010; 201:336–40
Ances et al, J Acquir Immune Defic Syndr 2012; 59: 469-77

HIV x Age Interaction $p < 0.06$
Biomarker Correlates of HAND May Differ in Older & Younger HIV+ Adults

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

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

<table>
<thead>
<tr>
<th>Biomarker Correlates</th>
<th>Correlation</th>
<th>Interaction</th>
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<tbody>
<tr>
<td></td>
<td>Age</td>
<td>GDS</td>
</tr>
<tr>
<td>Viral</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>Neuronal</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>Aging</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>Macrophage/Glial</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>
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<tr>
<td>- Neopterin</td>
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</tr>
<tr>
<td>- GFAP</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Metabolic/Vascular/Inflammation</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>
</tr>
<tr>
<td>- D-dimer</td>
<td>X</td>
<td>-</td>
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<tr>
<td>- hsCRP</td>
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<tr>
<td>- Amyloid β1-42</td>
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</tbody>
</table>
Higher HIV DNA Levels are Associated with Older Age and HAND


Graph Courtesy Jean-Pierre Routy, McGill University

NCI=Neurocognitive Impairment; BDI=Beck Depression Inventory; Impuls=Impulsivity; Sens Seek=Sensation Seeking; HIV Transm=HIV Transmission Behavior

- HIV Effect, \( p = 0.0032 \)
- HIV by Age Interaction: \( p = 0.13 \)

Unpublished Interim Data
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Leeansyah et al, JID 2013, 207:1157
Accelerated Aging in Brain Tissue by DNA Methylation Array

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

Levine et al, J Neurovirol 2016; 22(3):366-75
Reduced CD4+/CD8+ Ratio

CD8+ T-Cell Proliferation

Target and Bystander Cell Damage

Cellular Infection and Viral Replication

Accumulation of CD57+CD28- T-Cells

Immune Senescence

Reduced T-Cell Repertoire Diversity

CMV-Specific T-Cell Response

Cell Recruitment & Immune Modulation

Bystander Inflammation

Worse Health Outcomes

Gianella & Letendre, J Inf Dis 2016; 214 Suppl 2:S67-74
Anti-CMV IgG is Associated with Neurocognitive Performance

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

*Letendre, et al, J Infect Dis, 2016, Submitted*
Unsuccessful CNS Aging

Host-Related
- Genetic
- Comorbidities
- Behavior

Drug-Related
- ART Toxicity
- Stimulant & Opiate Use
- Poly pharmacy

HIV-Related
- Advanced Immune Suppression
- Persistent HIV Replication
- Viral Proteins

Other Organism Related
- CMV
- Viral Hepatitis
- Gut Microbiome

Protein Glycation

Chronic Inflammation

Cellular Toxins

Oxidative Stress

Coagulation Imbalance

CMV
Management of HAND in Aging HIV+ Adults

- Earlier initiation of ART
  - Consider changing ART based on symptoms
- Treat mood, sleep, & substance use disorders
- Manage vascular/metabolic risk & disease
  - Healthy diet, regular exercise, smoking cessation
  - Treat dyslipidemia and insulin resistance/diabetes
- Treat co-infections (HCV, Syphilis, ?CMV)
- Limit polypharmacy, drug-drug interactions
- Role of other interventions is unclear
  - Anti-inflammatories, neurotrophins/growth factors
  - AChE inhibitors, NMDA-R antagonists
  - Probiotics, hormone replacement
Aerobic Fitness & Exercise are Associated with Better Neurocognitive Performance

- Assessed 37 HIV+ adults older than 50 on a treadmill
- Peak VO\textsubscript{2} (oxygen consumption) related to verbal and visual memory, visual perception, and language
- **Lower peak VO\textsubscript{2} associated with more HAND** (p = 0.01)

- 335 HIV+ adults with self-reported activity within 72 hours
- **Exercisers were less likely to have global neurocognitive impairment** (odds ratio = 0.38, p < 0.05)

*Mapstone et al, Aging and Disease 2013, 4(6): 311-9*  
*Dufour et al, J Neurovirol 2013, 19(5):410-7*
Smoking Cessation Reduces Risk of Cardiovascular Events

- More than 27,000 HIV+ adults 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

Cognitive Decline May Be Linked to Drug Distribution into CSF

Zhang, et al, CROI 2015, Abstract 56; Ma et al, CROI 2015, Abstract 444
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

Robertson et al, J Neurovirol 2012, 18: 388-299

Hinckley et al, CROI 2016, Abstract 395

<table>
<thead>
<tr>
<th></th>
<th>Mitochondrial Assay</th>
<th>Neurite Outgrowth Assay</th>
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<tbody>
<tr>
<td></td>
<td>MMP</td>
<td>ROS</td>
</tr>
<tr>
<td>Abacavir</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>1.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>-13.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>-6.2</td>
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</tr>
<tr>
<td>Elvitegravir</td>
<td>-10.4</td>
<td>2.1</td>
</tr>
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<td>Dolasetravir</td>
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</tr>
<tr>
<td>Atazanavir</td>
<td>-2.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Darunavir</td>
<td>2.1</td>
<td>0.4</td>
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<tr>
<td>Ritonavir</td>
<td>-5.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Cobicistat</td>
<td>-12.0</td>
<td>7.7</td>
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<tr>
<td>Menadione</td>
<td>-12.0</td>
<td>10.6</td>
</tr>
<tr>
<td>Staurosporine</td>
<td>7.1</td>
<td>9.6</td>
</tr>
<tr>
<td>BIO118</td>
<td>-2.2</td>
<td>-0.4</td>
</tr>
</tbody>
</table>

Max. Z-score

-5  5
HAND May Improve with Maraviroc Intensification

- Open-label MVC intensification in 12 adults on suppressive ART
- MVC reduced circulating CD14+CD16+ monocytes and monocyte HIV DNA content
- Neurocognitive performance improved in the 6 subjects who were impaired at entry


- 12-month open-label, randomized, placebo-controlled trial
- 14 adults on suppressive ART with recent progression to HAND
- Large difference at 6-months and medium difference at 12-months
  - Arm x Time interaction: p < 0.05

Gates et al, AIDS. 2016; 30(4): 591-600
Cell-Targeted, Circulation-Stabilized, ART-Loaded Magnetic Nanoparticles


CNS Immune Response in HIV Can Result in Life-Threatening Complications

CNS IRIS

CD8+ T-Cell Encephalitis


Lescure et al, Clin Infect Dis 2013, 57(1):101–8
## Acknowledgements & Conflicts

### Study Volunteers

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- Cris Achim
- David Moore
- Brookie Best
- Edmund Capparelli

**CHARTER or ACTG**
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- David Clifford
- Justin McArthur
- Ann Collier
- David Clifford

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- ...Mental Health
- ...Drug Abuse
- ...Allergy and Infectious Diseases

**Industry**
- Gilead Sciences
- Janssen
- Merck, Inc.
- ViiV Healthcare

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- Davey Smith
- Sara Gianella
- Connie Benson
- Chip Schooley
- Cris Achim
- Tom Marcotte
- Debra Rosario

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**National Institutes of Health**

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- Tom Marcotte
- Debra Rosario
8th International Workshop on HIV & Aging
25-26 September 2017
Washington, DC
CNS Safety-Focused Summary of Latency Reversal/Epigenetic Drugs

- **Direct TCR Stimulation**: OKT3 + rhIL-2
  - Headaches, stiff neck, seizure reported

- **Histone Deacetylase (HDAC) inhibition**
  - Valproic acid, Vorinostat, Disulfiram, Romidepsin
  - CNS side effects reported: Mood changes, headache, concentration changes, lethargy, nausea

- **Other drugs in development**
  - Panobinostat, Entinostat, Bryostatin, Trichostatin A, Chaetocin, BIX-01294, Prostratin, PMA, JQ1
  - Immune checkpoint: Anti-PD-1, anti-CTLA-4

*Kumar et al, Clinical Epigenetics (2015) 7:103*
Persistent Inflammation

Dyslipidemia
Visceral Fat

Insulin Resistance

Steatohepatitis
Liver Fibrosis

Brain Disease
Vascular Disease
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
Chang et al, Neurology 2014;82:2213–2222