HIV and Aging: Optimizing Neurocognitive Function

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Disclosures

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- ViiV Healthcare

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HIV+ Adults Are Aging but Their Survival Has Not Yet Normalized

~9 years shorter life expectancy even among those with no comorbidity

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

Legarth et al, JAIDS 2016, 71(2):213-8

Graphs Courtesy Sara Gianella & Peter Hunt

HIV Management | Hepatitis's Management | THE NEW YORK COURSE
Evidence of Premature Aging Has Been Found in Nearly Every Organ System

► Nervous System
  – Cognitive Disorders
  – Mood Disorders
  – Sleep Disorders
  – Neuropathy

► Vascular System
  – Cardiovascular
  – Cerebrovascular

► Endocrine/Metabolic
  – Diabetes
  – Hypogonadism

► Immune System

► Liver
  – ↓ Drug Metabolism
  – ↓ Synthetic Function

► Kidney
  – Renal Insufficiency

► Musculoskeletal
  – Osteoporosis
  – Frailty/Sarcopenia

► Pulmonary System
  – Pulmonary Hypertension

HIV May Accelerate Neurocognitive Decline

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


ANI = Asymptomatic Neurocognitive Impairment
MND = Mild Neurocognitive Disorder
HAD = HIV-Associated Dementia
HIV May Accelerate White Matter Injury in the Brain

Unpublished CHARTER Data

HIV x Age Interaction p = 0.003

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
Some Studies Do Not Support Accelerated Brain Aging

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

Ances et al, J Infect Dis, 2010; 201:336


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

Cole et al, CROI 2017 Abstract 359LB
Other Biomarkers May Be Better Indicators of Accelerated Aging


Graph Courtesy Jean-Pierre Routy, McGill University

HIV & Inflammation May Correlate with Shorter Telomere Length

Leeansyah et al, JID 2013; 207:1157
Srinivasa et al, JAIDS 2014; 67: 414

HIV x sCD163 Interaction: p = 0.12
Shorter Telomeres and Worse Neurocognitive Performance

Unpublished UCSD Data
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$n = 47$
Accelerated Aging in Brain by DNA Methylation “Epigenetic Clock”

Blood

Brain

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

Levine et al, J Neurovirol 2016; 22(3):366-75
Higher Anti-CMV IgG Is Associated with Worse Cognitive Performance

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

Letendre, et al, AIDS 2017, 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

Vascular and Metabolic Disease Increase Risk for Cognitive Impairment

- 292 HIV+ adults in the START study
  
  Wright et al. Neurology 2010; 75: 864

- Prior CVD was associated with NCI
  
  Wright et al. Neurology 2010; 75: 864

- 55 older HIV+ adults in the CHARTER study

- Diabetes and larger 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>
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<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>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Risk</th>
<th>OR</th>
<th>p</th>
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<tbody>
<tr>
<td>AIDS</td>
<td>Yes</td>
<td>49.6</td>
<td>0.01</td>
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<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
ART Toxicity May Also Contribute

Protease Inhibitors

LaBounty et al, HIV Medicine 2016, 17(7):516-23

NRTIs

Leeansyah et al, J Infect Dis 2013, 207:1157

Marcus et al, JAIDS 2016; 71:413–419

Soontornniyomkij et al, AIDS 2014, 28:1297–1306
Blood-Brain Barrier Permeability Increases with Age and May Alter Drug Distribution into the CNS

\[ r = 0.28 \]
\[ p < 0.001 \]

\[ p = 0.05 \]

Letendre et al, 18\textsuperscript{th} CROI, 2011, Abstract 408

Croteau et al, 19\textsuperscript{th} CROI, 2012, Abstract 592
Higher Concentrations of ART Drugs Can Injure Neurons *in vitro*


Hinckley et al, CROI 2016, Abstract 395
Higher Efavirenz Distribution into the CNS Linked to Cognitive Decline

Zhang, et al, CROI 2015, Abstract 56
Ma et al, CROI 2015, Abstract 444
Unsuccessful CNS Aging

Host-Related
- Genetic
- Comorbidities
- Behavior

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

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

Other Organism Related
- Gut Microbiome
- Viral Hepatitis
- CMV

Genetic

Comorbidities

Behavior

Host-Related
- Protein Processing
- Chronic Inflammation

HIV-Related
- Cellular Toxins

Drug-Related
- Oxidative Stress
- Coagulation Imbalance

Other Organism Related
- Unsuccessful CNS Aging

Viral Hepatitis

CMV

Gut Microbiome

Poly-pharmacy

Advanced Immune Suppression

Persistent HIV Replication

Viral Proteins

ART Toxicity

Stimulant & Opiate Use
Optimizing Neurocognitive Performance in Aging Adults

► Early initiation of ART
  – Follow current treatment guidelines
  – Consider changing ART based on symptoms

► Manage vascular/metabolic risk & disease
  – Healthy diet, regular exercise, smoking cessation
  – Treat dyslipidemia and insulin resistance/diabetes

► Treat coinfections (HCV, Syphilis, CMV)

► Treat mood, sleep, & substance use disorders

► Limit polypharmacy, drug-drug interactions

► Role of other interventions is unclear
  – Antiinflammatories, neurotrophins/growth factors
  – Probiotics, hormone replacement
  – AChE inhibitors, NMDA-R antagonists
Aerobic Fitness & Exercise Linked to Better Cognitive Performance

- Assessed 37 HIV+ adults older than 50 on a treadmill
- Peak VO$_2$ (oxygen consumption) related to verbal and visual memory, visual perception, and language
- **Lower peak VO$_2$ 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 were less likely to have global neurocognitive impairment** (odds ratio = 0.38, $p < 0.05$)

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 Training May Improve or Maintain Cognitive Abilities

Cognitive Training May Improve or Maintain Cognitive Abilities

Faytell et al, Neuropsychol Rehabil. 2015, 21:0-14


Chang et al, Ann Neurol 2017;81:17–34

Newer NNRTIs Have Fewer CNS Side Effects Than Efavirenz

<table>
<thead>
<tr>
<th></th>
<th>RPV n=288</th>
<th>EFV n=255</th>
<th>p value</th>
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<tbody>
<tr>
<td>Dizziness</td>
<td>10.4%</td>
<td>27.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>7.6%</td>
<td>13.7%</td>
<td>0.02</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2.8%</td>
<td>6.3%</td>
<td>0.06</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>1.4%</td>
<td>3.9%</td>
<td>0.10</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.0%</td>
<td>3.1%</td>
<td>0.13</td>
</tr>
<tr>
<td>Attention Disturbance</td>
<td>0.7%</td>
<td>2.4%</td>
<td>0.16</td>
</tr>
<tr>
<td>Depressive Disorder</td>
<td>4.5%</td>
<td>2.7%</td>
<td>0.36</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>DOR n=108</th>
<th>EFV n=108</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>6.5%</td>
<td>25.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>5.6%</td>
<td>14.8%</td>
<td>0.04</td>
</tr>
<tr>
<td>Headache</td>
<td>2.8%</td>
<td>5.6%</td>
<td>0.50</td>
</tr>
<tr>
<td>Nightmares</td>
<td>5.6%</td>
<td>8.3%</td>
<td>0.59</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>4.6%</td>
<td>6.5%</td>
<td>0.77</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6.5%</td>
<td>2.8%</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Behrens et al, AIDS Pat Care & STDs 2014, 28(4): 168
Gatell et al, CROI 2016, Abstract 470
Greater Than Expected Dolutegravir Intolerance in Holland

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total (N=387)</th>
<th>ART-Naive (n=65)</th>
<th>ART-Experienced (n=322)</th>
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<tbody>
<tr>
<td>Sleep Disturbance</td>
<td>19 (4.9%)</td>
<td>5 (7.7%)</td>
<td>14 (4.3%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>18 (4.6%)</td>
<td>4 (6.2%)</td>
<td>19 (5.9%)</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>12 (3.1%)</td>
<td>3 (4.6%)</td>
<td>9 (2.8%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (2.3%)</td>
<td>1 (1.5%)</td>
<td>8 (2.5%)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (2.1%)</td>
<td>0 (0%)</td>
<td>8 (2.5%)</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>6 (1.6%)</td>
<td>0 (0%)</td>
<td>6 (1.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (1.6%)</td>
<td>2 (3.1%)</td>
<td>4 (1.2%)</td>
</tr>
</tbody>
</table>

- Overall 62 of 387 (16%) discontinued dolutegravir
- 56 of 62 these (90.3%) discontinued due to adverse events
- These 56 had 78 adverse events:
  54 (69.2%) were nervous system-related

van den Berk et al, CROI 2016, Abstract 948
Headache Onset Usually within 12 Weeks and Then Typically Resolves

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Week 2</th>
<th>Week 16</th>
<th>Change (%)</th>
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<tbody>
<tr>
<td>DTG Plasma, total*</td>
<td>3360</td>
<td>3210</td>
<td>-4.5%</td>
</tr>
<tr>
<td>DTG Plasma, unbound*</td>
<td>17.1</td>
<td>23.9</td>
<td>+39.8%</td>
</tr>
<tr>
<td>DTG CSF, total*</td>
<td>18.2</td>
<td>13.2</td>
<td>-27.5%</td>
</tr>
<tr>
<td>CSF–total plasma ratio, %</td>
<td>0.516</td>
<td>0.412</td>
<td>-20.2%</td>
</tr>
</tbody>
</table>

*ng/mL
All values are medians

**Legend:**
- **Switch group**
- **No-switch group**

Pozniak et al, Lancet Infectious Disease 2014; 14: 590–99
Letendre et al, Clin Infect Dis 2014;59(7):1032–7
NRTI-Sparing ART May Be As Effective As Traditional ART

Dual Therapy with Dolutegravir-Lamivudine May Be Effective

Sued et al, CROI 2016, Abstract 947

Dolutegravir-based monotherapy or dual therapy maintained a high proportion of viral suppression even in highly experienced HIV-1-infected patients

Gubavu et al, JAC 2016; 71: 1046–1050

Virological control and metabolic improvement in HIV-infected, virologically suppressed patients switching to lamivudine/dolutegravir dual therapy


<table>
<thead>
<tr>
<th>AE</th>
<th>Grade I</th>
<th>Grade II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Adverse Events possible related to DTG

All AEs were reported at the first week of treatment

No grade 3-4 laboratory toxicities were reported through 24 weeks
No SAEs reported

Figueroa et al, EACS 2015, Abstract LBPS4/1
Summary and Conclusions

► HIV appears to accelerate aging of the CNS
  – May be due to prior injury

► Neurocognitive impairment in older HIV+ adults has multiple contributors
  – Managing metabolic and vascular disease may benefit the CNS
  – Exercise and cognitive training may also be valuable

► Optimal ART regimens in older adults are being investigated
  – Switching or simplification may be viable options
Acknowledgements & Conflicts

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- Santiago
- Donald Franklin
- Debra Cookson
- Constance Benson
- Chip Schooley

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

Industry
- Gilead Sciences
- Janssen
- ViiV Healthcare
8th International Workshop on HIV & Aging
2-3 October 2017
New York, NY
