Central Nervous System Complications of Hepatitis C

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University of California, San Diego
Disclosures

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• National Institutes of Health
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• Merck & Co., Inc.
• ViiV Healthcare

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• Merck & Co., Inc.
• ViiV Healthcare

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• Gilead Sciences
• Janssen
Hepatitis C infection, antiviral treatment and mental health: A European expert consensus statement

Martin Schaefer, Lucile Capuron, Astrid Friebe, Crisanto Diez-Quevedo, Geert Robaesys, Sergio Neri, Graham R. Foster, Achim Kautz, Daniel Forton, Carmine M. Pariante

Journal of Hepatology 2012 vol. 57 | 1379–1390
Neurocognitive Findings from UCSD

Letendre, AIDS, 2005, 19 Suppl 3:S72-8
Cherner, Neurology, 2005, 64(8):1343-7
Other Selected Findings

Hinkin, J Addict Dis 2008

Thames et al, Neurol Neuroimmunol Neuroinflamm 2015

Campagna, Liver International 2015
<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Size</th>
<th>Method</th>
<th>People with HCV had...</th>
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<tbody>
<tr>
<td>Forton</td>
<td>Hepatology</td>
<td>2002</td>
<td>43</td>
<td>Computer-based</td>
<td>Worse concentration and speed of information processing</td>
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<td>Hilsabeck</td>
<td>JINS</td>
<td>2003</td>
<td>21</td>
<td>4 tests</td>
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<td>Ryan</td>
<td>Neurology</td>
<td>2004</td>
<td>116</td>
<td>12 tests</td>
<td>Worse executive functioning</td>
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<td>Weissenborn</td>
<td>J Hepatology</td>
<td>2004</td>
<td>45</td>
<td>10 tests</td>
<td>Worse executive functioning and attention</td>
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<tr>
<td>Martin</td>
<td>JINS</td>
<td>2004</td>
<td>156</td>
<td>1 test</td>
<td>Worse reaction time</td>
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<tr>
<td>Cherner</td>
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<td>2005</td>
<td>430</td>
<td>14 tests</td>
<td>Worse functioning in multiple domains</td>
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<tr>
<td>Letendre</td>
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<td>526</td>
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<tr>
<td>McAndrews</td>
<td>Hepatology</td>
<td>2005</td>
<td>83</td>
<td>9 tests</td>
<td>Worse learning</td>
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<td>Morgello</td>
<td>AIDS</td>
<td>2005</td>
<td>137</td>
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<td>Richardson</td>
<td>AIDS</td>
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<td>220</td>
<td>8 tests</td>
<td>More frequent global impairment</td>
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<tr>
<td>Hinkin</td>
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<td>2008</td>
<td>118</td>
<td>8 domains</td>
<td>Worse learning and memory</td>
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<tr>
<td>Thiyagarajan</td>
<td>Clin Micro Inf</td>
<td>2010</td>
<td>72</td>
<td>IHDS, CogState</td>
<td>Worse IHDS; Trend worse executive function</td>
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<tr>
<td>Garvey</td>
<td>PLoS One</td>
<td>2012</td>
<td>81</td>
<td>CogState</td>
<td>Worse processing speed and executive function</td>
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<tr>
<td>Thames</td>
<td>Neurol Neuroimmunol</td>
<td>2015</td>
<td>96</td>
<td>13 tests</td>
<td>Worse global, processing speed, verbal fluency</td>
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<tr>
<td>Campagna</td>
<td>Liver Intl</td>
<td>2015</td>
<td>180</td>
<td>6 tests</td>
<td>Worse working memory but cirrhosis and alcohol accounted for more variance</td>
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</tbody>
</table>
Absence of neurocognitive effect of hepatitis C infection in HIV-coinfected people

<table>
<thead>
<tr>
<th>Deficit score</th>
<th>Unadjusted model</th>
<th>Adjusted model (1)</th>
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<tbody>
<tr>
<td></td>
<td>( \Delta^a )</td>
<td>95% CI</td>
</tr>
<tr>
<td>GDS</td>
<td>-0.008</td>
<td>-0.07</td>
</tr>
<tr>
<td>Verbal DDS</td>
<td>-0.069</td>
<td>-0.144</td>
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<tr>
<td>Executive functioning DDS</td>
<td>-0.043</td>
<td>-0.137</td>
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<tr>
<td>SIP DDS</td>
<td>-0.042</td>
<td>-0.114</td>
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<tr>
<td>learning DDS</td>
<td>-0.004</td>
<td>-0.092</td>
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<tr>
<td>Recall DDS</td>
<td>0.081</td>
<td>-0.005</td>
</tr>
<tr>
<td>Work memory DDS</td>
<td>0.018</td>
<td>-0.069</td>
</tr>
<tr>
<td>Motor DDS</td>
<td>-0.063</td>
<td>-0.171</td>
</tr>
</tbody>
</table>

\( N = 1,582 \)

Clifford et al, Neurology 2015;84:241–250
ART Drugs Might Influence CNS Complications of HCV

Letendre et al, J Neurovirol 2015, Epub, PMID: 26407716
ApoE ε4 May Protect Against HCV-Induced Brain Injury

- ApoE ε4 allele protects against HCV-induced liver damage
- 100 HCV+ adults with mild liver disease
- Lower ApoE ε4 allele frequency was associated with worse working memory (p=0.003) and attention (p=0.008)

Greater Neuronal Connectivity May Compensate for HCV Injury

- 19 HCV+ and 23 HCV- women
- Higher resting state fMRI eigenvector centrality (EC) in right superior temporal lobe
- Secondary analysis showed increased connectivity of this cluster with primary and secondary somatosensory cortex and temporal and occipital lobes
- This was associated with better memory and attention

Masouleh et al, J Viral Hepat 2016; 1–10
Selected Neuroimaging Findings


Monaco, World J Gastroenterol 2015; 21(42): 11974-11983

Gongvatana, J Neurovirol 2011; 17(5):477-86
HCV is Associated with Thinner Frontal & Occipital Cortex

- 43 HCV+ adults without severe liver fibrosis, substance abuse, or comorbid HIV or HBV
- 43 age and sex matched controls
- Reduced cortical thickness in occipital and frontal lobes
- This did not correlate with fatigue or depression

Hjerrild et al, Metab Brain Dis (2016) 31:311–319
## Consistent Neuroimaging Findings

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>N</th>
<th>Method</th>
<th>People with HCV had…</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forton</td>
<td>Lancet</td>
<td>2001</td>
<td>30</td>
<td>MRS</td>
<td>Worse choline/creatine ratios</td>
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<tr>
<td>Forton</td>
<td>Hepatology</td>
<td>2002</td>
<td>17</td>
<td>MRS</td>
<td>Worse choline in basal ganglia, white matter</td>
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<tr>
<td>Taylor</td>
<td>JINS</td>
<td>2004</td>
<td>26</td>
<td>MRS</td>
<td>Worse N-acetyl aspartate</td>
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<tr>
<td>Weissenborn</td>
<td>J Hepatology</td>
<td>2004</td>
<td>45</td>
<td>MRS</td>
<td>Worse N-acetyl aspartate</td>
</tr>
<tr>
<td>McAndrews</td>
<td>Hepatology</td>
<td>2005</td>
<td>37</td>
<td>MRS</td>
<td>Worse choline, N-acetyl aspartate</td>
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<tr>
<td>Forton</td>
<td>J Hepatology</td>
<td>2008</td>
<td>25</td>
<td>MRS</td>
<td>Worse myo-inositol</td>
</tr>
<tr>
<td>Gongvatana</td>
<td>J Neurovirol</td>
<td>2011</td>
<td>85</td>
<td>DTI</td>
<td>Worse fractional anisotropy &amp; mean diffusivity</td>
</tr>
<tr>
<td>Heeren</td>
<td>J Cerebral Blood Flow</td>
<td>2011</td>
<td>15</td>
<td>MRI,PET</td>
<td>Worse striatal DA and midbrain SERT availability, glucose metabolism</td>
</tr>
<tr>
<td>Jernigan</td>
<td>J Neurovirol</td>
<td>2011</td>
<td>251</td>
<td>sMRI</td>
<td>Worse volume of abnormal white matter</td>
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<tr>
<td>Nagarajan</td>
<td>Int J Hepatol</td>
<td>2012</td>
<td>28</td>
<td>L-COSY</td>
<td>Worse myo-inositol; Higher glutathione</td>
</tr>
<tr>
<td>Garvey</td>
<td>PLoS One</td>
<td>2012</td>
<td>36</td>
<td>MRS,PET</td>
<td>Worse myo-inositol; no microglial activation effect</td>
</tr>
<tr>
<td>Grover</td>
<td>J Viral Hepatitis</td>
<td>2012</td>
<td>11</td>
<td>MRS,PET</td>
<td>Worse myo-inositol and microglial activation</td>
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<tr>
<td>Bladowska</td>
<td>PLoS One</td>
<td>2014</td>
<td>56</td>
<td>PwMRI</td>
<td>Worse blood flow in parietal &amp; frontal cortex</td>
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<tr>
<td>Thames</td>
<td>Neurol Neuroimmunol</td>
<td>2015</td>
<td>29</td>
<td>MRS</td>
<td>Worse N-acetyl aspartate in parietal white matter, myo-inositol in frontal white matter</td>
</tr>
</tbody>
</table>
Multiple Mechanisms for HCV-Associated CNS Injury

- Infection of glial cells and brain endothelia
  - CNS adaptation
  - Glial activation
  - BBB permeability
- Neurotoxic HCV proteins in the CNS
- Immune activation & inflammation
  - Cryoglobulins
- Liver disease
  - Glutamate-related neurotoxicity
- HCV-associated metabolic & vascular disease
- Comorbid conditions:
  - Drug & alcohol use
  - Coinfections (HIV)
Serum HCV RNA is Not Consistently Associated with Cognition

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Size</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal</td>
<td>JAIDS</td>
<td>2012</td>
<td>1338</td>
<td>In fully adjusted GLM, HCV viremia was not associated with scores on any of the cognitive tests</td>
</tr>
<tr>
<td>Clifford</td>
<td>Neurology</td>
<td>2009</td>
<td>172</td>
<td>No difference based on HCV RNA</td>
</tr>
<tr>
<td>Letendre</td>
<td>AIDS</td>
<td>2005</td>
<td>112</td>
<td>Higher HCV RNA associated with worse memory</td>
</tr>
</tbody>
</table>

Letendre, AIDS, 2005, 19 Suppl 3:S72-8

HCV Can Adapt to Brain Tissue

Compartmentalization in CSF

- Deep sequencing of HCV from CSF and blood found evidence compartmentalization, mostly in E2, in 3/6 cognitively impaired adults

Most Studies Found Evidence of HCV Adaptation to the CNS

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>N</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morsica</td>
<td>J Med Virology</td>
<td>1997</td>
<td>19</td>
<td>HCV RNA was detected in 5 (26%) and sequences did not differ between CSF and serum</td>
</tr>
<tr>
<td>Radkowski</td>
<td>J Virology</td>
<td>2002</td>
<td>6</td>
<td>HCV RNA detected in brain tissue from 3 (50%)</td>
</tr>
<tr>
<td>Laskus</td>
<td>J Virology</td>
<td>2002</td>
<td>13</td>
<td>HCV sequences were found in 8 (62%) CSF specimens: 4 exhibited differences from other tissues</td>
</tr>
<tr>
<td>Vargas</td>
<td>Liver Transpl</td>
<td>2002</td>
<td>2</td>
<td>HCV RNA sequences from brain differed from consensus serum sequences in both patients</td>
</tr>
<tr>
<td>Forton</td>
<td>J Virology</td>
<td>2004</td>
<td>2</td>
<td>HCV RNA sequences from brain differed from other tissues; Identified 2 unique brain-derived mutations</td>
</tr>
<tr>
<td>Bagaglio</td>
<td>AIDS</td>
<td>2005</td>
<td>21</td>
<td>HCV RNA was detected in 5 (24%); sequences in 2 of these 5 differed from plasma and PBMCs</td>
</tr>
<tr>
<td>Fishman</td>
<td>J Infect Dis</td>
<td>2008</td>
<td>7</td>
<td>Brain HCV sequences differed from liver and blood in 4 (57%)</td>
</tr>
<tr>
<td>Tully</td>
<td>Liver Intl</td>
<td>2016</td>
<td>6</td>
<td>CSF HCV sequences differed from blood in 3 of 6 (50%)</td>
</tr>
</tbody>
</table>
Autopsy Brain Tissue Supports that HCV can Infect Glial Cells

HCV antigens in brains by heparin columns by WB

NS5a in astrocytes of HIV+ HCV+ cases


NS3 in astrocytes and microglia of HIV+ HCV+

HCV Can Infect Brain Endothelial Cells

- 10 HCV-infected adults
- Detected HCV RNA in brain tissue but at substantially lower levels than in liver
- Brain endothelial cells expressed HCV entry receptors
- Endothelial cell cultures:
  - HCV entry and replication
  - HCV infection affected endothelial permeability and cellular apoptosis

Fletcher, et al, Gastroenterol 2012;142:634–643
HCV Core Protein May be Neurotoxic

HCV Core in CSF Correlates with Better Cognitive Performance

Letendre, Unpublished Data

Anderson et al, JID 2017; 215(1):105-113

Crowell et al, JID 2015; 211:1692–702
HCV Induces Cytokine Production by Microglia and HBMEC

Rajalakshmy et al, PLoS One 2015; DOI:10.1371/journal.pone.0125419


HCV Increases Risk for Metabolic and Vascular Disease

- 68% Increased Odds of Diabetes
  
  *White et al, J Hepatol 2008; 49: 831–844*

- 97% Increased Odds of Stroke
  
  *He et al, PLoS One 2013 8(11): e81305*
Progressive Improvement in HCV Response Rates

Webster et al, Lancet 2015; 385: 1124–35
<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>N</th>
<th>Finding</th>
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</thead>
<tbody>
<tr>
<td>Capuron</td>
<td>Biol Psychiatr</td>
<td>2005</td>
<td>10</td>
<td><strong>Improved</strong> activation in the anterior cingulate cortex on functional MRI with IFN-α</td>
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<tr>
<td>Thein</td>
<td>HIV Medicine</td>
<td>2007</td>
<td>34</td>
<td><strong>Improvement</strong> in some measures of cognitive function with SVR</td>
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<tr>
<td>Zignego</td>
<td>Dig Liver Dis</td>
<td>2007</td>
<td>89</td>
<td><strong>Improved</strong> macrophage IDO activity, plasma TRP and KYN levels and psychopathology after viral clearance</td>
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<tr>
<td>Comai</td>
<td>Pharmacologic Research</td>
<td>2011</td>
<td>45</td>
<td>Worsened KYN during treatment, with an increase of the KYN/TRP ratio, an index of IDO activity</td>
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<td>Pattullo</td>
<td>Liver Intl</td>
<td>2011</td>
<td>40</td>
<td><strong>No change</strong> in low NAA in the globus pallidus with viral clearance</td>
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<tr>
<td>Byrnes</td>
<td>J Hepatology</td>
<td>2012</td>
<td>15</td>
<td><strong>Improved</strong> choline and MI in basal ganglia with SVR, not in non-responders/relapsers</td>
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<tr>
<td>Kraus</td>
<td>Hepatology</td>
<td>2013</td>
<td>168</td>
<td><strong>Improved</strong> working memory, attention, and vigilance with SVR to PEG IFN-α + RBV</td>
</tr>
<tr>
<td>Cattie</td>
<td>J Neurovirol</td>
<td>2014</td>
<td>40</td>
<td><strong>Worse</strong> neurocognitive performance during PEG IFN-α that did not return to baseline after completion of therapy</td>
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<td>Haroon</td>
<td>Brain, Behavior, &amp; Immunity</td>
<td>2015</td>
<td>31</td>
<td><strong>Worse</strong> glutamate in basal ganglia in older adults during PEG IFN-α</td>
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<tr>
<td>Golabi</td>
<td>Medicine</td>
<td>2016</td>
<td>100</td>
<td>Improved mental and emotional health with SVR to SOF-LED ± RBV</td>
</tr>
</tbody>
</table>
Cognitive Performance and Mood Worsened with SVR by Peg-IFN

*Cattie et al, J Neurovirol 2014, 20: 561-70*
Direct Acting Antivirals

<table>
<thead>
<tr>
<th>Viral protein</th>
<th>NS3/4A</th>
<th>NS5A</th>
<th>NS5B</th>
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<tbody>
<tr>
<td>Function</td>
<td>Serine protease</td>
<td>Component of HCV replication complex</td>
<td>RNA-dependent RNA polymerase</td>
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</tbody>
</table>
| Drugs         | Covalent (ketoamide)  
Boceprevir  
Telaprevir  
Noncovalent (tri peptide or macro cyclic)  
Faldaprevir  
Simeprevir  
Paritaprevir  
Asunaprevir  
Grazoprevir | Ledipasvir  
Daclatasvir  
Ombitasvir  
Elbasvir  
Samatasvir  
PPI-668  
Velpatasvir | Nucleoside analogs  
Sofosbuvir  
Nonnucleoside  
GS-9669  
Beclabuvir  
Dasabuvir |

DAA Regimens Recommended by EASL and AASLD (Treatment Naive without Cirrhosis)

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>Genotype 2</th>
<th>Genotype 3</th>
<th>Genotype 4</th>
<th>Genotype 5/6</th>
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<tr>
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<td><strong>AASLD</strong></td>
<td><strong>EASL</strong></td>
<td><strong>AASLD</strong></td>
<td><strong>EASL</strong></td>
</tr>
<tr>
<td>SOF-LED ± RBV</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>SOF-VEL ± RBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF-DAC ± RBV</td>
<td></td>
<td>1a</td>
<td></td>
<td></td>
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<tr>
<td>GRZ-ELB ± RBV</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>OMB-PAR/r-DAS ± RBV</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMB-PAR/r ± RBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOF-SIM ± RBV</td>
<td>1b</td>
<td></td>
<td></td>
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</tbody>
</table>

- **EASL Recommendations on Treatment of Hepatitis C 2016**: J Hepatol (2016), [http://dx.doi.org/10.1016/j.jhep.2016.09.001](http://dx.doi.org/10.1016/j.jhep.2016.09.001)
- **AASLD Recommendations**: [http://www.hcvguidelines.org](http://www.hcvguidelines.org)
Improved Performance after SVR with SOF-LED

- 100 HCV+ adults (genotype 1) received SOF-LED ± RBV
- At SVR, treatment reduced IL-10, PDGF, serotonin, tryptophan
- Improvements in neurobehavioral performance were associated with changes in IL-8, IL-1ra, and PDGF

### Predictors of Better Performance at SVR

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Direction</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emotional Role</strong></td>
<td>Δ IL-8</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Δ PDGF</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Emotional Well Being</strong></td>
<td>Δ IL-1ra</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>Δ PDGF</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Emotional Health</strong></td>
<td>Age</td>
<td>Younger</td>
</tr>
<tr>
<td><strong>Mental Health</strong></td>
<td>-</td>
<td>-</td>
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</table>

Golabi et al, Medicine (2016) 95:46(e5066)
## Physicochemical Characteristics of DAA Drugs

<table>
<thead>
<tr>
<th></th>
<th>NS5B Inhibitor (-buvir)</th>
<th>NS5A Inhibitor (-asvir)</th>
<th>NS3/4A Inhibitor (-previr)</th>
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</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Sofos- Gilead</td>
<td>Dasa- Abbvie</td>
<td>Ledip- Gilead</td>
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<tr>
<td><strong>Molecular Weight</strong></td>
<td>529.46</td>
<td>533.57</td>
<td>889.01</td>
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<tr>
<td><strong>Protein Binding</strong></td>
<td>61-65%</td>
<td>&gt; 99.5%</td>
<td>&gt; 99.8%</td>
</tr>
<tr>
<td><strong>LogP</strong></td>
<td>1.6</td>
<td>4.3</td>
<td>7.3</td>
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<tr>
<td><strong>Substrate for Molecular Transporters</strong></td>
<td>P-gp BCRP</td>
<td>P-gp</td>
<td>P-gp BCRP</td>
</tr>
</tbody>
</table>

Data provided by Gilead, Abbvie, PubChem, & Package Inserts
CNS-Focused DAA Project in San Diego

**Diagram Explanation**

- **Delayed Arm**
  - HIV- ([NC Blood, CSF, NI](#))
  - Start with Placebo* (n=30)
  - Followed by No Treatment (0-3 months)
  - Followed by Sofosbuvir Ledipasvir* (3-6 months)
  - Followed by No Treatment (6-9 months)
  - No Treatment for 9-12 months
  - No Treatment for 12-18 months
  - NC Blood

- **Immediate Arm**
  - HIV+ (n=12)
  - Start with Sofosbuvir Ledipasvir*
  - Followed by No Treatment (Short-Term Post-Treatment)
  - Followed by Placebo* (Long-Term Post-Treatment)

**Treatment Phases**

- **Fluids collected during Treatment Phases**:
  - **CSF**: Week 1
  - **Blood**: Weeks 1, 4, and 8

**Assessments**

- CSF and NI assessments noted here apply only to the Delayed Arm.
Conclusions

• HCV can infect, adapt to, and alter protein expression in glial and endothelial cells
• Most studies have found evidence of brain alterations in HCV+ adults
  – Few have convincingly controlled for liver disease severity and comorbidities
• Currently approved HCV drugs differ in few characteristics that would affect distribution into the CNS
• Whether attaining a DAA-induced sustained virologic response eradicates HCV from the CNS remains an open question
Acknowledgements & Conflicts

**Study Volunteers**

**UC San Diego**
- Ronald J. Ellis
- Igor Grant
- Robert Heaton
- J. Allen McCutchan
- Edmund Capparelli
- Brookie Best
- Jennifer Marquie
- Florin Vaida

**CHARTER or NNCTC**
- David Clifford
- Justin McArthur
- Ned Sacktor
- Ann Collier
- David Clifford

**National Institutes of Health**
- ...Mental Health
- ...Drug Abuse
- ...Allergy and Infectious Diseases

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

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Mi molto dispiace