Neuropsychiatric Complications & Management in HIV/HCV Infected Elderly Substance Abusing Patients

Anjay Bharti, MD
The ASAM State of the Art Course
October 7, 2016
Disclosure Information

Ajay Bharti, MD
No disclosures
Acute HCV and HIV in the Midwest

Community Outbreak of HIV Infection Linked to Injection Drug Use of Oxymorphone — Indiana, 2015

Caitlin Conrad¹, Heather M. Bradley², Dita Broz², Swamy Buddha¹, Erika L. Chapman¹, Romeo R. Galang²,³, Daniel Hillman¹, John Hon¹, Karen W. Hoover², Monita R. Patel²,³, Andrea Perez¹, Philip J. Peters², Pam Pontones¹, Jeremy C. Roseberry¹, Michelle Sandoval²,³, Jessica Shields⁴, Jennifer Walthall¹, Dorothy Waterhouse⁴, Paul J. Weidle⁵, Hsia Wu²,³, Joan M. Duwe¹,⁵ (Author affiliations at end of text)

MMWR / May 1, 2015 / Vol. 64 / No. 16

- 135 HIV cases
  - Average age 35
  - 55% male
  - 80% reported IDU; 17% not interviewed
- 114/135 (84%) with HCV co-infection
- Update from CROI
  - 188 HIV cases
  - >90% HCV co-infected
Increase in New HCV Infections

- Peaked in the 1980s at ~300,000 cases/year
- 45% increase in reported cases from 2010 to 2011 and 2011-2012
Extra-hepatic targets

- "Astrocytes?"
- Blood brain barrier, endothelial cells among the targets

Consequences

- Fatigue
- Depression
- Neuropsychiatric dysfunctions?
- Tolerance of HCV?
- Infection of dendritic cells, and T and B lymphocytes
- B cell proliferation
- Cryoglobulins
- Autoimmunity
- B-cell lymphoma
- Vasculitis
- Glomerulonephritis
- Arthralgia
- Purpura
- Thyroiditis

Feray C, Gastroenterology. 2012;142(3):428-31
Autopsy Brain Tissue Supports that HCV can Infect Glial Cells

HCV Infects 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


Multiple Potential Pathways for HCV-Associated CNS Injury

- Infection of glial cells and brain endothelial cells
  - CNS adaptation
  - Glial activation
  - BBB permeability
- Neurotoxic HCV proteins in the CNS
- Chronic inflammation

- Liver disease
  - Glutamate-related neurotoxicity
- HCV-associated vascular disease
  - Cryoglobulinemia-related vasculitis
- CNS injury from concomitant drug or alcohol use
- HIV co-infection
- Aging
### “Brain Fog” and Other CNS Syndromes

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
</tr>
<tr>
<td>Stroke, TIA, lacunar syndromes</td>
<td>Focal signs</td>
</tr>
<tr>
<td>Acute encephalopathic forms</td>
<td>Confusion, altered consciousness, incontinence</td>
</tr>
<tr>
<td>Leukoencephalopathy</td>
<td>Multifocal signs and symptoms, cognitive dysfunction, tetraparesis, aphasia</td>
</tr>
<tr>
<td>Encephalomyelitis</td>
<td>Motor, sensory and sphincter deficits, seizures</td>
</tr>
<tr>
<td>Myelitis</td>
<td>Sensory ataxia, spastic paraplegia</td>
</tr>
<tr>
<td><strong>Cognitive/Neuropsychiatric</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Sensation of physical and mental exhaustion</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>Alterations in verbal recall, working memory, sustained attention, concentration,</td>
</tr>
<tr>
<td></td>
<td>learning skills</td>
</tr>
<tr>
<td><strong>Peripheral Neuropathies</strong></td>
<td></td>
</tr>
<tr>
<td>Sensorimotor axonal polyneuropathies</td>
<td>Sensory loss, distal weakness</td>
</tr>
<tr>
<td>Large fibres sensory neuropathies</td>
<td>Reduced touch and proprioception sensations, sensory ataxia</td>
</tr>
<tr>
<td>Small fibres sensory neuropathies</td>
<td>Burning feet, pain, restless legs syndrome</td>
</tr>
<tr>
<td>Motor axonal polyneuropathies</td>
<td>Distal weakness</td>
</tr>
<tr>
<td>Mononeuropathies</td>
<td>Deep aching pain, truncular deficits</td>
</tr>
<tr>
<td>Mononeuropathy multiplex</td>
<td>Stocking-glove asymmetric neuropathy</td>
</tr>
<tr>
<td>Demyelinating forms</td>
<td>Sensory loss, distal weakness, areflexia</td>
</tr>
<tr>
<td><strong>Myopathies</strong></td>
<td></td>
</tr>
<tr>
<td>Noninflammatory</td>
<td>Progressive proximal/generalized weakness, atrophy</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Progressive symmetrical proximal weakness, atrophy, dysphagia, interstitial lung disease</td>
</tr>
</tbody>
</table>
Hepatitis C infection, antiviral treatment and mental health: A European expert consensus statement

Martin Schaefer\textsuperscript{1,2,*}, Lucile Capuron\textsuperscript{3}, Astrid Friebe\textsuperscript{4}, Crisanto Diez-Quevedo\textsuperscript{5}, Geert Robaey\textsuperscript{s}\textsuperscript{6}, Sergio Neri\textsuperscript{7}, Graham R. Foster\textsuperscript{8}, Achim Kautz\textsuperscript{9}, Daniel Forton\textsuperscript{10}, Carmine M. Pariante\textsuperscript{11}

Journal of Hepatology 2012 vol. 57 | 1379–1390

![Graph showing prevalence rates for various conditions among the general population and HCV patients.](image-url)
Early Cognitive Findings from UCSD

- Global deficit score for HCV serostatus:
  - HCV-: 0.32, 0.58
  - HCV+: 0.21, 0.42

- Global deficit score for number of risk conditions:
  - 0: 0.32, 0.42
  - 1: 0.42, 0.74
  - 2: 0.21, 0.42
  - 3: 0.74, 1.5

- Bar charts showing percentage impaired for different cognitive domains:
  - GLOBA $$***$$
  - Learn $$***$$
  - Recall $$***$$
  - Motor $$***$$
  - Abstr $$***$$
  - Atten $$^*$$
  - SIP $$^+$$
  - Verbal

Number of Risk Factors:
- 0
- 1
- 2
- 3

P < 0.001
<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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</thead>
<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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<tr>
<td>Hilsabeck</td>
<td>JINS</td>
<td>2003</td>
<td>21</td>
<td>4 tests</td>
<td>Worse functioning associated with worse liver fibrosis</td>
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<tr>
<td>Ryan</td>
<td>Neurology</td>
<td>2004</td>
<td>116</td>
<td>12 tests</td>
<td>Worse executive functioning</td>
</tr>
<tr>
<td>Weissenborn</td>
<td>J Hepatology</td>
<td>2004</td>
<td>45</td>
<td>10 tests</td>
<td>Worse executive functioning and attention</td>
</tr>
<tr>
<td>Martin</td>
<td>JINS</td>
<td>2004</td>
<td>156</td>
<td>1 test</td>
<td>Worse reaction time</td>
</tr>
<tr>
<td>Cherner</td>
<td>Neurology</td>
<td>2005</td>
<td>430</td>
<td>14 tests</td>
<td>Worse functioning in multiple domains</td>
</tr>
<tr>
<td>Letendre</td>
<td>AIDS</td>
<td>2005</td>
<td>526</td>
<td>14 tests</td>
<td>Worse global functioning</td>
</tr>
<tr>
<td>McAndrews</td>
<td>Hepatology</td>
<td>2005</td>
<td>83</td>
<td>9 tests</td>
<td>Worse learning</td>
</tr>
<tr>
<td>Morgello</td>
<td>AIDS</td>
<td>2005</td>
<td>137</td>
<td>14 tests</td>
<td>Worse executive functioning</td>
</tr>
<tr>
<td>Richardson</td>
<td>AIDS</td>
<td>2005</td>
<td>220</td>
<td>8 tests</td>
<td>More frequent global impairment</td>
</tr>
<tr>
<td>Hinkin</td>
<td>J Addict Dis</td>
<td>2008</td>
<td>118</td>
<td>8 domains</td>
<td>Worse learning and memory</td>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
</tbody>
</table>
Selected Neurocognitive Findings

Thames et al, Neurol Neuroimmunol Neuroinflamm 2015
Campagna, Liver International 2015
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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ°</td>
<td>95% CI</td>
</tr>
<tr>
<td>GDS</td>
<td>0.01</td>
<td>-0.061 - 0.082</td>
</tr>
<tr>
<td>Verbal DDS</td>
<td>-0.036</td>
<td>-0.128 - 0.056</td>
</tr>
<tr>
<td>Executive functioning DDS</td>
<td>0.026</td>
<td>-0.094 - 0.146</td>
</tr>
<tr>
<td>SIP DDS</td>
<td>0.015</td>
<td>-0.068 - 0.097</td>
</tr>
<tr>
<td>Learning DDS</td>
<td>-0.032</td>
<td>-0.148 - 0.083</td>
</tr>
<tr>
<td>Recall DDS</td>
<td>0.064</td>
<td>-0.047 - 0.175</td>
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<tr>
<td>Work memory DDS</td>
<td>0.027</td>
<td>-0.081 - 0.136</td>
</tr>
<tr>
<td>Motor DDS</td>
<td>-0.004</td>
<td>-0.131 - 0.122</td>
</tr>
<tr>
<td>GDS</td>
<td>0.062</td>
<td>-0.024 - 0.148</td>
</tr>
<tr>
<td>Verbal DDS</td>
<td>0.05</td>
<td>-0.062 - 0.162</td>
</tr>
<tr>
<td>Executive functioning DDS</td>
<td>0.136</td>
<td>-0.012 - 0.284</td>
</tr>
<tr>
<td>SIP DDS</td>
<td>0.064</td>
<td>-0.039 - 0.167</td>
</tr>
<tr>
<td>Learning DDS</td>
<td>0</td>
<td>-0.14 - 0.141</td>
</tr>
<tr>
<td>Recall DDS</td>
<td>0.092</td>
<td>-0.044 - 0.229</td>
</tr>
<tr>
<td>Work memory DDS</td>
<td>0.053</td>
<td>-0.081 - 0.187</td>
</tr>
<tr>
<td>Motor DDS</td>
<td>0.064</td>
<td>-0.095 - 0.224</td>
</tr>
</tbody>
</table>
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>
<th>People with HCV had…</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal</td>
<td>JAIDS</td>
<td>2012</td>
<td>1338</td>
<td>4 tests</td>
<td>In fully adjusted GLM, HCV viremia was <strong>not</strong> 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>3 tests</td>
<td><strong>No difference</strong> based on HCV RNA</td>
</tr>
<tr>
<td>Letendre</td>
<td>AIDS</td>
<td>2005</td>
<td>112</td>
<td>14 tests</td>
<td><strong>Higher</strong> HCV RNA associated with worse memory</td>
</tr>
</tbody>
</table>

Letendre, AIDS, 2005

Antiretrovirals Might Influence CNS Complications of HCV

Letendre et al, J Neurovirol 2015, Epub, PMID: 26407716
## 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>
</tr>
<tr>
<td>Taylor</td>
<td>JINS</td>
<td>2004</td>
<td>26</td>
<td>MRS</td>
<td>Worse N-acetyl aspartate</td>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
Selected Neuroimaging Findings

Decreased FA
- McAndrews, Hepatology 2005

Increased MD
- Bladowska, Eur J Radiol 2013 82: 686–692

Both FA & MD abnormal
- Gongvatana, J Neurovirol 2011
Interferon-Ribavirin Treatment Trial at UCSD

- 40 HCV+ adults starting IFN/RBV therapy
  - Comprehensive medical, psychiatric, and cognitive assessment before and up to 72 weeks after treatment initiation
- After 10 weeks, neurocognitive impairment rose from 27.5% to 47.5% (p < .05)
  - Infection with genotype 1 was associated with decline (p < .05)
- After 72 weeks, 42.5% remained impaired
  - Only initial 10-week neurocognitive decline predicted persistent impairment
  - Not viral clearance, severity of liver disease, or depressive symptoms

Cattie et al, J Neurovirol 2014, 20: 561-70
Cognitive Performance and Mood Worsened

Cattie et al, J Neurovirol 2014, 20: 561-70
<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>N</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capuron</td>
<td>Biol Psychiatr</td>
<td>2005</td>
<td>10</td>
<td>Improved activation in the anterior cingulate cortex on functional MRI with IFN-α</td>
</tr>
<tr>
<td>Thein</td>
<td>HIV Medicine</td>
<td>2007</td>
<td>34</td>
<td>Improvement in some measures of cognitive function with SVR</td>
</tr>
<tr>
<td>Zignego</td>
<td>Dig Liver Dis</td>
<td>2007</td>
<td>89</td>
<td>Improved macrophage IDO activity, plasma TRP and KYN levels and psychopathology after viral clearance</td>
</tr>
<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>
</tr>
<tr>
<td>Pattullo</td>
<td>Liver Intl</td>
<td>2011</td>
<td>40</td>
<td>No change in low NAA in the globus pallidus with viral clearance</td>
</tr>
<tr>
<td>Byrnes</td>
<td>J Hepatology</td>
<td>2012</td>
<td>15</td>
<td>Improved choline and MI in basal ganglia with SVR, not in non-responders/relapsers</td>
</tr>
<tr>
<td>Cattie</td>
<td>J Neurovirol</td>
<td>2014</td>
<td>40</td>
<td>Worse neurocognitive performance during IFN-α that did not return to baseline after completion of therapy</td>
</tr>
<tr>
<td>Haroon</td>
<td>Brain, Behavior, &amp; Immunity</td>
<td>2015</td>
<td>31</td>
<td>Worse glutamate in basal ganglia in older adults during IFN-α</td>
</tr>
</tbody>
</table>
Progressive Improvement in HCV Response Rates

- Interferon
- Interferon + ribavirin
- Peginterferon + ribavirin
- Peginterferon + ribavirin + PI
- Interferon-free combination

Sustained virological response rates (%)

Year
- 1990
- 1998
- 2001
- 2011
- 2014

- 7-10%
- 25%
- 40-50%
- 60-70%
- >90%
## Direct Acting Antivirals

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

RNA-dependent RNA polymerase
### Characteristics of HCV Antiviral Classes

<table>
<thead>
<tr>
<th>Class</th>
<th>Antiviral Potency</th>
<th>Genotype Activity</th>
<th>Resistance barrier</th>
<th>FDA Approved</th>
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</thead>
<tbody>
<tr>
<td><strong>NS3 Protease Inhibitors</strong></td>
<td>+++ to ++++</td>
<td>1 (and 4)</td>
<td>Low to moderate</td>
<td>Simeprevir (2013)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Paritaprevir (2014)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grazoprevir (2016)</td>
</tr>
<tr>
<td><strong>NS5B Nucleoside/tide</strong></td>
<td>++ to ++++</td>
<td>1-6</td>
<td>Very High</td>
<td>Sofosbuvir (2013)</td>
</tr>
<tr>
<td><strong>NS5B Non-nucleoside</strong></td>
<td>++ to +++</td>
<td>1</td>
<td>Very low</td>
<td>Dasabuvir (2014)</td>
</tr>
<tr>
<td><strong>NS5A Inhibitors</strong></td>
<td>++++</td>
<td>1, 4-6 (+/- 2,3)</td>
<td>Low</td>
<td>Ledipasvir (2014)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ombitasvir (2014)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Elbasvir (2016)</td>
</tr>
</tbody>
</table>
Overview of HCV Treatment Approaches

- Genotype 1
  - 12-16 weeks for non-cirrhotic patients
    - RBV for GT1a with some regimens
    - Baseline resistance testing with EBR/GZP in GT1a
  - 12-24 weeks for cirrhotic patients (+/- RBV)
- Genotype 2: 12-16 weeks SOF/RBV
- Genotype 3: 12-24 weeks SOF + DCV (+/- RBV)
  - Potential limited role for IFN
  - Cure rates >95% (exception GT3 cirrhotics)
# HCV Therapy and ART Drug Interactions

<table>
<thead>
<tr>
<th></th>
<th>SOF</th>
<th>SOF/LDV</th>
<th>SMV</th>
<th>DCV</th>
<th>PrO-D</th>
<th>EBR/GZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF</td>
<td></td>
<td>RAL/DTG</td>
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<tr>
<td>HIV PI/EFV</td>
<td></td>
<td>(↑TDF)</td>
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<tr>
<td>EFV</td>
<td></td>
<td></td>
<td>↓SMV</td>
<td>DCV 90mg</td>
<td></td>
<td>↓GZP</td>
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<tr>
<td>RLP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑RLP</td>
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</tr>
<tr>
<td>RAL/DTG</td>
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<tr>
<td>ATV/r</td>
<td></td>
<td></td>
<td>↑SMV</td>
<td>DCV 30mg</td>
<td></td>
<td>↑GZP</td>
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<tr>
<td>DRV/r</td>
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<td></td>
<td>↑SMV</td>
<td></td>
<td></td>
<td>↑GZP</td>
</tr>
<tr>
<td>EVG/c/FTC/TDF</td>
<td></td>
<td></td>
<td>↑SMV*</td>
<td>DCV 30mg*</td>
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<td>↑GZP</td>
</tr>
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<td>EVG/c/FTC/TAF</td>
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</tbody>
</table>

*estimated, not formally studied
HCV Re-infection Rates from Published Studies

- Low risk: 21.8%
- IVDU/prisoner: 4.1 years
  - 6046 patients
  - 4.1 years
- HIV co-infected: 5.0 years
  - 1203 patients
  - 5.0 years
  - 1285 patients
  - 3.3 years

Graph showing differences in re-infection rates.
Conceptual Model of the Effect of HCV & HIV on the Brain

Bloodborne Infections
- HCV
- HIV

HCV RNA
HCV Core Protein
HIV RNA

Mediators
- Inflammation
- Oxidative Stress

IFN-inducible Proteins
Macrophage Activation
Ox. Stress End-products

Brain Injury
- Neuronal Injury
- Neurocognitive & Functional Impairment

Neurofilament-Light
MR Spectroscopy
Neurocognitive Testing
New DAA Project in San Diego

Delayed

HIV-

n=30

NC Blood CSF NI

Placebo*
No Treatment
Sofosbuvir Ledipasvir*

Short-Term Post-Treatment

Blood CSF

NC Blood CSF NI

No Treatment

Long-Term Post-Treatment

Blood CSF

NC Blood CSF NI

No Treatment

Immediate

HIV+

n=30

NC Impairment Meth Dependence

No Bridging Fibrosis

No Hepatic Encephalopathy

Sofosbuvir Ledipasvir* No Treatment

Short-Term Post-Treatment

Placebo*
No Treatment

Long-Term Post-Treatment

Blood CSF

NC Blood CSF NI

No Treatment

n=12

Fluids collected during Treatment Phases:

- CSF: Week 1
- Blood: Weeks 1, 4, and 8

*CSF and NI assessments noted here apply only to the Delayed Arm
Questions
CURING HCV IN PEOPLE WHO INJECT DRUGS

David Thomas, MD
Professor of Medicine
Johns Hopkins School of Medicine
The ASAM State of the Art Course
October 7, 2016
Disclosure Information

David Thomas, MD
No Disclosures
Annual number of hepatitis C-related deaths vs. other nationally notifiable infectious conditions in the US, 2003-2013

Source: Centers for Disease Control and Prevention
HCV Infection Can Be Cleared Or Persist

HCV Clearance

HCV Persistence

Log HCV RNA (IU/ml)

ALT IU/ml

Months after acute infection
Clinical expression of long-term HCV infection

http://www.hepcentro.com.br/images/ascite2.jpg
75% of HCV Infections in The USA Are in Those Born 1945-1965

Distribution of HCV by Age in the USA,
NHANES 1999-2002

Figure modified from Hanafiah Hepatology 2013
Cirrhosis Due to HCV Infection is Projected to Increase in United States

Increasing Incidence Of Acute HCV Infection
USA, 2000-2013

There Are Multiple Viral And Host Targets

1. Entry
2. Endosomal release and IRES dependent translation
3. Protease cleavages
4. Membranous web formation
5. NS5B RNA dependent polymerase (RdRp)
6. Lipoprotein assembly linked to NS5A
7. Cellular targets
HCV Treatment Can Produce Durable Sustained Virologic Response (SVR)

www.aasld.org
Cure Of HCV Reduces Liver Failure

Cure of HCV Reduces Liver Cancer

Cure of HCV Reduces Mortality

HCV Infection is Usually Initially Treated With a 12 Week Course of Well-Tolerated Pills

Kowdley NEJM 2014; Feld NEJM 2014; Zeuzem AASLD 2015
Adverse Events are Uncommon

### Initial Treatment

<table>
<thead>
<tr>
<th>Events</th>
<th>LDV-SOF x 8 wk n=215</th>
<th>LDV-SOF RBV x 8 wk n=216</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse event (SAE)</td>
<td>4 (2%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Discontinuation due to SAE</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

### Retreatment

<table>
<thead>
<tr>
<th>Events</th>
<th>LDV-SOF x 12 wk n=109</th>
<th>LDV-SOF RBV x 24 wk N=109</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse event (SAE)</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Discontinuation due to SAE</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Knowdley, *NEJM* 2014; Afdhal *NEJM* 2014.
Sofosbuvir & Velpatasvir For 12 Weeks Among 624 Patients With Chronic Hepatitis C
Sofosbuvir & Velpatasvir For 12 Weeks Among 104 Patients With Chronic Hepatitis C & HIV

- Total: 95%
- Genotype 1a: 95%
- Genotype 1b: 92%
- Genotype 2: 100%
- Genotype 3: 92%
- Genotype 4: 100%
Injection Drug Users & Prisoners Have a High Rate of HCV Infection

- 1,546,500 of 10 million prisoners infected
  - E. Europe and Central Asia ~20.2%
  - USA and W. Europe ~15.4%
  - "Able” to test and treat*
- ~8,000,000 of 16 million PWID infected
  - 48-92% prevalence

*WHO recommendation

Efficacy Of GZR + EBR In PWID Receiving Opioid Agonist Therapy

HCV Reinfection In PWID After SVR

- 39% relapsed into IDU after SVR
- Reinfection in 10 of 94 (11%)
- IR 1.7/100 PYs overall
- IR 4.9/100 PYs in IDU relapsers
- 10 (27%) of 37 who relapsed to IDU
Strategies to Improve Outcomes Among PWID

- Network-based strategies

Will Need To **Scale Up Prevention Services Simultaneously To Achieve Maximum Benefit**

![Graph illustrateing the impact of OST and HCNSP coverage on annual treatments per 1000 PWID based on baseline HCV chronic prevalence.](image-url)

- No coverage of OST or HCNSP
- Coverage of OST and HCNSP = 20%
- Coverage of OST and HCNSP = 40%
- Coverage of OST and HCNSP = 60%
Road to Cure in Drug Users in India is Hard
Road to Cure in Drug Users in India is Hard
Summary: HCV Treatment for PWID

- Most important risk group in USA
- Treatment is indicated and the same
- Most drugs fine with opiate substitution therapy
- Reinfection possible
  - May need to treat network
- Resources needed to expand testing AND treatment
Costs of new drugs for hepatitis C per person, 12-week course

New generation drugs for HCV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost in USA</th>
<th>Minimum production price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td>$84,000</td>
<td>$68–$136</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>$66,000</td>
<td>$130–$270</td>
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<tr>
<td>Daclatasvir</td>
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<td>$10–$30</td>
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