Hepatitis C
New Horizons

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Clinical Professor of Internal Medicine and
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Objectives

To appreciate
  the prevalence of Hepatitis C
  the importance of screening for HCV
  the natural history of HCV
  role of Hepatitis C in Liver Cancer
To review the new treatments available
Define the challenges for the future
CASE PRESENTATION

55 yo female presented “to establish with internist.”

in good health generalized fatigue, occasional myalgias and arthalgias.

Fleeting rash on LE --not present at the visit.

On no medications except MVI and OTC antacids.

PE –

normal except for BP 140/93 and focal areas of minimal hyperpigmentation on LE.

Baseline labs:

CBC, glucose, creatinine, TSH and electrolytes normal

Liver Enzymes –normal except for

ALT 42 IU/ml/( nl =40)
2 weeks later..
Came in to be seen..
with rash.

? Diagnosis...............
Leukocytoclastic vasculitis - causes*

- Infections
  - **HCV**, HBV, HIV
  - Strep pyogenes

- Medications
  - Antibiotics
    - Sulfa, β-lactams, minocycline)
  - anti TNF, NSAIDS

- Malignancy

- Autoimmune connective tissue diseases
  - SLE, RA, Sjogrens

- Inflammatory conditions
  - IBD, cryoglobulinemia
  - Behcets

*Not complete list
Additional history and testing

• History of blood transfusions – Texas in 1975
• Remote history of IVDA 1960’s
• Additional laboratory data
  – Anti HCV Ab + --> HCV RNA= 2,195,000 IU/ml
  HCV GT1a
  – Albumin, INR normal
  – Urinalysis normal
  – **ANA +**, Rheumatoid Factor -, Cryoglobulins -.
  – HBsAg – ,anti HBcAb +, anti HBsAb +
  – HIV neg.
What Is Hepatitis C?

- RNA Virus
  - Hepatic necro-inflammation -> Fibrosis → Cirrhosis → decompensation cancer and death
- Transmission:
  - blood to blood,
  - Sexual (inefficient)
- 6 distinct genotypes
  - Mutates easily
    - Escapes destruction by the immune system

Smith BD et al, MMWR Recomm Rep 2012; 61: 1-32
Extrahepatic manifestations of HCV

- **Dermatologic**
  - *Leukocytoclastic vasculitis*
  - Lichen planus
  - Porphyria cutanea tarda

- **Renal**
  - Glomerulonephritis
    - MPGN
      - Nephrotic syndrome

- **Endocrine**
  - Thyroiditis
    - *Diabetes mellitus*

- **Cryoglobulinemia**
  - Meltzer’s triad
    - Arthralgia, myalgia and palpable purpura

- **Hematologic**
  - Aplastic anemia
  - Thrombocytopenia
  - Non Hodgkins B cell lymphoma

WHO recommendations for HCV screening

- Persons who have received medical or dental care in settings where infection control practices are substandard
- History of transfusion prior to 1990 or in countries where serologic testing of blood donations for HCV is not routinely performed
- Persons who inject drugs
- Persons who have used intranasal drugs
- Persons who had tattoos or body piercing where infection control practices are substandard
- Persons who are HIV+
- Prisoners and Persons previously incarcerated
- Children born to HCV+ mothers
- Abnormal ALT, Hemodialysis patients, HBsAg+, Health care workers and public safety workers after exposure with Needle stick or mucosa. Spouses of HCV+ patients, Sexual contacts
Evidence Suggests Highest Prevalence of HCV Among Adults Born Between 1945 and 1965: The “Baby Boomers”

Prevalence of HCV antibody, by year of birth

- Analysis of NHANES data from 1999-2002

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1910</td>
<td>1</td>
</tr>
<tr>
<td>1920</td>
<td>2</td>
</tr>
<tr>
<td>1930</td>
<td>3</td>
</tr>
<tr>
<td>1940</td>
<td>4</td>
</tr>
<tr>
<td>1950</td>
<td>5</td>
</tr>
<tr>
<td>1960</td>
<td>6</td>
</tr>
<tr>
<td>1970</td>
<td>5</td>
</tr>
<tr>
<td>1980</td>
<td>4</td>
</tr>
<tr>
<td>1990</td>
<td>3</td>
</tr>
</tbody>
</table>

5X higher prevalence of HCV antibody in adults born between 1945 and 1965 vs adults born in other years

Adapted from CDC MMWR Recommendations and Reports 2012 Vol. 61/No. 4.

More than 75% of adults with chronic HCV infection were born between 1945 and 1965

CDC, Centers for Disease Control and Prevention; NHANES, National Health and Nutrition Examination Survey.
50% don’t know they are infected*

*Smith BD et al, MMWR Recomm Rep 2012; 61: 1-32
Results of screening our patient’s family

• Husband
  – Anti HCV Ab+
  – HCV RNA 3,950,000 IU/ml
    Genotype 3a

• 2 children
  – Ages 28,30
  – Anti HCV Ab-
Chronic Hepatitis C
Global Prevalence

USA 3.9 M
South America 10 M
West Europe 9 M
East Mediterranean 20 M
South East Asia 30 M
Africa 32 M
Far East Asia 60 M
Australia 0.2 M

WHO, 1999
Worldwide Genotype Distribution
HCV

## South and Central America - HCV prevalence

<table>
<thead>
<tr>
<th>Country</th>
<th>Anti -HCV +(%)</th>
<th>No. HCV infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>1.9</td>
<td>743,750</td>
</tr>
<tr>
<td>Belize</td>
<td>0.75</td>
<td>2100</td>
</tr>
<tr>
<td><strong>Bolivia</strong></td>
<td><strong>4.7</strong></td>
<td><strong>471,457</strong></td>
</tr>
<tr>
<td>Brazil</td>
<td>1.4</td>
<td>2609,670</td>
</tr>
<tr>
<td>Chile</td>
<td>0.85</td>
<td>143,150</td>
</tr>
<tr>
<td><strong>Costa Rica</strong></td>
<td><strong>0.75</strong></td>
<td><strong>32,453</strong></td>
</tr>
<tr>
<td>Mexico</td>
<td>1.00</td>
<td>1,106,450</td>
</tr>
<tr>
<td>Nicaragua</td>
<td>0.35</td>
<td>19,803</td>
</tr>
<tr>
<td>Venezuela</td>
<td>0.94</td>
<td>272,076</td>
</tr>
</tbody>
</table>

*Clin Microbiol Infect 2011; 17: 107–115*
Complications of HCV

• 350,000 deaths each year worldwide from HCV related liver diseases**
• HCV is the leading cause of Cirrhosis in US
• and leading indication for Liver Transplantation ..... in US and Europe

HCV is the leading cause of Liver Cancer in US

• 48% due to HCV*

*Younossi AM et al EASL 2015 NCI data
**World Health Organization
Screening for HCV

- Anti HCV Antibody
  - neg
  - POS

- HCV RNA
  - Neg
  - POS

- HCV RNA genotype

- Linkage to HCV care

Up to 30% with HCV AB + will NOT have chronic hepatitis C
Initial work up of HCV infection

• “LFTs”
  – ALT, AST,
  – alkaline phosphatase,
  – Bilirubin
  – INR
  – Albumin
  – CBC with platelets

• Check for renal disease
  – Creatinine
  – Urinanalysis

• Rule out other liver diseases
  – HBV
  – Check Ferritin
  – ANA

• And then …
  – TSH
  – Glucose
  – HIV
ETOH, cigarette smoking, marijuana → increase rate of fibrosis...

41% --- predicted probability of cirrhosis 30 years after infection.*

*A modeling analysis of 111 studies involving 33,121 chronic HCV patients
Thein HH et al Hepatology 2008; 48(2): 418-31
Survival in patients with cirrhosis


Survival Probability

- Compensated
- After first major complication

Pts at Risk, n
384 376 342 288 236 165 126 79 52 39 25

Mortality and progression to decompensated cirrhosis in HCV patients with biopsy confirmed fibrosis in the Chronic Hepatitis Cohort Study (CHeCS)

CHeCS Cohort 2004-2011
N=14,256

Liver Biopsy
N=2,110

Stage F2
N=616 (29%)
- Decomp. = 3.6%
- HCC = 1.0%
- Death = 4.9%

Stage F3
N=336 (16%)
- Decomp. = 10.1%
- HCC = 2.7%
- Death = 10.4%

Stage F4
N=300 (14%)
- Decomp. = 27.7%
- HCC = 8.3%
- Death = 23.7%

Median Follow-up ~4 years

Decompensation associated with: Black race, biopsy stage, platelets and albumin < "normal", co-morbidities
Receipt of any antiviral therapy was protective: Adjusted Hazard Ratio = 0.7

Moorman AC et al AASLD 2014 Abst 174
Hepatic decompensation

- Variceal bleeding
- Ascites
- Encephalopathy
Stage of Fibrosis In Chronic Hepatitis

Four Stages of Fibrosis in Chronic Hepatitis:

1. Portal
2. Periportal
3. Septal
4. Cirrhosis
Diagnosis of fibrosis / cirrhosis

Clinical status
laboratory data
AST / ALT
Platelets
INR, Albumin

Simple tests
APRI
FiB-4

Serum markers of fibrosis
Fibrosure, hepascore

liver biopsy

Fibroscan
## Fibroscan

<table>
<thead>
<tr>
<th>Disease</th>
<th>F0–F1 (Kpa)</th>
<th>F2 (Kpa)</th>
<th>F3 (kpa)</th>
<th>F4 (kpa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>$\leq 6.0$</td>
<td>$\geq 6.0$</td>
<td>$\geq 9.0$</td>
<td>$\geq 12.0$</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>$\leq 7.0$</td>
<td>$\geq 7.0$</td>
<td>$\geq 9.5$</td>
<td>$\geq 12.0$</td>
</tr>
<tr>
<td>HCV–HIV coinfection</td>
<td>$\leq 7.0$</td>
<td>$\leq 10$</td>
<td>$\geq 11.0$</td>
<td>$\geq 14.0$</td>
</tr>
<tr>
<td>Cholestatic liver disease</td>
<td>$\leq 7.0$</td>
<td>$\geq 7.5$</td>
<td>$\geq 10.0$</td>
<td>$\geq 17.0$</td>
</tr>
<tr>
<td>NAFLD/NASH</td>
<td>$\leq 7.0$</td>
<td>$\geq 7.5$</td>
<td>$\leq 10$</td>
<td>$\geq 14.0$</td>
</tr>
</tbody>
</table>

Sebastiani and Albert, J Virol 2012
Why all the fuss?

• **Screening** will identify patients with HCV infection
  – Allow education on life style changes
    • to decrease progression to fibrosis

• **Knowing stage of Fibrosis**
  – Allow identification of those you suspect have advanced fibrosis
    • Many use fibrosis to prioritize treatment
    • Cirrhosis = screen for hepatocellular carcinoma
Impact of Antiviral Treatment on Survival in HCV Cirrhosis

Bruno S, et al Hepatology 2007; 45:579
Impact of Antiviral Treatment* on Risk of HCV-related Complications


Effects of SVR on the risk of liver transplant, hepatocellular carcinoma, death and re-infection: meta-analysis of 129 studies in 23,309 patients with HCV

- Meta-analysis of 129 studies w/over 23,000 patients
- Estimated relative reductions in risk of liver transplant, HCC, all-cause mortality for SVR vs non-SVR after antiviral therapy
- RR substantially reduced for all groups with SVR

<table>
<thead>
<tr>
<th>Category</th>
<th>Studies</th>
<th>Patients</th>
<th>Avg. FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>18</td>
<td>29,269</td>
<td>4.6 years</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>9</td>
<td>2,734</td>
<td>6.6 years</td>
</tr>
<tr>
<td>HIV/HCV</td>
<td>5</td>
<td>2,560</td>
<td>5.1 years</td>
</tr>
</tbody>
</table>

5-Year All Cause Mortality

- General: 4.5% SVR, 10.5% No SVR
- Cirrhotic: 3.6% SVR, 11.3% No SVR
- Co-infected: 1.3% SVR, 10.0% No SVR

Saleem, Abst# 44

Hill AM, Saleem J et al AALSLD 2014 Abst 44
Historical Treatment Response Rates

Adapted from Jordan Feld, MD, MPH Assistant Professor of Medicine. Toronto Western Hospital, Sandra-Rotman Centre for Global Health, University of Toronto “ A Primer to the future treatment of HCV,” Abbott Satellite Symposium, Barcelona, Spain, April 2012.
Life cycle of HCV virus

Entry inhibitors
LDL-R, SR-B1, CD81

HCV

CLDN1

Occludine

HCV proteins

fusion uncoating

RNA replication

assembly release

α-glucosidase inhibitors
NS5B inhibitors
Cyclophilin B inhibitors

translational polyprotein procession

NS3/4A inhibitors

NS5A inhibitors
DIRECT ACTING ANTI VIRALS: SITE OF ACTION

- **Boceprevir**
- **Telaprevir**
- **Simeprevir**
- **Paritaprevir**
- **Daclatasvir**
- **Ledipasvir**
- **ombitasvir**
- **Sofosbuvir**
- **Dasabuvir**

**Entry inhibitors**
- LDL-R
- SR-B1
- CD81

**NS3/4A inhibitors**
- Occludine
- CLDN1

**NS5A inhibitors**
- assembly release
- RNA replication
- translation polyprotein procession

**NS5B inhibitors**
- Cyclophilin B inhibitors

**α-glucosidase inhibitors**
Direct Acting Antiviral Drugs available for the treatment of HCV

<table>
<thead>
<tr>
<th>Year</th>
<th>2011</th>
<th>2013</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
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<tbody>
<tr>
<td></td>
<td>Boceprevir</td>
<td></td>
<td></td>
<td></td>
<td>July 24, 2015</td>
</tr>
<tr>
<td></td>
<td>Telaprevir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Simeprevir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Sofosbuvir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Daclatasvir</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>Daclat ( USA)</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Sofosbuvir/ledipasvir</strong></td>
<td><strong>HARVONI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Paritaprevir. /ritonavir</strong></td>
<td><strong>Ombitasvir</strong></td>
<td><strong>Paritaprevir, /ritonavir</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Dasabuvir</strong></td>
<td><strong>VIEKiRA PAK</strong></td>
<td><strong>Ombitasvir</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>TECHNIVIE</strong></td>
</tr>
</tbody>
</table>

RIBAVIRIN is still an important drug in treatment of HCV
## Treatment options 2015

<table>
<thead>
<tr>
<th>Interferon free regimens</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFOSBUVIR / RIBAVIRIN</td>
<td>2,3</td>
</tr>
<tr>
<td>SOFOSBUVIR / LEDIPASVIR ( +/- RIBAVIRIN)</td>
<td>1,4,5,6</td>
</tr>
<tr>
<td>OMBITASVIR/PARITAPREVIR/RITONAVIR+ DASABUVIR ( +/- Ribavirin)</td>
<td>1</td>
</tr>
<tr>
<td>SOFOSBUVIR/SIMEPREVIR ( +/- RIBAVIRIN)</td>
<td>1,4</td>
</tr>
<tr>
<td>SOFOSBUVIR / DACLATASVIR ( +/- RIBAVIRIN)</td>
<td>ALL</td>
</tr>
<tr>
<td>OMBITASVIR/PARITAPREVIR/RITONAVIR ( +/- RIBAVIRIN)</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interferon containing regimens</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG IFN + RIBA + SOFOSBUVIR</td>
<td>ALL</td>
</tr>
<tr>
<td>Peg IFN + RIBA + SIMEPREVIR</td>
<td>1,4</td>
</tr>
</tbody>
</table>
GOAL = Cure

• REALITY:
• There are many patients with HCV
• Treatment is expensive.....
Treatment selection based on certain characteristics

- HCV genotype
  - viral load
- Prior treatment experience
- Severity of disease
  - Cirrhosis -> aggressive treatments (using ribavirin) or longer treatment
- Side effects of medications
- Comorbidities
  - ie Sofosbuvir plus another DAA and amiodarone
- Drug Drug Interactions (DDI)
  - [www.hep-druginteractions.org](http://www.hep-druginteractions.org)
What are the treatment options available for our patient and her husband?

**Our patient**
- HCV GT1a
- Viral load
  - 2,195,000 IU/ml
- Naïve to treatment
- Fibroscan 7.5 kpa
- APRI 0.42

**Her Husband**
- HCV GT3a
- Viral load
  - 3,950,000
- Naïve to treatment
- Fibroscan 12.8 kpa
- APRI 2.1
## Interferon free Treatment options 2015  
**genotype 1a**

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>No cirrhosis</th>
<th>cirrhosis</th>
<th>Decompensated cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOFOSBUVIR / LEDIPASVIR (+/- RIBA)</strong></td>
<td>8-12 w</td>
<td>12 w +/- riba 24 w alone</td>
<td>12w +Riba 24 w alone</td>
</tr>
<tr>
<td><strong>OMBITASVIR/PARITAPREVIR/RITONAVIR+ DASABUVIR (+/- Riba)</strong></td>
<td>12 w +RIBA</td>
<td>24 w + RIBA</td>
<td>No</td>
</tr>
<tr>
<td><strong>SOFOSBUVIR/SIMEPREVIR (+/- RIBA)</strong></td>
<td>12 w</td>
<td>12w + RIBA 24 w alone</td>
<td>No</td>
</tr>
<tr>
<td><strong>SOFOSBUVIR / DACLATASVIR (+/- RIBA)</strong></td>
<td>12 w alone</td>
<td>12 w + RIBA 24 w alone</td>
<td>12 w + riba 24 w alone</td>
</tr>
</tbody>
</table>

*Pawlotsky JM 2015 ILC presentation EASL guidelines*
ION 3: SVR12 With 8 or 12 Wks SOF/LDV ± RBV in Tx-Naive Noncirrhotic Patients

- SVR12 rates did not differ by GT1a vs GT1b in any treatment arm
- Virologic failure: 23 relapses (11 in 8-wk SOF/LDV, 9 in 8-wk SOF/LDV/RBV, 3 in 12-wk SOF/LDV)

Study ION-3: Relapse Rates by Baseline Viral Load after 8 and 12 Weeks of Treatment in Naïve non-cirrhotic subjects with HCV G1

<table>
<thead>
<tr>
<th></th>
<th>Harvoni 8 w (215)</th>
<th>Harvoni 12 w (216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12</td>
<td>202 / 215</td>
<td>206 / 216</td>
</tr>
<tr>
<td>Response rate</td>
<td>93.9%</td>
<td>95%</td>
</tr>
<tr>
<td>Relapsers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load &lt; 6 million*</td>
<td>2% 2/123</td>
<td>2/131</td>
</tr>
<tr>
<td>Viral load &gt;=6 million</td>
<td>10% 9/92</td>
<td>1/85</td>
</tr>
</tbody>
</table>

SVR for VL<6 million = 119/123 = 97%

Kowdley NEJM May 2014
SAPPHIRE I: SVR12 With 3 DAAs + RBV in Treatment-Naive Pts by HCV Subtype

- High response rates in treatment-naive patients across subgenotypes

LDV/SOF x 12 Weeks
SVR12 in HCV Mono-infected and HCV/HIV Co-infected

Similar response rates in HCV/HIV co-infected patients compared to HCV mono-infected patients

TURQUOISE-I: SVR12 in HCV/HIV Coinfected Patients Treated with ABT-450/r/Ombitasvir, Dasabuvir +RBV

- Randomized to 12 or 24 weeks of 3-Drug regimen + RBV
  - Treatment-naïve (65%) or Experienced (35%)
  - Cirrhotic ~20% (CP-A)
  - HIV ART Regimen: Atazanavir (44%) or Raltegravir (56%)
- AE: Mild fatigue, nausea, insomnia; No SAE

![Diagram showing treatment outcomes]

HCV/HIV Co-infected

<table>
<thead>
<tr>
<th>Weeks</th>
<th>N=31</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3D + RBV</td>
<td>94%</td>
</tr>
</tbody>
</table>

| N=32   | 3D + RBV | 91%   |

3D = Paritaprevir/r (PI) + Ombitasvir (NS5A) + Dasabuvir (NNI)

Wyles, Abst# 1939
Pooled Data: Impact of Tx Duration and RBV in Cirrhotic GT1 Pts (LDV/SOF)

- Pooled data (ONESTAR, ELECTRON, ELECTRON-2, 337-0113, ION-1, ION-2, SIRIUS)
- No difference in SVR rate by HCV subtype

<table>
<thead>
<tr>
<th></th>
<th>12 wks of LDV/SOF</th>
<th>24 wks of LDV/SOF</th>
<th>12 wks of LDV/SOF + RBV</th>
<th>24 wks of LDV/SOF + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>92%</td>
<td>96%</td>
<td>98%</td>
<td>100%</td>
</tr>
<tr>
<td>Treatment Naive</td>
<td>96%</td>
<td>98%</td>
<td>97%</td>
<td>100%</td>
</tr>
<tr>
<td>Treatment Experienced</td>
<td>90%</td>
<td>96%</td>
<td>98%</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Treatment Naive</th>
<th>Treatment Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12 (%)</td>
<td>118%</td>
<td>47%</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>204%</td>
<td>45%</td>
<td>159%</td>
</tr>
<tr>
<td></td>
<td>133%</td>
<td>33%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>58%</td>
<td>36%</td>
<td>22%</td>
</tr>
</tbody>
</table>

SVR in HCV cirrhosis treated with Paritaprevir/ritonavir, Ombitasvir, Dasabuvir with Ribavirin

Figure 1. Sustained Virologic Response at Post-Treatment Week 12 in Each Treatment Group, Overall and According to Subgroups.

Poordad F et al NEJM 2014 ; April 12
What are the treatment options available for our patients?

**Our patient**
- HCV GT1a
- Viral load
  - 2,195,000 IU/ml
- Naïve to treatment
- Fibroscan 7.5 kpa
- APRI 0.42

**Her Husband**
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- Naïve to treatment
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- APRI 2.1
### Treatment options 2015
#### Genotype 3

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<th>Treatment option</th>
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<th>cirrhosis</th>
<th>Decompensated cirrhosis</th>
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<tbody>
<tr>
<td>SOFOSBUVIR / with RIBAvirin</td>
<td>24 w</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>SOFOSBUVIR / DACLATASVIR (+/- RIBAVIRIN)</td>
<td>12 w alone</td>
<td>24 w + RIBA</td>
<td>24 w + RIBA</td>
</tr>
<tr>
<td>Peg IFN/ Ribavirin + Sofosbuvir</td>
<td>12 w</td>
<td>12 w</td>
<td>no</td>
</tr>
</tbody>
</table>

*Pawlotsky JM 2015 ILC presentation EASL guidelines*
SVR12 in GT 3 by Treatment History and Cirrhosis Status

Error bars represent 95% confidence intervals.

Foster GR EASL 2015 aBST
ALLY-3: DCV + SOF x 12 weeks in HCV GT 3

SVR12 Results

- Relapse: n=16 (11/16 had cirrhosis)
- NS5A Y93H RAVs emerged at relapse in 9/16 patients

Nelson, AASLD, 2014, Oral #LB-3
Challenges

Treatment now vs later?

- $$$
  - Fibrosis score
- Genotype 3
- Renal failure
- Decompensated
  - ?Transplant candidate
- Post transplant
- DAA Treatment experienced
  - Need to consider RAVS
Courtesy Jordan Feld, MD, MPH Assistant Professor of Medicine, Toronto Western Hospital, Sandra-Rotman Centre for Global Health, University of Toronto
“A Primer to the future treatment of HCV,” Abbott Satellite Symposium, Barcelona, Spain, April 2012
The future

- **Grazoprevir + Elbasvir**
  - Good for GT1
  - And renal failure
- More potent Pangenotypic NS5A inhibitors
  - GS 5816 + Sofosbuvir
- **TRIPLETS**
  - Mk-Grazoprevir, 8408, 3682,
  - GS- 9857, 5816, SOF
- Shorter treatment
Genotype 4 SVR summary

Figure 2. Results of treatment with Direct-acting antivirals (DAAs) for HCV genotype 4 infection [reference (23-27)]. Abbreviations: SOF, sofosbuvir; PR, pegylated interferon/ribavirin; DCV, daclatasvir; SMV, simeprevir.
C EDGE
Treatment Naïve patients

- Grazoprevir (2\textsuperscript{nd} generation PI)
- and Elbasvir (NS5A inhibitor)
- x12 w TN G 1,4,6
- 22% cirrhosis
- AE
  - Increased bili >2
  - Increased ALT >2 nl (2.3%)
  - Increased ALT >5 nl (1.3%)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>SVR (number)</th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>299 / 316</td>
<td>95%</td>
</tr>
<tr>
<td>G 1a</td>
<td></td>
<td>92%</td>
</tr>
<tr>
<td>G 1b</td>
<td></td>
<td>99%</td>
</tr>
<tr>
<td>G 4</td>
<td>18 / 18</td>
<td>100%</td>
</tr>
<tr>
<td>G 6</td>
<td>8 / 10</td>
<td>80%</td>
</tr>
</tbody>
</table>

Zeuzem EASL 2015 G07
Treatment HCV GT1 CKD stage 4 and 5

**SVR12: IMMEDIATE TREATMENT GROUP (ITG)**

![Graph showing treatment outcomes](image_url)

- **Modified Full Analysis Set**: 99% (115/116)
- **Full Analysis Set**: 94% (115/122)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Modified Full Analysis Set</th>
<th>Full Analysis Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>1*</td>
<td>1</td>
</tr>
<tr>
<td>Discontinued unrelated to Tx</td>
<td>0</td>
<td>6†</td>
</tr>
</tbody>
</table>

MFAS = primary efficacy analysis; FAS was a secondary analysis

*Noncirrhotic, interferon-intolerant patient with HCV GT1b infection relapsed at FW12
†Lost to follow-up (n=2), n=1 each for death, non-compliance, withdrawal by subject, and withdrawal by physician (due to violent behavior)
Short Duration Treatment with GS-9857 + Sofosbuvir/GS-5816 for HCV G1

- GS-9857 (HCV NS3/4A protease inhibitor) + sofosbuvir/GS-5816 (NS5A inhibitor)
- Treatment-naïve and DAA-experienced with and without cirrhosis
- Shortening treatment duration to 4 weeks associated with higher relapse rate

SVR12 (%)

<table>
<thead>
<tr>
<th></th>
<th>4 Weeks Treatment Naïve No Cirrhosis</th>
<th>6 Weeks Treatment Naïve No Cirrhosis</th>
<th>6 Weeks Treatment Naïve Cirrhosis</th>
<th>6 Weeks - Prior DAA Failure ± Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4/15</td>
<td>14/15</td>
<td>13/15</td>
<td>20/30</td>
</tr>
</tbody>
</table>

Gane EJ, et al. et al. Poster presented at: EASL 2015; April 22-26, 2015; Vienna, Austria. Poster LP03.
Treatment GT 1

HCV G1: PRIMARY EFFICACY RESULTS SVR12
MODIFIED INTENT TO TREAT ANALYSIS*

<table>
<thead>
<tr>
<th></th>
<th>Non-cirrhotic</th>
<th>Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks</td>
<td>10 30*</td>
<td>26 30</td>
</tr>
<tr>
<td>6 weeks</td>
<td>87</td>
<td>80</td>
</tr>
<tr>
<td>8 weeks</td>
<td>94</td>
<td>94</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks</td>
<td>33</td>
</tr>
<tr>
<td>6 weeks</td>
<td>87</td>
</tr>
<tr>
<td>8 weeks</td>
<td>94</td>
</tr>
</tbody>
</table>

**Breakthrough**: 0 0 0 0

**Relapse**: 20 4 4 1

**Excluded**: 1 0 0 3†

*Excluded patients who discontinued due to reasons other than virologic failure
† One of the 3 patients who discontinued had HCV G2 at discontinuation
Treatment of HCV with DAAs
pearls and perils

• Ribavirin is still important in many regimens
  – Increases SVR and shortens duration
• We have to consider Drug -Drug Interactions
  – www.hep-druginteractions.org
• Treatment will involve combinations of DAAs
• Treatment failure can be associated with Resistant variants
  – RAVs against NS 3 4 A protease inhibitors may be short lived
  – RAVs against NS5A inhibitors can be long lasting and impact SVR retreatment
• Retreatment options are limited
Summary I

1. HCV related liver disease is responsible for 350,000 deaths worldwide and is the leading indication for Liver transplant

2. It is the leading cause of Hepatocellular Carcinoma in US and Europe.

3. There are currently 170 million infected with Hepatitis C and many are not yet diagnosed and are at risk for progression to cirrhosis and hepatocellular carcinoma.

4. It is necessary screen widely for HCV as it allows us to identify pts who are candidates for treatment and to educate pt in life style changes that may decrease progression to fibrosis.
5. Effective interferon free Treatment is available for most patients with HCV.

6. Newer treatments are in development that will surpass what we have now.

7. Treatment of patients with cirrhosis will decrease the incidence of liver related complications and death from HCV in those who respond.

8. Treatment does not eliminate the need for screening for liver cancer even in those who achieve SVR
Looking forward to even better treatments

...............*on the Horizon*
Appendix
# Interferon free Treatment options 2015 genotype 1b

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>No cirrhosis</th>
<th>cirrhosis</th>
<th>Decompensated cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFOSBUVIR / LEDIPASVIR ( +/- RIBA)</td>
<td>8-12 w</td>
<td>12 w +/- riba</td>
<td>12w +Riba 24 w alone</td>
</tr>
<tr>
<td>OMBITASVIR/PARITAPREVIR/RITONAVIR+</td>
<td>12 w - RIBA</td>
<td>12-w + RIBA</td>
<td>No</td>
</tr>
<tr>
<td>DASABUVIR ( +/- Riba)</td>
<td></td>
<td>24 w wo riba</td>
<td></td>
</tr>
<tr>
<td>SOFOSBUVIR/SIMEPREVIR (+/- RIBAVIRIN)</td>
<td>12 w</td>
<td>12w + RIBA</td>
<td>No</td>
</tr>
<tr>
<td>24 w alone</td>
<td></td>
<td>24 w alone</td>
<td></td>
</tr>
<tr>
<td>SOFOSBUVIR / DACLATASVIR (+/- RIBAVIRIN)</td>
<td>12 w alone</td>
<td>12 w + RIBA</td>
<td>12 w + riba 24 w alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 w alone</td>
<td></td>
</tr>
</tbody>
</table>

Pawlotsky JM 2015 ILC presentation EASL guidelines
## Interferon free Treatment options 2015
### genotype 2

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>No cirrhosis</th>
<th>cirrhosis</th>
<th>Decompensated cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFOSBUVIR / with RIBAvinir</td>
<td>12 w</td>
<td>16w – 20 w</td>
<td>16 – 20 w</td>
</tr>
<tr>
<td>SOFOSBUVIR / DACLATASVIR (+/- RIBAVIRIN)</td>
<td>12 w alone</td>
<td>12 w alone</td>
<td>12 w + riba</td>
</tr>
</tbody>
</table>

*Pawlotsky JM 2015 ILC presentation EASL guidelines*
SOF plus RBV for Genotype 2

*SOV/RBV (12 wks) non-inferior to PEG-IFN+RBV (24 wks) and has fewer side effects and treatment discontinuations

## Interferon free Treatment options 2015
genotype 4

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>No cirrhosis</th>
<th>cirrhosis</th>
<th>Decompensated cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFOSBUVIR / LEDIPASVIR ( +/- RIBA)</td>
<td>12 w</td>
<td>12 w +/- riba 24 w alone</td>
<td>12w +Riba 24 w alone</td>
</tr>
<tr>
<td>OMBITASVIR/ PARITAPREVIR/ RITONAVIR (+/- Riba)</td>
<td>12 w + RIBA</td>
<td>24 w + riba*</td>
<td>No</td>
</tr>
<tr>
<td>SOFOSBUVIR/ SIMEPREVIR (+/- RIBAVIRIN)</td>
<td>12 w</td>
<td>12w + RIBA 24 w alone</td>
<td>No</td>
</tr>
<tr>
<td>SOFOSBUVIR / DACLATASVIR (+/- RIBAVIRIN)</td>
<td>12 w alone</td>
<td>12 w + RIBA 24 w alone</td>
<td>12 w + riba 24 w alone</td>
</tr>
</tbody>
</table>

Maybe 12 weeks will be enough
Pawlotsky JM 2015 ILC presentation EASL guidelines
## Interferon free Treatment options 2015
### genotype 5 and 6

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>No cirrhosis</th>
<th>Cirrhosis</th>
<th>Decompensated cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFOSBUVIR / LEDIPASVIR (+/- RIBA)</td>
<td>12 w alone</td>
<td>12 w +/- riba 24 w alone</td>
<td>12w +Riba 24 w alone</td>
</tr>
<tr>
<td>SOFOSBUVIR / DACLATASVIR (+/- RIBAVIRIN)</td>
<td>12 w alone</td>
<td>12 w +RIBA 24 w alone</td>
<td>12 w + riba 24 w alone</td>
</tr>
</tbody>
</table>

Pawlotsky JM 2015 ILC presentation EASL guidelines
Table 5  Diagnostic performance of serum biomarkers in chronic hepatitis C

<table>
<thead>
<tr>
<th>Index</th>
<th>AUC</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronan</td>
<td>0.73-0.86/</td>
<td>64.5-75/</td>
<td>81.0-91.2/</td>
<td>41.0-86.3/</td>
<td>78.5-93/</td>
<td>3.94-7.32/</td>
<td>0.30-0.38/</td>
</tr>
<tr>
<td></td>
<td>0.89-0.92/</td>
<td>79.2-100/</td>
<td>80.0-89.4/</td>
<td>63.0-100/</td>
<td>99.0-100/</td>
<td>5.00-7.47/</td>
<td>0.00-0.23/</td>
</tr>
<tr>
<td></td>
<td>0.55-0.89/</td>
<td>80.5-89/</td>
<td>84.1-89.9/</td>
<td>82.0-86.3/</td>
<td>77.6-82.5/</td>
<td>5.56-7.97/</td>
<td>0.13-0.21/</td>
</tr>
<tr>
<td></td>
<td>0.91</td>
<td>94.1</td>
<td>87.6</td>
<td>68</td>
<td>94.7</td>
<td>7.46</td>
<td>0.06</td>
</tr>
<tr>
<td>FibroScore</td>
<td>0.82-0.87/</td>
<td>71.8-93.0/</td>
<td>66.0-73.9/</td>
<td>60.9-82.6/</td>
<td>77.7-94/</td>
<td>2.73-2.75/</td>
<td>0.10-0.24/</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hepascore</td>
<td>0.79-0.85/</td>
<td>53.0-82/</td>
<td>65.0-92.0/</td>
<td>70-88/</td>
<td>63.5-78/</td>
<td>2.34-6.62/</td>
<td>0.27-0.51/</td>
</tr>
<tr>
<td></td>
<td>0.85-0.94/</td>
<td>71.0-76.5/</td>
<td>84.0-89.8/</td>
<td>64.9</td>
<td>89.6-98</td>
<td>4.78-6.96/</td>
<td>0.27-0.32</td>
</tr>
<tr>
<td>ELF score</td>
<td>0.80/</td>
<td>90/</td>
<td>31/</td>
<td>27.5/</td>
<td>92/</td>
<td>1.30/</td>
<td>0.32/</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>AAR</td>
<td>NA/NA</td>
<td>NA/NA</td>
<td>NA/NA</td>
<td>NA/NA</td>
<td>NA/NA</td>
<td>NA/NA</td>
<td>NA/NA</td>
</tr>
<tr>
<td>APRI</td>
<td>0.51-0.83/</td>
<td>46.7-78.0/</td>
<td>95.9-100/</td>
<td>73.7-100/</td>
<td>80.7-89/</td>
<td>19.02</td>
<td>0.22-0.43/</td>
</tr>
<tr>
<td>LokIndex</td>
<td>0.69-0.88/</td>
<td>41-91/</td>
<td>47-95/</td>
<td>61-88/</td>
<td>64-86/</td>
<td>1.71-8.20/</td>
<td>0.19-0.62/</td>
</tr>
<tr>
<td></td>
<td>0.61-0.94/</td>
<td>57-89/</td>
<td>75-93/</td>
<td>38-57/</td>
<td>93-98/</td>
<td>3.56-8.14/</td>
<td>0.10-0.46/</td>
</tr>
<tr>
<td></td>
<td>0.78-0.81/</td>
<td>37-92/</td>
<td>30-94/</td>
<td>32-75/</td>
<td>84-91/</td>
<td>1.31-6.16/</td>
<td>0.26-0.67/</td>
</tr>
<tr>
<td>Forns’ Index</td>
<td>0.60-0.86/</td>
<td>79.3-94/</td>
<td>61.2-95.0/</td>
<td>66.9-97/</td>
<td>65.8-96/</td>
<td>2.42-15.96/</td>
<td>0.09-0.21/</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fib-4</td>
<td>0.52-0.89/</td>
<td>37.6-74.3/</td>
<td>80.1-95.2/</td>
<td>82.1/</td>
<td>94.7/</td>
<td>3.73-20.77/</td>
<td>0.32-0.63/</td>
</tr>
<tr>
<td></td>
<td>0.79-0.91/</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fibrotest</td>
<td>0.74-0.87/</td>
<td>65-77/</td>
<td>72-91/</td>
<td>76-80/</td>
<td>66.7-81/</td>
<td>2.75-7.22/</td>
<td>0.31-0.38/</td>
</tr>
<tr>
<td></td>
<td>0.71-0.87/</td>
<td>50-87/</td>
<td>70-92.9/</td>
<td>57.9-93/</td>
<td>44-90.5/</td>
<td>2.9-7.04/</td>
<td>0.17-0.53/</td>
</tr>
</tbody>
</table>

AUC: Area under the curve; NA: Not available; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; AAR: AST-to-ALT ratio; APRI: AST-to-platelet ratio index.