Faster, Higher, Stronger: The New Standards for treatment of Chronic Hepatitis C disease

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COI disclosure

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Objectives from this session

- Review only chronic hepatitis C disease, not acute hepatitis C.
- Focus on mono-infection, less on HCV-HIV co-infection
- Discuss new advances in diagnosis and improved treatment outcomes
- Explore upcoming advances to the treatment paradigm
Epidemiology
HCV Most Common Chronic Bloodborne Viral Infection in the United States (2006)\(^1\)

180 Million Individuals Infected Worldwide\(^2\)

Global Prevalence of HCV Infection\(^4,5\)

- <1.0%
- 1.0% - 1.9%
- 2.0% - 2.9%
- >2.9%
- Not included in a WHO region

Sources of Infection for Persons With HCV in the United States\(^1\)

- Injecting drug use 60%
- Sexual 15%
- Transfusion 10% (before screening)
- Other* 5%
- Unknown 10%

*Hemodialysis, healthcare work, perinatal
Source: Centers for Disease Control and Prevention

Prevalence of Hepatitis C by Age and Sex

Retrospective review of claims from 1997–1999 in US Health Plan with 3.9 million members

Progressive Increase in Incidence of HCV-Related Cirrhosis and HCC in US

Annual Prevalence Rates Between 1996 and 2006 Among HCV-Infected Veterans

By 2007, Deaths From HCV Surpassed Those From HIV

Change in Mortality Rates From 1999 to 2007

HCV Can Now Be Cured in Most Patients

- Unlike HIV and HBV infection, HCV infection is a curable disease
  - HCV does not archive its genome
- What does cure mean?
  - Undetectable HCV RNA 12 weeks after completion of antiviral therapy for chronic HCV infection
  - SVR12 is almost invariably durable

CDC and USPSTF Recommendations for HCV Screening

• Regardless of risk factors, one-time testing for HCV of adults born between 1945–1965\textsuperscript{1,2}
  – Testing of persons of all ages \textit{at risk} for HCV infection

• CDC also recommends for those identified with HCV infection\textsuperscript{1}
  – Brief alcohol screening and intervention as clinically indicated
  – Referral to appropriate care and treatment services for HCV infection and related conditions

\textsuperscript{1} Centers for Disease Control and Prevention (CDC). \textit{MMWR}. 2012;61(4):1-18
Global Distribution and Prevalence of HCV Genotypes: US Focus on GT 1

Transmission of HCV

~ 30% of patients do not know how they got HCV

Modes of Transmission

- Illicit injection drug use
- Clotting factors before 1987
- Blood product/organ/tissue transplant before 1992
- Illicit intranasal drug use
- Tattoos, body piercing
- Nosocomial or occupational exposure
- Mother-to-infant
- Shared personal items with infected individuals
- High-risk sexual activity

HCV Genotypes in US

- Hepatitis C virus
  - RNA virus – high mutation rates
  - Evolved different genotypes
- Genotypes 1–3 are the most common in the United States
- Genotype and viral load do not impact disease progression
- Predicts treatment response and may help to determine treatment duration

Distribution of HCV Genotypes

- Genotype 1: 75%
- Genotype 2: 10%
- Genotype 3: 10%
- Genotype 4, 5, 6: 5%

Natural History of HCV Infection

Exposure (Acute Phase)

- 15% Resolved
- 85% Chronic

- 20% Cirrhosis

- ~20 year progression rate accelerated with HIV, HBV, alcohol

- 6%/yr ESLD
- 4%/yr HCC
- 3% to 4%/yr Transplant/death

5-year survival in patients with HCC is < 5%

Time (yr)

- 10
- 20
- 30

HCC = hepatocellular carcinoma
ESLD = end-stage liver disease

Challenges in Diagnosis
Normal ALT Does Not Mean “Healthy”

- Up to 40% of HCV patients may have persistently normal ALT\(^1\)
- ALT levels fluctuate in and out of the normal range over the course of HCV infection\(^2,3\)

Typical ALT pattern in Chronic Hepatitis C Infection

HCV Disease Progression in Patients With Normal ALT

- Randomized, controlled trial of two interferon dosing regimens in patients with elevated (n = 58) or persistently normal (n = 37) serum ALT levels\(^1\)

- Despite ‘persistently normal’ ALT levels, > 75% have some degree of liver damage on biopsy\(^1\)

- There are no known factors that predict which patient with persistently normal ALT will have disease progression\(^2\)

![Pie chart showing disease progression](chart)

**Normal ALT* (n = 37)**

- Portal fibrosis: 26%
- Bridging: 6%
- Cirrhosis: 6%
- No fibrosis: 23%
- Portal inflammation: 40%

*Total value exceeds 100% due to rounding*

Options for Assessment of fibrosis
Biomarkers (HCV FibroSURE®) can predict significant fibrosis in patients with chronic hepatitis C (CHC) - The first prospective validation in a United States (US) cohort

Puneet Puri2*, Sakhdisapol Katanyutanon1, Jessica Dodge1, Arun J Sanyal2, and George Abraham1

BACKGROUND

Chronic hepatitis C is the leading cause of cirrhosis and hepatocellular carcinoma in the US. The degree of liver fibrosis influences management decisions and prognosis of disease. At present, liver biopsy (LB) is needed to stage fibrosis (F0–4) and grade inflammatory activity (A0–3) according to Metavir score validated for CHC. Given the complications, sampling error and variability in interpretation of LB, alternative noninvasive markers are being developed and validated.

METHODS

42 consecutive patients undergoing both LB and FibroSURE® for evaluation of CHC were studied. All patients were HCV treatment naïve and had routine hematologic, biochemical and serologic testing. A single pathologist unaware of FibroSURE® results staged and graded liver biopsies according to Metavir and Knodell systems. We used MedCalc Software (V8.2.1.0, Belgium) to analyze for insignificant (stage 0–1, grade 0–1) and significant (stage 2–4, grade 2–3) fibrosis and activity by area under the receiver operating curve (AUROC) analysis, sensitivities, specificities, positive and negative likelihood ratios.

RESULTS (3) – Metavir Vs FibroSURE®

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>45.8 ± 8.2</td>
</tr>
<tr>
<td>Male (%): Female (%)</td>
<td>30 (71): 12 (29)</td>
</tr>
</tbody>
</table>

RESULTS (4) – Metavir Vs Fibrosure ROC

CONCLUSIONS

1. Are highly predictive of insignificant liver fibrosis (F0–1)
2. Can accurately identify significant fibrosis (F2–4)
3. Segregation into individual F2, F3 & F4 stage is not accurate
4. Are in concordance with significant Metavir activity (≥2)

CLINICAL IMPLICATIONS:
- A non-invasive screening tool for hepatic fibrosis
- Can obviate LB in patients with significant fibrosis
- In patients with significant fibrosis, LB is gold standard
Fibrosure Vs Metavir (Activity Grade)

ROC Curve

1 - Specificity

Diagonal segments are produced by ties.
Distribution of Fibrosure Stage by Metavir Staging (Fibrosis)
Distribution of Fibrosure Stage by Metavir Staging (Fibrosis)
Fibrosure Vs Metavir (Fibrosis Stage)

ROC Curve

1 - Specificity

Diagonal segments are produced by ties.
Results

- The AUROC for HFS activity >2 was 0.744 (95% CI 0.586 to 0.866, +LR of 4.03, p<0.002).

- The AUROC for HFS fibrosis was 0.982 (95% CI 0.883 to 0.995, +LR of 9.5, p<0.0001).
Conclusion

- The correlation between HFS and LB was better for fibrosis than for inflammatory activity.

- Clinically, the correlation for fibrosis is more important than the inflammatory activity.
Vibration Controlled Transient Elastography (Fibroscan®)
Work up for Chronic HCV
Lab tests to be ordered

- CBC, BMP, LFT, uric acid, TSH, iron/TIBC, ferritin, ANA, PT
- Hepatitis A IgG Ab, Hepatitis B surface Ag, Hepatitis B surface Ab, HIV
- HCV RNA RT-PCR (viral load), HCV genotype, HCV Fibrosure®, IL-28B, HCV NS3/4 Genosure® testing (Q80K mutation assay), AFP
- Fibrosis assessment, ultrasound/EGD if cirrhosis suspected
Challenges In Management
Hepatitis C Is the Leading Indication for Liver Transplant

Liver transplants have increased over the last decade

Highest percentage of liver transplants attributable to HCV.
Based on OPTN data as of November 16, 2009.
Organ Procurement and Transplantation Network. Available at: www.optn.org.
Liver Cancer has the Fastest Growing Death Rate in the US

Trends in US Liver Cancer Death Rates

-2 -1.5 -1 -0.5 0 0.5 1 1.5 2

Corpus & Uterus, NOS
Testis
Lung and Bronchus (Female)
Esophagus
Thyroid
Liver


National Cancer Institute Website, August 2006
HCV Screening Algorithm

- **EIA for anti-HCV**
  - **NEGATIVE** → **Stop testing**
  - **POSITIVE** → **RT-PCR for HCV RNA**
    - **NEGATIVE** → **Repeat RT-PCR for HCV RNA in 3–6 months**
    - **POSITIVE** → **Diagnosis of chronic HCV**
      - Perform work-up for disease staging and possible treatment
      - **Refer to specialist**

- **Stop testing; diagnosis of prior HCV infection likely**

*False negatives may occur in immunosuppressed patients. HCV, hepatitis C virus; anti-HCV, antibody to hepatitis C virus; EIA, enzyme immunoassay; RT-PCR, reverse transcriptase polymerase chain reaction.*

Hepatitis C: Goals of Therapy

Primary goal
- Eradicate HCV infection

Secondary goal(s)
- Improve histology
- Slow progression to ESLD, including HCC

ESLD = end-stage liver disease
HCC = hepatocellular carcinoma

Milestones Achieved, Still Miles to Go

PEG IFN Alfa-2a (180 µg): Mean Serum Concentration With Single or Multiple Doses

PEGASYS and COPEGUS: SVR by Genotype

For genotypes 2 and 3, treatment duration was 48 weeks for Fried and 24 weeks for Hadziyannis. The COPEGUS dose was weight based (1,000/1,200 mg once daily) for Fried and 800 mg once daily for Hadziyannis.

**Week 4: Response Definition**

**HCV RNA (IU/mL)**

**RVR (Rapid Virologic Response):** Defined as undetectable HCV RNA level at week 4 of treatment

Due to differences in assay sensitivities, for the purposes of this presentation, we are using a limit of detection of 50 IU/mL.

**Week 12: Response Definitions**

**EVR (Early Virologic Response):** Defined as a $\geq 2 \log_{10}$ reduction in, or an undetectable, HCV RNA level 12 weeks after initiating therapy$^{1,2}$

- **Complete EVR (cEVR):** Undetectable HCV RNA level 12 weeks after initiating therapy$^{3}$
- **Partial EVR (pEVR):** $\geq 2 \log_{10}$ reduction in HCV RNA level 12 weeks after initiating therapy, but with detectable HCV RNA level$^{3}$

Due to differences in assay sensitivities, for the purposes of this presentation, we are using a limit of detection of 50 IU/mL.

1. Dienstag JL, McHutchison JG. *Gastroenterology*. 2006;130:231-264
Definitions of Treatment Failure

Null Responder: \(<1 \log_{10}\) reduction in HCV RNA level at week 12

Partial Responder: \(>1 \log_{10}\) reduction in HCV RNA level, but \(<2 \log_{10}\) reduction by 12 weeks

Due to differences in assay sensitivities, for the purposes of this presentation, we are using a limit of detection of 50 IU/mL. These terms were defined by an FDA Antiviral Products Advisory Committee; however, ongoing clinical trials may use other definitions.

Weeks 12-72: Response Definitions

Sustained Virologic Response (SVR):
Clearance of viral RNA 24 weeks following completion of treatment
Highly durable, primary treatment outcome of antiviral therapy for HCV

Due to differences in assay sensitivities, for the purposes of this presentation, we are using a limit of detection of 50 IU/mL.

Definitions of Treatment Failure

Null Responder (Patients 2 & 3):
<1-log_{10} reduction in HCV RNA level at week 12

Partial Responder:
>1-log_{10} reduction in HCV RNA level, but <2-log_{10} reduction by 12 weeks

Responder Relapsers:
Achieves full clearance of HCV RNA copies by end of treatment, but then experiences a relapse by week 24 or beyond

Due to differences in assay sensitivities, for the purposes of this presentation, we are using a limit of detection of 50 IU/mL. These terms were defined by an FDA Antiviral Products Advisory Committee; however, ongoing clinical trials may use other definitions.

Considerations in Treatment Response
Predictors of Response to HCV Therapy

Patient Factors
- Race/ethnicity
- Metabolic
- Advanced liver disease/cirrhosis
- Age
- Coinfection (HIV, HBV)
- Hepatic iron overload
- Adherence
- Genetic Contributions
  - IL28B type

Viral Factors
- Genotype
- Viral load

On-treatment Factors
- Type of interferon
- Viral response

Efficacy of Current HCV Therapy Differs With Genotype

- **Genotype 2 or 3**
  - 46–92% response rate\(^1\-^3,^5\)

References:
Progression of Fibrosis to Stage F4 Based on Age at Infection

- Regardless of age at infection, fibrosis starts progressing more rapidly after age 50.

HCV: Factors Influencing Response

Factors Influencing Response to Current Antiviral Therapy

- Genotype
- Viral Load
- Age
- Duration of Infection
- Ethnicity
- Gender
- Fibrosis Stage
- Body Weight
- Steatosis/NASH

Pegylated Interferon + Ribavirin

SVR: 54-63%

Prevalence of Obesity in the United States

http://www.nhlbi.nih.gov/guidelines/obesity/practgde.htm
Association of Hepatic Steatosis and Fibrosis

P-value <0.001

SVR Decreased in Insulin Resistant Patients with HCV Genotype 1

Photomicrographs of Paired Liver Bx Pre- and Post-Weight Reduction

Serum Leptin Levels with Steatosis and Fibrosis in Genotype 1 Patients

[Graph showing serum leptin levels with steatosis and no steatosis for men and women.]

IL28B Genetic Variation and Viral Clearance*: Background

- In patients with chronic HCV infection, the identification of pretreatment factors that accurately predict response to treatment is a high clinical priority.

- Researchers have recently identified a polymorphism upstream of the IL28B encoding (IFN-λ-3) gene to be associated with an increase in SVR rate in adherent genotype 1 HCV patients.

- Genetic association study of G1 HCV patients in the IDEAL study
  - Results from IDEAL revealed significantly lower efficacy of PegIFN therapy in the different ethnic groups studied.

*Currently there is no FDA Approved test available

IL28B Genetic Variation and Viral Clearance: Distribution by Race/Ethnicity

- **TT** = thymine-thymine
- **CT** = cytosine-thymine
- **CC** = cytosine-cytosine

Caucasians: n = 1,171
- TT: 12%
- CT: 37%
- CC: 51%

African Americans: n = 300
- TT: 14%
- CT: 37%
- CC: 49%

Hispanics: n = 116
- TT: 22%
- CT: 49%
- CC: 29%

CC IL28B-type is more common in Caucasians than African Americans or Hispanics

IL28B Genetic Variation and Viral Clearance: Results

- A polymorphism on chromosome 19, rs12979860 (T/T, T/C, or C/C), was strongly associated with SVR in all patient groups.

IL28B Genetic Variation and Viral Clearance: Authors’ Conclusions

- In genotype 1 patients, the CC type of IL28B is strongly associated with SVR
- Differences in IL28B type explain much of the difference in response rates between the ethnic groups

Extrahepatic Manifestations Associated With HCV

Hematologic
- Mixed cryoglobulinemia\(^1\)
- Aplastic anemia\(^2\)
- Thrombocytopenia\(^2\)
- Non-Hodgkin’s b-cell lymphoma\(^2\)

Dermatologic
- Porphyria cutanea tarda\(^1\)
- Lichen planus\(^2\)
- Cutaneous necrotizing vasculitis\(^2\)

Renal
- Glomerulonephritis\(^1\)
- Nephrotic syndrome\(^2\)

Endocrine\(^2\)
- Hypothyroidism
- Diabetes mellitus

Ocular\(^2\)
- Corneal ulcer
- Uveitis

Vascular\(^2\)
- Necrotizing vasculitis
- Polyarteritis nodosa

Neuromuscular\(^2\)
- Weakness/myalgia
- Peripheral neuropathy
- Arthritis/arthritis

Autoimmune Phenomena\(^2\)
- CREST syndrome

Neuropsychiatric\(^1\)
- Depression

Treatment
HCV Lifecycle and DAA Targets

Receptor binding and endocytosis

Fusion and uncoating

Transport and release

Virion assembly

(+) RNA

Translation and polyprotein processing

NS3/4 protease inhibitors

NS5B polymerase inhibitors

Membranous web

ER lumen

NS5A* inhibitors

*Role in HCV lifecycle not well defined

HCV NS3/4A Serine Protease: The “Master Switch” for Replication

Multi-targeted Approach for Treatment: Approved Protease, Polymerase and NS5A Inhibitors

*agents in red will be briefly discussed but are investigational in the US

Adapted from McGovern B, Abu Dayyeh B, and Chung RT. *Hepatology.* 2008; 48:1700-12
Sofosbuvir + ribavirin ± pegIFN
Ledipasvir/ sofosbuvir
Sofosbuvir + daclatasvir
Ombitasvir/ paritaprevir/ ritonavir + dasabuvir
Simeprevir + sofosbuvir

2015 Agents
## Genotype 1 HCV Agents

<table>
<thead>
<tr>
<th>Protease Inhibitors</th>
<th>Polymerase Inhibitors</th>
<th>NS5A Inhibitors</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir</td>
<td>Sofosbuvir</td>
<td>Ledipasvir</td>
<td>Ribavirin</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir</td>
<td>Dasabuvir</td>
<td>Ombitasvir</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daclatasvir</td>
<td></td>
</tr>
</tbody>
</table>
### Genotype 1 HCV: FDA-Approved Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Approval for Genotype 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir + peginterferon + ribavirin*</td>
<td>24-48 wks</td>
</tr>
<tr>
<td>Sofosbuvir + peginterferon + ribavirin</td>
<td>12 wks</td>
</tr>
<tr>
<td>Sofosbuvir + ribavirin</td>
<td>Interferon ineligible, 24 wks; HCC awaiting transplant, up to 48 wks</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>8-24 wks</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir, dasabuvir, ± ribavirin</td>
<td>12-24 wks</td>
</tr>
<tr>
<td>Simeprevir + sofosbuvir</td>
<td>12-24 wks</td>
</tr>
</tbody>
</table>

*Screening pts with genotype 1a HCV infection for NS3 Q80K polymorphism strongly recommended and alternative therapy should be considered if Q80K detected.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
## Genotype 1 HCV: AASLD/IDSA-Recommended Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Genotype 1</th>
<th>Regimen Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir + peginterferon + ribavirin</td>
<td>Not recommended</td>
<td>QD-QWK; multiple tablets + injection</td>
</tr>
<tr>
<td>Sofosbuvir + peginterferon + ribavirin</td>
<td>Not recommended</td>
<td>QD-QWK; multiple tablets + injection</td>
</tr>
<tr>
<td>Sofosbuvir + ribavirin</td>
<td>Not recommended</td>
<td>QD; multiple tablets</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>Recommended</td>
<td>QD; single-tablet regimen</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir, dasabuvir, ± ribavirin</td>
<td>Recommended</td>
<td>QD-BID; multiple tablets</td>
</tr>
<tr>
<td>Simeprevir + sofosbuvir ± ribavirin</td>
<td>Recommended</td>
<td>QD; multiple tablets</td>
</tr>
</tbody>
</table>

[http://www.hcvguidelines.org](http://www.hcvguidelines.org)
Genotype 1 HCV Treatment Naive

- AASLD-IDSA guidelines
  - 3 regimens recommended

<table>
<thead>
<tr>
<th>Genotype 1a, no cirrhosis</th>
<th>12 wks</th>
<th>12 wks + RBV</th>
<th>12 wks ± RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a, cirrhosis</td>
<td>12 wks</td>
<td>24 wks + RBV</td>
<td>24 wks ± RBV</td>
</tr>
<tr>
<td>Genotype 1b, no cirrhosis</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
</tr>
<tr>
<td>Genotype 1b, cirrhosis</td>
<td>12 wks</td>
<td>12 wks + RBV</td>
<td>24 wks</td>
</tr>
</tbody>
</table>

*Ledipasvir/sofosbuvir for 8 wks can be considered in naive, noncirrhotic pts with baseline HCV RNA < 6 million IU/mL.*

http://www.hcvguidelines.org
### Genotype 1 HCV Treatment Naive Noncirrhotic

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Wks</th>
<th>Study</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/sofosbuvir (HCV RNA &lt; 6 M IU/mL)</td>
<td>8</td>
<td>ION-3(^{[1,2]})</td>
<td>119/123 (97%)</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>12</td>
<td>ION-3(^{[1]})</td>
<td>206/216 (95%)</td>
</tr>
<tr>
<td>Simeprevir + sofosbuvir*</td>
<td>8-12</td>
<td>OPTIMIST-1(^{[3]})</td>
<td>8 wks: 128/155 (83%) 12 wks: 150/155 (97%)</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir, dasabuvir (GT1b)</td>
<td>12</td>
<td>PEARL III(^{[4]})</td>
<td>207/209 (99%)</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir, dasabuvir, ribavirin (GT1a)</td>
<td>12</td>
<td>PEARL IV(^{[4]})</td>
<td>97/100 (97%)</td>
</tr>
<tr>
<td>Sofosbuvir + daclatasvir</td>
<td>12</td>
<td>AI444040(^{[5]})</td>
<td>41/41 (100%)</td>
</tr>
</tbody>
</table>

\(^*\)GT1a + Q80K-8 wks: 36/49 (73%); GT1a + Q80K-12 wks: 44/46 (96%).

2. Ledipasvir/sofosbuvir [package insert].
### Genotype 1 HCV PegIFN/RBV Treatment Experienced

- **AASLD-IDSA guidelines**
  - 3 regimens recommended

<table>
<thead>
<tr>
<th>Genotype 1a, no cirrhosis</th>
<th>12 wks</th>
<th>12 wks + RBV</th>
<th>12 wks ± RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a, cirrhosis</td>
<td>24 wks</td>
<td>24 wks + RBV</td>
<td>24 wks ± RBV</td>
</tr>
<tr>
<td><strong>12 wks + RBV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 1b, no cirrhosis</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks ± RBV</td>
</tr>
<tr>
<td>Genotype 1b, cirrhosis</td>
<td>24 wks</td>
<td>12 wks + RBV</td>
<td>24 wks ± RBV</td>
</tr>
<tr>
<td><strong>12 wks + RBV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[http://www.hcvguidelines.org](http://www.hcvguidelines.org)
Genotype 1 HCV Previous PI Failure

- AASLD-IDSA guidelines
  - 1 regimen recommended

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment Duration</th>
<th>Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir</th>
<th>Simeprevir + Sofosbuvir ± Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a, no cirrhosis</td>
<td>12 wks</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1a, cirrhosis</td>
<td>24 wks</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1b, no cirrhosis</td>
<td>12 wks</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1b, cirrhosis</td>
<td>24 wks</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

http://www.hcvguidelines.org
## Genotype 1 HCV Previous PI Failure

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cirrhosis</th>
<th>Wks</th>
<th>Study</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>No</td>
<td>12</td>
<td>ION-2(^{[1]})</td>
<td>50/52 (96%)</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>Yes</td>
<td>24</td>
<td>ION-2(^{[1]})</td>
<td>14/14 (100%)</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir, ribavirin</td>
<td>Yes</td>
<td>24</td>
<td>SIRIUS(^{[2]})</td>
<td>75/77 (97%)</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir, ribavirin</td>
<td>Yes</td>
<td>12</td>
<td>SIRIUS(^{[2]})</td>
<td>74/77 (96%)</td>
</tr>
<tr>
<td>Sofosbuvir + daclatasvir</td>
<td>Mix</td>
<td>24</td>
<td>AI444040(^{[3]})</td>
<td>21/21 (100%)</td>
</tr>
<tr>
<td>Sofosbuvir, daclatasvir, ribavirin</td>
<td>Mix</td>
<td>24</td>
<td>AI444040(^{[3]})</td>
<td>19/20 (95%)</td>
</tr>
</tbody>
</table>

TURQUOISE II: OBV/PTV/RTV + DSV + RBV in Cirrhotic Pts With GT1 HCV

- **Pts (N = 380):**
  - Treatment-naive and experienced pts
  - All compensated cirrhosis

- **Design**
  - Open-label phase III

- **Regimen**
  - Paritaprevir/ritonavir, dasabuvir, ombitasvir, ribavirin
  - Duration: 12 vs 24 wks

<table>
<thead>
<tr>
<th>Safety Outcome</th>
<th>12 Wks (n = 208)</th>
<th>24 Wks (n = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE, n (%)</td>
<td>13 (6.2)</td>
<td>8 (4.7)</td>
</tr>
<tr>
<td>AE leading to d/c, n (%)</td>
<td>4 (1.9)</td>
<td>4 (2.3)</td>
</tr>
<tr>
<td>Fatigue, %</td>
<td>32.7</td>
<td>46.5</td>
</tr>
<tr>
<td>Headache, %</td>
<td>27.9</td>
<td>30.8</td>
</tr>
</tbody>
</table>

SIRIUS: LDV/SOF in Pts With GT1 HCV and Previous PegIFN/RBV ± PI Failure

- **Pts:**
  - Treatment-experienced, failure of both pegIFN/RBV and PI + pegIFN/RBV regimens
  - Compensated cirrhosis

- **Design**
  - Randomized, double-blinded

- **Regimens**
  - Placebo 12 weeks followed by LDV/SOF + RBV for 12 wks
  - LDV/SOF + Placebo for 24 wks

- 2 AEs higher with LDV/SOF vs placebo during first 12 wks
  - Headache: 35% vs 21%
  - Fatigue: 17% vs 4%

<table>
<thead>
<tr>
<th>Safety Outcome, %</th>
<th>Placebo 12 wks Then LDV/SOF + RBV 12 wks (n = 78)</th>
<th>LDV/SOF 24 wks (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>AE leading to d/c</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>27</td>
<td>40</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
<td>19</td>
</tr>
</tbody>
</table>

LDV/SOF + RBV in Pts With Genotype 1 HCV and Previous Sofosbuvir Failure

- **Pts**
  - GT1 treatment-experienced pts who experienced failure of prior SOF regimens (n = 51)
    - SOF + pegIFN/RBV: 49%
    - SOF + RBV: 39%
    - SOF placebo + pegIFN/RBV: 10%
    - GS-0938 monotherapy: 2%
  - 16% black
  - 59% GT1a
  - 27% cirrhosis

- **Design**
  - Open-label cohort

- **Regimen**
  - Ledipasivr/sofosbuvir + RBV for 12 wks

<table>
<thead>
<tr>
<th>Prior Regimen</th>
<th>SVR12, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PegIFN/RBV/SOF</td>
<td>25/25 (100)</td>
</tr>
<tr>
<td>SOF/RBV</td>
<td>19/20 (95)</td>
</tr>
</tbody>
</table>

- 1 pt relapsed: genotype 3a

Genotype
Non-1
infection
Genotypes 2 and 3

- AASLD-IDSA guidelines

<table>
<thead>
<tr>
<th>Genotype 2</th>
<th>Sofosbuvir + Ribavirin</th>
<th>Peginterferon-α, Ribavirin + Sofosbuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naive</td>
<td>12 wks</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>(16 wks for cirrhosis)</td>
<td></td>
</tr>
<tr>
<td>PegIFN/RBV nonresponders</td>
<td>12-16 wks</td>
<td>12 wks (alternative)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 3</th>
<th>Sofosbuvir + Ribavirin</th>
<th>Peginterferon-α, Ribavirin + Sofosbuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naive</td>
<td>24 wks</td>
<td>12 wks (alternative)</td>
</tr>
<tr>
<td>PegIFN/RBV nonresponders</td>
<td>24 wks</td>
<td>12 wks (alternative)</td>
</tr>
</tbody>
</table>

http://www.hcvguidelines.org
BOSON: SVR12 With SOF-Based Regimens in GT3 by Tx History and Cirrhosis Status

Sofosbuvir + PegIFN/RBV or RBV in Pts With GT3 HCV and Previous SOF Failure

- **Pts**
  - SOF + RBV treatment failures from FISSION, POSITRON, FUSION
  - Cirrhosis included

- **Design**
  - Open-label cohorts
  - Pt/investigator selected regimen

- **Regimen**
  - Sofosbuvir + ribavirin for 24 wks
  - PegIFN/RBV + sofosbuvir for 12 wks

**LDV/SOF + RBV in Treatment-Experienced Pts With Genotype 3 HCV**

- **Ledipasvir/sofosbuvir?**
  - No data in sofosbuvir failure
- **Pts:**
  - Treatment naive and experienced
  - With and without cirrhosis
- **Design**
  - Open-label cohorts
- **Regimen**
  - Ledipasvir/sofosbuvir + RBV for 12 wks

### SVR12 (%)

<table>
<thead>
<tr>
<th></th>
<th>Naive</th>
<th>No Cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>100/26</td>
<td>89/25</td>
<td>73/16</td>
</tr>
</tbody>
</table>

Daclastavir + Sofosbuvir in Tx-Naive and Tx-Exp’d Pts With Genotype 3 HCV

**ALLY-3**

- **Pts:**
  - Treatment naive and experienced
    - Prior sofosbuvir and alisporivir included
    - Prior NS5A inhibitors excluded
  - Cirrhosis: 21%

- **Design**
  - 2 open-label cohorts
  - Phase III

- **Regimen**
  - Daclatasvir + sofosbuvir once daily for 12 wks

---

**EASL recommendations for DCV + SOF in GT3**

- No cirrhosis: DCV + SOF for 12 wks
- Compensated cirrhosis: DCV + SOF + RBV for 24 wks

---

# Genotype 4 HCV Treatment Experienced

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Wks</th>
<th>FDA Approved</th>
<th>AASLD/IDSA</th>
<th>Study</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + pegIFN/RBV</td>
<td>12</td>
<td>Yes</td>
<td>Recommended</td>
<td>NEUTRINO[1]</td>
<td>27/28* (96%)</td>
</tr>
<tr>
<td>Sofosbuvir + ribavirin</td>
<td>24</td>
<td>No</td>
<td>Recommended</td>
<td>Ruane et al[2]</td>
<td>13/15 (87%)</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>12</td>
<td>No</td>
<td>Recommended</td>
<td>Multiple[3,4]</td>
<td>19/20†[3]; 20/22[4] (91-95%)</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir, ribavirin</td>
<td>12</td>
<td>No</td>
<td>Recommended</td>
<td>PEARL-I[5]</td>
<td>49/49 (100%)</td>
</tr>
</tbody>
</table>

*Study included treatment-naive pts only.
†Treatment-naive and treatment-experienced pts.

# Genotype 5/6 HCV Treatment Naive

- **AASLD-IDSA guidelines**

## Recommended Regimen

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Sofosbuvir + ribavirin + peginterferon</td>
<td>12 wks</td>
</tr>
<tr>
<td>6</td>
<td>Ledipasvir/sofosbuvir</td>
<td>12 wks</td>
</tr>
</tbody>
</table>

## Alternative Regimen

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Peginterferon + ribavirin</td>
<td>48 wks</td>
</tr>
<tr>
<td>6</td>
<td>Sofosbuvir + ribavirin + peginterferon</td>
<td>12 wks</td>
</tr>
</tbody>
</table>

[http://www.hcvguidelines.org](http://www.hcvguidelines.org)
Future HCV Treatment: Shorter Duration With Triple-Drug Regimens

- **Pts**
  - Treatment naive, genotype 1 (N = 60)

- **Design**
  - Single-center, open-label, phase IIA trial

- **Regimens**
  - 12 wks of SOF + LDV
  - 6 wks of SOF, LDV, GS-9669
  - 6 wks of SOF, LDV, GS-9451

Short-Duration Sofosbuvir/GS-5816 + GS-9857: Efficacy Results

- All pts who did not achieve SVR12 relapsed
- SVR12 rates for treatment-experienced pts: no cirrhosis, 68% (17/25 pts); cirrhosis, 60% (3/5 pts)

Gane EJ, et al. EASL 2015. Abstract LP03.
Guidance for HCV/HIV Coinfection

- Same recommendations as in HCV-monoinfected pts
- Consider drug–drug interactions
  - Need to adjust or withhold RTV if receiving a boosted PI with OMV/PTV/RTV + DSV
  - Potential for LDV-mediated increase in tenofovir levels, especially if tenofovir used with RTV
    - Avoid LDV if CrCl < 60 mL/min or if receiving tenofovir with RTV-boosted PI
  - Do not interrupt antiretroviral therapy
  - Other interactions at aidsinfo.nih.gov/guidelines, hiv-druginteractions.org
- Do not use OMV/PTV/RTV ± DSV in coinfected pts not taking antiretroviral therapy

AASLD/IDSA HCV Guidelines.
What About Resistance?

- **HCV RNA (log_{10} IU/mL)**
  - SOF/LDV 8 Wks
  - Post-treatment
  - Retreatment: SOF/LDV + RBV 24 Wks

**NS5A:**
- Q30L (4.50%)
- L31M (> 99%)
- Y93H (96.74%)
- S282T (91.24%)

**NS5B:**
- No RAVs

- **NS5A:** L31M 25.5%
- **NS5B:** No RAVs

---

In Summary
2015 and beyond

Citius
Altius
Fortius

In search of PERFECTOVIR
Summary

- First-generation PIs have now been replaced
- IFN will hang around for a short while...  
  - IFN-free therapy for GT1 is here
- Challenges
  - GT1a vs GT1b
  - One size fits all vs GT1b regimens
  - GT3 may still need IFN, at least for now
- Will simplify with time and we will have something for everyone
- The greatest challenge is paying for perfectovir!
Applause !!