What is new in hepatitis C virus screening & treatment?
Focus on HIV/HCV Coinfection

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Disclosures

• Grant support
  – Vertex Pharmaceuticals
  – Merck and Co.
  – Gilead Sciences
  – Genentech
  – Abbott Molecular
  – Abbvie

• Committee/advisor
  – Roche Diagnostics
  – Tibotec/Janssen
  – Abbott Diagnostics
  – Merck and Co.
Hepatitis C: A Global Health Problem

170-200 Million Carriers Worldwide (2% of the World’s population)

* Chak, Liver International, 2011

Most Patients with Chronic Hepatitis C in the US Are Not Aware That They Are Infected

~5,300,000 individuals are infected with the hepatitis C virus in the United States

1,325,000 (~25%) AWARE

3,975,000 (~75%) UNAWARE

www.buffalo.edu/reachingothers
Disease burden of patients infected 20 years or more is peaking now

Complications from chronic hepatitis C develop slowly over a period of 20–30 years

Patients infected
Infected > 20 y

Prevalence (%)


Davis GL. Rev Gastroenterol Disord 2004;4:7-17.

Deaths from HCV in the United States continue to rise; deaths from HBV and HIV are decreasing

HCV was the contributing or underlying cause of death for 15,106 individuals in 2007

Incident Cases of Severe Consequences of HCV Infection

Prevalence of HCV among Persons Born 1945-1965

- 74% of 2.7-3.9 M HCV infected
- Prevalence 5.3 times higher than other ages (3.29% vs 0.55%)²
- 73% of all HCV-associated mortality ⁴

References:
Annual Incident HCV Complications

- A validated Markov model\(^1\) forecasting morbidity and mortality due to HCV infection over the next 50 years projected…
  - 1.76 million will develop cirrhosis
  - 418,000 will develop liver cancer, and
  - 1,071,000 will die from complications of hepatitis C infection or…

1/3 of all persons currently infected

- More people died from HCV than from HIV in 2007 (~15,000 vs. ~13,000)

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New CDC Recommendation

- Adults born during 1945 through 1965 should receive one-time testing for HCV without prior ascertainment of HCV risk factor. (strong recommendation, moderate quality of evidence)
- Benefits
  - 70% reduction in HCC
  - 50% reduction in all cause mortality
HCV TREATMENT

Milestones in HCV Therapy: Average SVR* Rates from Clin Trials

*SVR=Sustained Virologic Response; **DAAs=Direct Acting Antivirals

Adapted from US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring MD.
Limitations of Current Regimens and Importance of SVR

- Need Interferon!
  - Side effects
    - Flu
    - Drops blood counts
    - Causes depression

- SVR
  - Durable
  - Improved QOL
  - Lessens consequences of ESLD, HCC
  - Improved glycemic control
  - Recovery of neurocognitive function
Sofosbuvir

- **NS5B nucleoside polymerase inhibitor**
- **Easy to take!**
- **Oral therapy**
- **No side effects**
- **No resistance**
Sofosbuvir: SVR by Genotype


>90% OF PATIENTS HAVE UNDETECTABLE VIRUS AFTER 2 WEEKS AND ARE CURED!

Summary: Sofosbuvir

• BUT – still need interferon!!! 😊

• 12 weeks of SOF+PEG+RBV cured 90% of HCV patients –regardless of genotype

• This regimen was well tolerated


Simipravir

• oral HCV NS3/4A protease inhibitor
• Well tolerated
• Genotype 1
• Some resistance
  • Q80K
  • 34% of geno 1a
  • No benefit
What about Simipravir and Sofobuvir together??

- Without horrible interferon??

**Patients cured with 12 weeks of pills**

![Graph showing treatment outcomes](image-url)
### Most Common AEs: Cohorts 1 and 2 Combined

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>24 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SMV + SOF + RBV (n=54)</td>
<td>SMV + SOF (n=31)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (37.0)</td>
<td>10 (32.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (20.4)</td>
<td>7 (22.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (11.1)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>9 (16.7)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Rash</td>
<td>7 (13.0)</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>9 (16.7)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Photosensitivity/sunburna</td>
<td>2 (3.7)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 (20.4)</td>
<td>1 (3.2)</td>
</tr>
</tbody>
</table>


*No sun-protective measures were in place for this trial.

RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir

### HIV/HCV Co-infection

- One quarter of HCV infected people also have HIV!
- Equivalent responses in HIV/HCV co-infected people!!
- Challenges are potential DDI with ARVs
SOF + RBV in HIV Co-infected Patients

7% Cirrhotic

WOW!!

SVR 12 (%)

76%
88%
92%

Genotype 1
87/114

Genotype 2
23/26

Genotype 3
12/13

Preliminary SVR rates in HIV/HCV coinfected patients treated with Simprevir+PR

Overall

Naïve*

Relapse*

SVR12

Patients (%)

Overall

Naïve*

Relapse*

SVR12

86
77
84
75
90
80

30/35
10/13
21/25
6/8
9/10
4/5

PR, pegIFN-α2a + ribavirin; SMV, simeprevir
What about Cirrhotics and Prior Null-responders

![Image of liver](image)

### Hallmark-Dual: Daclatasvir + Asunaprevir in Geno 1B

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Patients, n</th>
<th>SVR12, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naive</td>
<td>203</td>
<td>90</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>205</td>
<td>82</td>
</tr>
<tr>
<td>- Null response</td>
<td>119</td>
<td>82</td>
</tr>
<tr>
<td>- Partial response</td>
<td>84</td>
<td>81</td>
</tr>
<tr>
<td>Interferon ineligible/intolerant</td>
<td>235</td>
<td>82</td>
</tr>
<tr>
<td>- Depression</td>
<td>71</td>
<td>80</td>
</tr>
<tr>
<td>- Anemia/neutropenia</td>
<td>87</td>
<td>91</td>
</tr>
<tr>
<td>- Advanced fibrosis/cirrhosis with thrombocytopenia</td>
<td>77</td>
<td>73</td>
</tr>
</tbody>
</table>

2014 EASL
C-WORTHY: MK-5172 + MK-8742 ± RBV in GT1 Cirrhotics and Null Responders

- Interim results from a randomized phase IIb trial
- Primary endpoint: SVR12

<table>
<thead>
<tr>
<th>Treatment-naive pts with GT1 HCV and cirrhosis (N = 123)</th>
<th>Wk 12</th>
<th>Wk 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-5172 + MK-8742 (n = 31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MK-5172 + MK-8742 (n = 29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MK-5172 + MK-8742 + RBV (n = 32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MK-5172 + MK-8742 (n = 31)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pts with GT1 HCV and null response to pegIFN/RBV (N = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-5172 + MK-8742 (n = 33)</td>
</tr>
<tr>
<td>MK-5172 + MK-8742 + RBV (n = 33)</td>
</tr>
<tr>
<td>MK-5172 + MK-8742 (n = 32)</td>
</tr>
</tbody>
</table>

MK-5172 100 mg once daily; MK-8742 50 mg once daily, RBV 1000-1200 mg divided twice daily.


C-WORTHY: Interim Results in Treatment-Naive Cirrhotic Pts and Null Responders

<table>
<thead>
<tr>
<th>SVR4 (%)</th>
<th>Treatment-Naive Pts With Cirrhosis</th>
<th>Null Responders ± Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>90/31</td>
<td>28/29, 30/31*</td>
<td>28/30*</td>
</tr>
<tr>
<td>97/31*</td>
<td>30/32</td>
<td>32/32*</td>
</tr>
</tbody>
</table>

*Excludes patients who have not yet reached SVR4 time point.

C-WORTHY: Adverse Events in Treatment-Naive Cirrhotic Pts and Null Responders

<table>
<thead>
<tr>
<th>AEs, n (%)</th>
<th>Treatment-Naive With Cirrhosis</th>
<th>Null Responders ± Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With RBV (n = 63)</td>
<td>No RBV (n = 63)</td>
</tr>
<tr>
<td>Any serious AE, n (%)</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>AE leading to discontinuation, n (%)</td>
<td>2 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Laboratory abnormalities, n (%)
- Hemoglobin < 10 g/dL: 8 (13) | 0 | 4 (6) | 0
- Hemoglobin < 8.5 g/dL: 1 (2) | 0 | 0 | 0
- Total bilirubin > 2 x ULN: 6 (10) | 0 | 9 (14) | 3 (5)
- Total bilirubin > 5 x ULN: 0 | 0 | 0 | 0
- ALT/AST > 2 x ULN*: 0 | 2 (3) | 1 (2) | 3 (5)
- ALT/AST > 5 x ULN*: 0 | 0 | 1 (2) | 0

*After initial normalization.


SOF + RBV in Patients With Cirrhosis and Portal Hypertension ± Decompensation

- Interim results of an open-label phase II trial
- Primary endpoint: SVR12

Sofosbuvir 400 mg once daily; ribavirin 1000-1200 mg/day divided twice daily.
*Among 25 patients allocated sofosbuvir + ribavirin, 10 had GT1a HCV, 9 had GT1b, 2 had GT2, 2 had GT3, and 2 had GT4.

Highlights From EASL 2014

Virologic Response to SOF + RBV in Patients With Portal Hypertension


<table>
<thead>
<tr>
<th>Clinical Events, n</th>
<th>Ascites</th>
<th>Hepatic Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOF + RBV (n = 25)</td>
<td>Observation (n = 25)</td>
</tr>
<tr>
<td>Baseline</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Wk 12</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Wk 24</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

Costs of HCV Therapy

*SVR=Sustained Virologic Response; **DAAs=Direct Acting Antivirals

Hepatology 2014;59: 1246-48
Cost effectiveness of DAA therapy

- Average annual cost for liver disease patients 2003-2010
  - $17,277 cirrhotics
  - $22,752 well-compensated cirrhosis
  - $59,995 ESLD
  - $270,000 Total lifetime cost for cirrhosis
  - $577,100 Total cost for transplantation

What to do with your HCV patients?

- Limit alcohol
- Vaccinate for HAV and HBV
- Consider referral for all patients
  - Especially
    - With any liver dysfunction (elevated bili, low plts)
    - Any symptoms of liver disease
Time for Optimism in HCV Treatment among Drug Users

- HCV treatment uptake remains low among drug users
  - Less than 1/3 of those REFERRED to specialty clinics appear for appointment
  - Less than 20% of those evaluated initiate antiviral therapy.
  - Why?

<table>
<thead>
<tr>
<th>Education</th>
<th>Treatment</th>
<th>Insurance coverage and access</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of HCV knowledge</td>
<td>Needles may promote relapse</td>
<td>Stigmatization in health venues</td>
</tr>
<tr>
<td>Low perceived treatment need</td>
<td>“Treatment worse than disease”</td>
<td>Coexisting mental health diagnosis</td>
</tr>
<tr>
<td>Lack of knowledge of serostatus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Provider Concerns

Adherence
- Occasional drug use does not impact on adherence, treatment completion or SVR.
- Frequent drug use (daily or every other day) does lower adherence and SVR\(^1\).
- Recent meta-analysis with active injectors pooled SVR = 56\(^2\)

Reinfection
- Occurs at rate of 1% to 5% per year after successful treatment.
- Translates into 0.8 to 4.7 per 100 person-years (PY).
- Increased if report ongoing use post treatment (6.44 per 100 PY)\(^3\).
- Largely also depends upon background HCV level in community.

\(^1\)Robaey's, CID 2013;57:S129; \(^2\)Aspinall, CID 2013;57:S80; \(^3\)Grady et al, CID 2013;57:S105;
Treatment Completion in Drug Users

- Overall treatment completion = 83.4%
  - Addiction treatment increases HCV treatment completion.
  - After adjusting sex & co-infection, support services increase treatment completion.

PEG-IFN/RBV SVR Percentages in Drug Users

- Pooled SVR = 55.5%
- SVR affected by genotype 1/4 and proportion of HIV co-infected DU.
  - After adjustment, SVR increased with presence of multidisciplinary team.
Prevention, Evaluation and Treatment of HCV

- Telemedicine offers opportunity to remotely link patients with physicians geographically separated.
- HCV management via tele-care
  - Prior limited attempts in prisons\(^1,\text{2}\) and at rural clinics\(^2\)
  - Never attempted in drug treatment facility.
- Study objectives
  - To demonstrate feasibility of HCV management via tele-care in opiate treatment program.
  - To assess staff and patient knowledge and perception changes towards HCV treatment after educational intervention.

\(^1\) Sterling et al, Amer J Gastro, 2004:99:866; \(^2\) Arora, Hepatology 2010; 52:1124

Study schema: Stage 1-Visit 1

- Patients
  - Active recruitment
  - Baseline knowledge assessment
  - HCV antibody
  - HCV RNA
  - IL28B
  - Education intervention
  - Post intervention knowledge assessment
  - HCV antibody and RNA results discussed with patient
- Staff
  - Baseline knowledge assessment
  - Education intervention
  - Post intervention knowledge assessment
- Spontaneous resolvers
  - HCV RNA negative
  - Stage II
- HCV RNA positive
Study schema: Stage 2

Visit 1: Screening interview, informed consent, HCV evaluation: (HCV genotype, Fibrosure, HIV and HBV serology, optional liver biopsy)

Visit 2: Results to patients and discussion of treatment initiation

Visit 3: Initiation of HCV treatment

On treatment monitoring

End of treatment response

Sustained virological response

HCV management via tele-care with onsite physician extender

Treatment as Prevention

• Modest increases in HCV treatment could lead to substantial reduction in HCV prevalence.
  – Generated from observations in HIV
  – HCV is curable
  – Treatment is circumscribed in duration

• Targeting treatment by age affects outcomes
HCV treatment as prevention in the IFN-free DAA era

Time for Optimism-Patient Factors

<table>
<thead>
<tr>
<th>Obstacle</th>
<th>Resolution</th>
<th>Relevance to DU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low perceived treatment need</td>
<td>Improved antiviral efficacy</td>
<td>HCV education targeted to DUs</td>
</tr>
<tr>
<td>Low treatment initiation</td>
<td>Expanded insurance coverage</td>
<td>Medical home: Enables multispecialty care and education</td>
</tr>
<tr>
<td>“Treatment worse than disease”</td>
<td>Reduced side effects</td>
<td>Expanded screening reimbursements</td>
</tr>
<tr>
<td>Lack of knowledge of serostatus</td>
<td>HCV screening of boomers 1945-65</td>
<td></td>
</tr>
<tr>
<td>Needles may promote relapse</td>
<td>All oral administration</td>
<td></td>
</tr>
<tr>
<td>Coexisting mental health diagnosis</td>
<td>Improved mental health Rx access</td>
<td>No interferon</td>
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<td>Stigmatization in health venues</td>
<td>On site treatment in medical home</td>
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Improved drug efficacy; Improved screening guidelines; Affordable care act
Time for Optimism with HCV Treatment in DUs

- General optimism toward care of HCV in DUs
- Building blocks are present
  - New therapeutic regimens
  - Expanded health access
  - New screening guidelines
- Strategies and due diligence can lead to significant improvement in treatment outcomes in this population

Conclusion

- Almost everyone with hepatitis C is curable
- Soon, no interferon (with all its side effects)
- Well tolerated
- All pills
- Only 12 weeks of treatment and potentially getting shorter
- Enormous cost!!!