Hepatitis C in HIV Patients: The *Speeding* Sidecar

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Meharry Medical College
Patient: Mr. DW

- 40 year old AAM admitted with fever, non-productive cough and hypoxemia

- PMHX: None

- SHX:
  - smokes crack cocaine, marijuana
  - no IDU
  - heterosexual, infrequent condom use
  - 15-20 partners in last 12 mos
Laboratory Findings

- HIV Elisa/Western Blot positive
- CD4 185 (12%), VL 450,600
- ALT 170, AST 184
- Hepatitis C Ab +
- HCV RNA 3.7 million IU/ml
- HCV genotype 1a
- Hep B cAb/sAb/sAg neg
Question 1

Which of the following is true?

a) Anti-HCV therapy is contraindicated with current crack cocaine use

b) Hepatitis B vaccination should be delayed until CD4 count rises above 200 cells

c) The presence of HIV infection increases the HCV viral load

d) Acquisition of HCV was likely via injection drug use
Outline

• Epidemiologic trends in HCV infection
• Impact of HCV/HIV coinfection on the natural course of both infections
• Novel methods for assessing hepatic fibrosis in coinfected patients
• HCV therapy in HIV-infected patients
• Key issues in adverse events and drug interactions
• Potential new chemotherapeutics
Hepatitis C Epidemiology

- Most common chronic liver disease
- Most common reason for liver transplantation in U.S.
- Leading cause of death from liver dz in USA
- Prevalence of anti-HCV antibodies 1.6% in U.S. population → 4.1 million persons
- Prevalence of HCV RNA = 1.3% or 3.2 million persons

Trends in Epidemiologic Characteristics of HCV

MMWR Surveillance Summaries 2008
### Table 2. Adjusted Relative Odds of the Presence of Antibody to Hepatitis C Virus among Participants 20 to 59 Years of Age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>1.0</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>1.9 (0.9–3.8)</td>
</tr>
<tr>
<td>Mexican American</td>
<td>2.6 (1.2–5.8)</td>
</tr>
<tr>
<td><strong>Place of birth</strong></td>
<td></td>
</tr>
<tr>
<td>Within United States</td>
<td>1.0</td>
</tr>
<tr>
<td>Outside of United States</td>
<td>0.2 (0.08–0.7)</td>
</tr>
<tr>
<td><strong>Ratio of family income to poverty threshold</strong></td>
<td></td>
</tr>
<tr>
<td>≥2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0–1.9</td>
<td>3.5 (1.9–6.4)</td>
</tr>
<tr>
<td>0.0–0.9</td>
<td>9.1 (4.5–18.2)</td>
</tr>
<tr>
<td><strong>Blood transfusion before 1992</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>2.6 (0.9–7.3)</td>
</tr>
<tr>
<td><strong>Illicit drug use (ever)</strong></td>
<td></td>
</tr>
<tr>
<td>Never (or marijuana only)</td>
<td>1.0</td>
</tr>
<tr>
<td>Noninjection drug use (except marijuana)</td>
<td>3.7 (1.7–7.9)</td>
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<tr>
<td>Injection drug use</td>
<td>148.9 (44.9–494)</td>
</tr>
<tr>
<td><strong>Lifetime number of sexual partners</strong></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>1.0</td>
</tr>
<tr>
<td>2–19</td>
<td>1.4 (0.3–6.0)</td>
</tr>
<tr>
<td>≥20</td>
<td>5.2 (1.5–18.2)</td>
</tr>
</tbody>
</table>
## Hepatitis C Outbreaks Among MSM with High Risk Sexual Practices

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Controls (%) n=130</th>
<th>Cases (%) N=60</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAI (no condom)</td>
<td>35.3</td>
<td>78.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>RAI (condom)</td>
<td>69.8</td>
<td>74.6</td>
<td>0.62</td>
</tr>
<tr>
<td>Insertive Fisting</td>
<td>26.3</td>
<td>74.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Receptive Fisting</td>
<td>12.6</td>
<td>57.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Group Sex</td>
<td>52.5</td>
<td>88.1</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Hepatitis C: Natural history

Hepatitis C Infection

- Clearance (15%)
- Chronic Infection (85%)
  - Cirrhosis (20%)
    - Decompensation (30%)
      - Disease Recurrence
    - HCC (25%)
      - Liver Transplant vs Death

Liang et al, Ann Intern Med, 2000
Prevalence of HCV/HIV Coinfection

Johns Hopkins HIV Clinic (N=1955)

“1/3”

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Impact of HIV on HCV Infection

- Decreased clearance of acute infection (5-10%)
- Increased HCV RNA levels (increased production/decreased clearance)
- Increased liver disease progression
- Increased ART-associated hepatotoxicity
- Decreased response to anti-HCV therapy

Hospital Admissions for Liver Complications


N=3730
Liver Disease is 2nd Leading Cause of Death in HIV-Infected Patients (1999-2004)

D:A:D study (n=23,441)
HCV positive: 22.5%
ART 88.7%
Nadir CD4: 200 cells
Liver related deaths = 181
Median CD4 at death = 196
HIV <400 copies at death = 55%
ART at death = 61%

Question 2

Which of the following is true?

a) HCV should always be treated before HIV
b) Peg-IFN/Ribavirin has not been adequately studied in this population
c) Non-invasive markers of liver fibrosis obviate the need for liver biopsy in most cases
d) He should be evaluated for anti-HCV therapy
Impact of HCV on HIV Infection

Impact of HCV on HIV - EuroSIDA

• N=5957
• 1960 (33%) HCV-neg and 3997 (67%) HCV-pos
• No association between an increased incidence of AIDS-defining illnesses or death and HCV serostatus was seen (adjusted IRR, 0.97 [95% CI 0.81–1.16])

Impact of HCV on HIV Viral Suppression

Impact of HCV on CD4 Response

B

HCV negative
HCV positive

≥50 cells/μL increase in CD4 cell count, %

P = .056 (log-rank test)

No. under follow-up
Negative 1465 1211 907 675 494 373 283
Positive 750 629 463 361 284 221 184

Months since initiation of HAART

Hepatotoxicity in HCV/HIV Coinfected Patients

- Factors that may contribute to higher rates of HCV-related hepatotoxic complications include:
  - Higher baseline HCV RNA
  - Continued alcohol use/abuse
  - Immunocompromised, especially CD4+ count <200 cells/mm³
  - Liver toxicity from certain ART
    - Protease inhibitor (P450 CYP3A) inhibition
    - NNRTI hepatotoxicity
  - Nucleoside analogue interaction with RBV
    - Mitochondrial dysfunction/lactic acidosis

HCV Coinfection Increases Risk of ART-Associated Hepatotoxicity

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Liver Biopsy

• Current status of the liver injury

• Helps with decision to start Rx

• May reveal advanced fibrosis or cirrhosis that necessitates HCC surveillance and/or screening for varices
## Noninvasive Fibrosis Indices in HIV/HCV Coinfected Patients

<table>
<thead>
<tr>
<th>Index</th>
<th>Stage</th>
<th>Cutoff</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
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<tbody>
<tr>
<td>APRI$^1$</td>
<td>2-4</td>
<td>&lt;0.5</td>
<td>92</td>
<td>33</td>
<td>66</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>0-1</td>
<td>&gt;1.5</td>
<td>51</td>
<td>91</td>
<td>87</td>
<td>57</td>
</tr>
<tr>
<td>Fibro-test$^2$</td>
<td>2-4</td>
<td>&lt;0.2</td>
<td>97</td>
<td>NA</td>
<td>NA</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>0-1</td>
<td>&gt;0.6</td>
<td>66</td>
<td>92</td>
<td>86</td>
<td>77</td>
</tr>
<tr>
<td>Forns$^1$</td>
<td>2-4</td>
<td>&lt;4.2</td>
<td>78</td>
<td>38</td>
<td>64</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>0-1</td>
<td>&gt;6.9</td>
<td>43</td>
<td>96</td>
<td>94</td>
<td>55</td>
</tr>
</tbody>
</table>

Elastography

The probe induces an elastic wave through the liver.

The velocity of the wave is evaluated in a region located from 2.5 to 6.5 cm below the skin surface.

Cirrhosis: sensitivity 87 %
specificity 91 %

Stage II-IV fibrosis: sensitivity 70 %
specificity 84 %

LB: 1/50,000 of the liver
FibroScan: 1/500 of the liver
Diagnostic Accuracy of Liver Stiffness Measurement in HIV/HCV Coinfected Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fibrosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSM cutoff value, kPa</td>
<td>≥9.3</td>
<td>≥12.3</td>
</tr>
<tr>
<td>AUC-ROC, % (95% CI)</td>
<td>0.81 (0.75–0.86)</td>
<td>0.81 (0.74–0.87)</td>
</tr>
<tr>
<td>Sensitivity, % (95% CI)</td>
<td>85.9 (75.6–93.0)</td>
<td>75.0 (60.4–86.4)</td>
</tr>
<tr>
<td>Specificity, % (95% CI)</td>
<td>75.2 (66.5–82.6)</td>
<td>86.1 (79.4–91.3)</td>
</tr>
<tr>
<td>PPV, % (95% CI)</td>
<td>67.0 (56.4–76.5)</td>
<td>64.3 (50.4–76.6)</td>
</tr>
<tr>
<td>NPV, % (95% CI)</td>
<td>90.1 (82.5–95.1)</td>
<td>91.2 (85.1–95.4)</td>
</tr>
<tr>
<td>Percentage of cases that were correctly classified</td>
<td>79.2</td>
<td>83.3</td>
</tr>
</tbody>
</table>

N=192

Kirk et al. Clinical Infectious Diseases 2009;48:963–972
Outline

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Barriers to Treatment

- Substance abuse
- Poorly controlled psychiatric disease
- Social instability
- Concerns regarding adherence
- Lack of expertise/experience
- Cost
Barrier to HCV Treatment in an Urban HCV/HIV Clinic

149 HCV/HIV-infected patients

Eligible 30%
Ineligible 70%

ESLD 12%
Drug use 23%
Non-adherence 23%
Psychiatric 21%
AI DS 13%
Other 8%

ESLD, end stage liver disease.
Treatment of HCV in Substance Abusers

- SVR and adherence rates in users are not different from non-users
  

- Continued alcohol consumption decreases the response to IFN therapy

Treatment Guidelines

• Anti HCV therapy *should* be considered for patients with ongoing drug use (other than alcohol)


Department of Veteran’s Affairs. VA treatment recommendations for patients with chronic Hep C. Federal Practitioner 2003.
Therapeutic Goals in HCV/HIV Coinfection

• Primary goal
  – Eradicate HCV infection
  – Achieve a sustained virologic response (SVR)

• Secondary goals
  – Suppress HCV disease activity to prevent ART-related hepatotoxicity
  – Delay histologic and clinical disease progression
  – Minimize side effects of HIV and HCV therapy

Question 3

Which of the following is not a positive predictive of SVR?

a) Caucasian
b) Weight under 75 kg
c) Female sex
d) HCV RNA 1,000,000 IU/ml
Peginterferon Alfa-2b and Ribavirin for the Treatment of Chronic Hepatitis C in Blacks and Non-Hispanic Whites

<table>
<thead>
<tr>
<th>Virologic Response</th>
<th>Blacks (N=100)</th>
<th>Non-Hispanic Whites (N=100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early†</td>
<td>40 (30–50)</td>
<td>69 (60–78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End of treatment</td>
<td>20 (12–28)</td>
<td>58 (48–68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sustained</td>
<td>19 (12–28)</td>
<td>52 (42–62)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Peginterferon Alfa-2a and Ribavirin in Latino and Non-Latino Whites with Hepatitis C

N=569

Early Viral Kinetics Responsible for Ethnic Variation?

N=341

What We Know: Factors Positively Impacting SVR

- Genotype non-1
- VL < than 600,000 IU/mL
- Doses of PEG-IFN & RBV
- Female gender
- <40 years age
- Non AA/Latino race
- Lower body weight (75 kg)
- Absence of insulin resistance
- Elevated ALT levels (3X ULN)
- Absence of advanced fibrosis or cirrhosis on liver biopsy
### Summary of Results From Coinfection Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment</th>
<th>SVR (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>All</td>
<td>GT 1</td>
<td>GT non-1</td>
</tr>
<tr>
<td>RIBAVIC</td>
<td>412</td>
<td>PEG IFN $\alpha$-2b + RBV 800</td>
<td>27</td>
<td>17</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IFN $\alpha$-2b + RBV 800</td>
<td>20</td>
<td>6</td>
<td>43</td>
</tr>
<tr>
<td>ACTG</td>
<td>133</td>
<td>PEG IFN $\alpha$ 2a + RBV 600</td>
<td>27</td>
<td>14</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IFN $\alpha$-2a + RBV 600</td>
<td>12</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>APRICOT</td>
<td>860</td>
<td>PEG IFN $\alpha$ 2a + RBV 800</td>
<td>40</td>
<td>29</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IFN $\alpha$-2a + RBV 800</td>
<td>12</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>LAGUNO</td>
<td>93</td>
<td>PEG IFN $\alpha$-2b + W/B RBV</td>
<td>44</td>
<td>38</td>
<td>53</td>
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<tr>
<td></td>
<td></td>
<td>IFN $\alpha$-2b + W/B RBV</td>
<td>21</td>
<td>7</td>
<td>47</td>
</tr>
<tr>
<td>PRESCO</td>
<td>389</td>
<td>PEG IFN $\alpha$-2a + W/B RBV</td>
<td>50</td>
<td>36</td>
<td>72</td>
</tr>
</tbody>
</table>
Response by CD4 strata in GT1

Opravil et al. JAIDS 2008;47:36-49.
SVR Rates Among Patients with CD4 Cell Counts 250 cells/mm³ or Less at the Start of HCV Therapy

Mira JA et al. CID 2009:49 (15 October)
PRESICO Trial in HCV/HIV Coinfection: Study Design

CHC, naïve, HIV-HCV co-infection, n = 389

- **G1/4**
  - n=45
  - Pegasys 180 µg plus Copegus 1000-1200 mg
  - Follow-up

- **G2/3**
  - n=96
  - Pegasys 180 µg plus Copegus 1000-1200 mg
  - Follow-up

- **Follow-up**
  - n=192
  - Pegasys 180 µg plus Copegus 1000-1200 mg

- **Follow-up**
  - n=45
  - Pegasys 180 µg plus Copegus 1000-1200 mg

- **Follow-up**
  - n=56
  - Pegasys 180 µg plus Copegus 1000-1200 mg

Only patients with EVR (≥2 log drop of HCV RNA at week 12) continue treatment; duration at the discretion of the investigator.

PRESESCO Trial in HCV/HIV Coinfection: Virologic Response by Genotype

Overall Genotype 1 Genotype 2/3 Genotype 4

SVR (%)

- Overall: 50% (n=193)
- Genotype 1: 36% (n=68)
- Genotype 2/3: 72% (n=110)
- Genotype 4: 33% (n=15)

PRESESCO: RBV 1000-1200 mg
APRICOT: RBV 800 mg

PRESCO Trial in HCV/HIV Coinfection: Virologic Response by Genotype and Duration

Proposed Optimal Duration of Therapy in HIV/HCV Coinfected Patients

Current IDSA guidelines recommend 48 weeks regardless of genotype

* Patients with low viral load and minimal fibrosis at baseline

Soriano et al. AIDS 2007, 21:1073-1089
Question 4

Maintenance Peg-IFN can decrease liver disease progression in coinfected patients who do not achieve an early virologic response.

a) True
b) False
c) Perhaps
Maintenance Therapy with Peg-IFN in Viral Nonresponders is NOT Effective

Peg-IFN 90 micrograms wkly x 3.5 yrs (n=517) vs observation (n=533) in HIV-negatives

ACTG 5178 (SLAM-C): Maintenance Peg-IFN Treatment For HCV/HIV Non-Responders

NR and naïve n=300

Pegasys 180 µg plus Copegus 800–1200 mg

HCV RNA ≥2 log drop

12 weeks

Stop treatment, observation period

72 weeks

Randomization

Prior Treatment with 12 weeks PEG/RBV Rx

HCV RNA <2 log drop

60 weeks

Pegasys 180 µg plus Copegus 800–1200 mg

Untreated Follow-up

24 weeks

No Change in Liver Histology in HCV/HIV Patients on Maintenance Peg-IFN

Question 5

Which of the following is the best positive predictor of SVR in HCV/HIV coinfected patients?

a) Complete EVR
b) Complete ETR
c) Complete RVR
d) None of the above
Response Patterns: Early Virologic Response (EVR)

- **PegIFN/RBV**
- Non-responder
- 2 log decline
- EVR
- ETR
- SVR
Response Patterns: Rapid Virologic Response

HCV RNA (log$_{10}$ IU/mL)

-6 0 6 12 18 24 30 36 42 48 54 60 66 72 78

Weeks

PegIFN/RBV

RVR (undetectable HCV RNA or > 2 log drop)

2 log decline

Jensen et al, Hepatology 2006; 43:954-960
Importance of RVR

Best predictor of SVR is the RVR

EVR is best negative predictor of SVR

Holds true in HIV/HCV patients

Ferenci et al, J Hepatol, 2005; 43:425-433
Chronic HCV1 Algorithm
Ghany et al 2009 AASLD Practice Guidelines

1. Eligible patient
   Anti-HCV positive

2. Determine quantitative HCV RNA
   Determine HCV genotype: if genotype 1

3. More than portal fibrosis. Begin treatment

4. Liver biopsy suggested

5. Elastography?

6. No fibrosis or portal fibrosis only. Consider no treatment

7. Treat with peginterferon plus ribavirin, 1,000mg ≤ 75kg:
   1,200mg > 75kg

8. HCV RNA at week 4

9. Consider 72 weeks in those with clearance b/t 12-24 wks

10. Determine quantitative HCV RNA at week 12

11. Complete EVR (HCV RNA-) continues for a total of 48 weeks

12. Partial EVR (HCV RNA↓>2 log)

13. Determine qualitative HCV RNA at week 24 week

14. HCV RNA negative

15. HCV RNA positive

16. Qualitative HCV RNA at week 48 (end of treatment) and at Week 72 (to establish sustained virological response)
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- Potential new chemotherapeutics
Since his CD4 count is < 200 cells, antiretroviral therapy is our first priority. Which of the following HIV medications would be the best choice to use with Peg-IFN and Ribavirin?

- a) DDI
- b) AZT
- c) ABC
- d) TDF
**Risk of Mitochondrial Toxicity Associated with Concomitant Administration of NRTIs and Ribavirin in Patients Coinfected with HCV/HIV.**

<table>
<thead>
<tr>
<th>NRTI(s)</th>
<th>OR</th>
<th>0.01</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
<th>100</th>
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<tbody>
<tr>
<td>Didanosine</td>
<td>12.434</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Didanosine + Stavudine</td>
<td>8.000</td>
<td></td>
<td></td>
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<td>Stavudine</td>
<td>3.295</td>
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<td>Abacavir</td>
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<td>Lamivudine</td>
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<td>Zidovudine</td>
<td>.057</td>
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</tbody>
</table>

Sustained Virologic Response Differs by NRTI Used?

- In an ITT analysis, 20 of 70 individuals (29%) receiving abacavir and 83 of 186 (45%) treated with tenofovir achieved SVR.

- Using a NRTI backbone containing tenofovir was an independent predictor of SVR in a multivariate analysis.

- HCV genotype 2 or 3, baseline LDL cholesterol > 100 mg/dL, lower baseline HCV RNA, and undetectable baseline HIV viral load also predicted SVR.

- The association between abacavir use and lower SVR rate was mainly seen in patients with HCV RNA > 600,000 IU/mL, HCV genotype 1 or 4, and those who received a lower dose of ribavirin.

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HCV Genome

Hepatitis C virus RNA
9600 nt bases
Gene encoding precursor polyprotein

5' NTR
Structural proteins
non-structural proteins
3' NTR

p22 gp35 gp70 p7 p23 p70 p8 p27 p56/58 p68

C E1 E2 NS1 NS2 NS3 NS4A NS4B NS5A NS5B

Envelope glycoproteins proteases co-factors RNA polymerase
transmembrane protein RNA helicase interferon resists protein
nucleocapsid
New Therapies for HCV

- Albinterferon ➔ no better than PEG-IFN
- Taribavirin ➔ lower efficacy than RBV
- Immune-augmenting treatments (IL-10,11, vaccines etc)
- Protease inhibitors
- Polymerase inhibitors
**SPRINT-1: Boceprevir + PegIFN/RBV in Treatment-Naive GT1 Patients**

**Phase II Trial**
Treatment-naive patients with GT 1 HCV; all liver histology grades 
(N = 520)*

- PegIFN alfa-2b/RBV
- PegIFN alfa-2b/RBV* + Boceprevir 800 mg TID (n = 107)
- PegIFN alfa-2b/RBV* + Boceprevir 800 mg TID (n = 103)
- PegIFN alfa-2b/RBV* (n = 104)

**Week 4**
- PegIFN alfa-2b/RBV
- PegIFN alfa-2b/RBV + Boceprevir 800 mg TID (n = 103)
- PegIFN/RBV + Boceprevir 800 mg TID (n = 103)
- PegIFN/RBV* (n = 104)

**Week 28**
- PegIFN alfa-2b/RBV
- PegIFN alfa-2b/RBV* + Boceprevir 800 mg TID (n = 107)
- PegIFN/RBV + Boceprevir 800 mg TID (n = 103)
- PegIFN/RBV* (n = 104)

**Week 48**
- PegIFN alfa-2b/RBV
- PegIFN alfa-2b/RBV* + Boceprevir 800 mg TID (n = 103)
- PegIFN/RBV + Boceprevir 800 mg TID (n = 103)
- PegIFN/RBV* (n = 104)

*This is a 2-part study; part 2 includes 2 additional arms that are not included in this interim analysis.

SPRINT-1: Boceprevir + PegIFN/RBV in Treatment-Naive GT1 Patients (N=520)


*SVR12 for 48-wk arms and SVR24 for 28-wk arms.

Phase II Trial
All liver histology grades
**PROVE-1: Telaprevir Improves SVR in GT1 Patients**

<table>
<thead>
<tr>
<th>Treatment week</th>
<th>T12PR24 (N=79)</th>
<th>T12PR48 (N=79)</th>
<th>T12PR12 (N=17)</th>
<th>PR48 (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>64 (81)</td>
<td>64 (81)</td>
<td>10 (59)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>12</td>
<td>54 (68)</td>
<td>63 (80)</td>
<td>12 (71)</td>
<td>34 (45)</td>
</tr>
<tr>
<td>24</td>
<td>45 (57)</td>
<td>56 (71)</td>
<td>NA</td>
<td>43 (57)</td>
</tr>
<tr>
<td>48</td>
<td>NA</td>
<td>51 (65)</td>
<td>NA</td>
<td>35 (47)</td>
</tr>
<tr>
<td>Follow-up week 24, when SVR was assessed†</td>
<td>48 (61)</td>
<td>53 (67)</td>
<td>6 (35)</td>
<td>31 (41)</td>
</tr>
</tbody>
</table>

P=0.02 b/t T12PR24 and PR48  
P=0.51 b/t T12PR24 and T12PR48  
P=0.002 b/t T12PR48 and PR48

### PROVE 2: Telaprevir and Peginterferon With or Without Ribavirin for Chronic HCV Infection

<table>
<thead>
<tr>
<th>Week</th>
<th>Undetectable Viral RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T12PR24 (N=81)</td>
</tr>
<tr>
<td>Treatment week — no. (%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>56 (69)</td>
</tr>
<tr>
<td>12</td>
<td>59 (73)</td>
</tr>
<tr>
<td>24</td>
<td>57 (70)</td>
</tr>
<tr>
<td>48</td>
<td>NA</td>
</tr>
<tr>
<td>Follow-up week 24, when SVR was assessed†</td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>56 (69)</td>
</tr>
<tr>
<td>95% CI‡</td>
<td>58–79</td>
</tr>
</tbody>
</table>

Potential Evolution of HCV Therapy

- **1st Stage**: 1989-1998
  - 10% Sustained Virologic Response (SVR)
  - PEG-IFN + ribavirin

- **2nd Stage**: 1998-2001
  - 35% SVR
  - PEG-IFN + ribavirin

- **3rd Stage**: 2001-2008
  - 42-50% SVR
  - PEG-IFN + ribavirin + Pol Inhibitor

- **4th Stage**: 2009-2011
  - Estimated 65-70% SVR
  - PEG-IFN + ribavirin + Pol Inhibitor or Prot Inhibitor

- **5th Stage**: 2011-2014
  - Estimated 85-90% SVR
  - PEG-IFN + ribavirin + Pol Inhibitor + Prot Inhibitor
  - Oral immune modulators
  - Other direct antivirals

- **6th Stage**: 2014+
  - All Oral Therapy

- **Potential Evolution**: 10% to 85-90% SVR over time with the introduction of new therapies.
Patient DW: Follow Up Visit

- Returns to discuss HCV therapy
- Some baseline data
  - Wt 70 kg
  - Depression screen negative
  - CBC without anemia or neutropenia
  - TSH wnl

→ Prescribe weekly clinic-administered Peg-IFN and Ribavirin (1000 mg for <75 kg)
Patient DW: On Therapy

- He tolerates therapy fairly well
- Develops depression which is treated with Citalopram 20 mg/d
- Anemia with Hgb of 11.0 g/dl not requiring EPO
- CD4 count decreases but CD4% unchanged
High-Dose RBV and Epoetin: Study Design

- Prospective, randomized trial

Week 0

HCV1, Tx-naive, N = 150

Week 48

PegIFN + RBV ~13.3 mg/kg/d (n = 50)

PegIFN + RBV ~13.3 mg/kg/d + EPO (n = 50)

PegIFN + RBV ~15.2 mg/kg/d + EPO (n = 50)

Week 72

Off-treatment follow-up

High-Dose RBV and Epoetin: Virologic Response and Relapse

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PegIFN + RBV ~13.3 mg/kg/d</th>
<th>PegIFN + RBV ~13.3 mg/kg/d + EPO</th>
<th>PegIFN + RBV ~15.2 mg/kg/d + EPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETR</td>
<td>51</td>
<td>37</td>
<td>54</td>
</tr>
<tr>
<td>SVR</td>
<td>34</td>
<td>22</td>
<td>49*</td>
</tr>
<tr>
<td>Relapse</td>
<td>36</td>
<td>40</td>
<td>8*</td>
</tr>
</tbody>
</table>

*P < .05 vs weight-based ribavirin dosing groups.

Patient DW: HCV Response

- Baseline: 3.6 million \((6.5 \log_{10})\) IU/ml
- Week 4: 187,000 \((5.3 \log_{10})\) IU/ml
- Week 12: 945 \((2.9 \log_{10})\) IU/ml
- Week 24: <10 IU/ml

- WK 12 Hemoglobin drops from 14→10g/dl
- Wk 18 ANC drops to 750 mm³
# PEG-IFN Hematologic Dose Modification Guidelines

<table>
<thead>
<tr>
<th>Laboratory Value</th>
<th>Dose Reduction</th>
<th>Discontinue If:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &lt;750/mm³</td>
<td>135 μg</td>
<td>ANC &lt;500 mm³ → D/C Pegasys until ANC &gt;1000 mm³ then restart at 90 μg and monitor ANC</td>
</tr>
<tr>
<td>Platelets &lt;50,000/mm³</td>
<td>90 μg</td>
<td>Platelet count &lt;25,000/mm³</td>
</tr>
</tbody>
</table>

ANC = absolute neutrophil count.  
D/C = discontinue.  
Pegasys (Peginterferon alfa-2a) [package insert]. Nutley, NJ: Hoffmann-La Roche Inc.
# Ribavirin Dose Modification Guidelines

<table>
<thead>
<tr>
<th>Laboratory Values</th>
<th>Reduce Only Copegus Dose to 600 mg/Day* If:</th>
<th>Discontinue Copegus If:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin in patients with no cardiac disease</td>
<td>&lt;10 g/dL</td>
<td>&lt;8.5 g/dL</td>
</tr>
<tr>
<td>Hemoglobin in patients with history of stable cardiac disease</td>
<td>≥2 g/dL decrease in Hgb during any 4 week period treatment</td>
<td>&lt;12 g/dL despite 4 weeks at reduced dose</td>
</tr>
</tbody>
</table>

Copegus (Ribavirin, USP) [package insert]. Nutley, NJ: Hoffmann-La Roche Inc.
Question 7

What is the likelihood of SVR at 48 weeks in our patient?

a) 0%
b) 15%
c) 25%
d) 50%
e) 100%
HCV/HIV Summary 1

- Sexual transmission of HCV happens
- Active substance abuse not a contraindication to treatment
- Combined multidisciplinary approach is best
- Potential future role of elastography
- Genotype, VL, RBV exposure, race influence treatment response
Summary 2

• RVR is best *positive* predictor of SVR
• EVR is best *negative* predictor of SVR
• Promising new treatment options
• Escalating need for anti-HCV in HCV/HIV