HCV Patient Management: Translating Molecular Diagnostics into Clinical Care
Hepatitis C

- Family Flaviviridae
- Enveloped, RNA virus
  - Highly mutable genome
  - Rapid mutation in a hypervariable region of the genome coding for the envelope proteins and escapes immune surveillance by the host
- Occurs *in vivo* as a group of “quasispecies”
Hepatitis C

- Hepatitis C virus is the most common chronic blood-borne viral infection in North America.

- HCV is a major cause of chronic hepatitis.
  - Causes progressive hepatic fibrosis which leads to cirrhosis and an increased risk of hepatocellular carcinoma

- Chronic Hepatitis C is the leading indication for liver transplantation
# The Clinical Burden of Viral Hepatitis

<table>
<thead>
<tr>
<th>Virus</th>
<th>Geographical spread</th>
<th>Transmission</th>
<th>Symptoms</th>
<th>Long-term prognosis</th>
<th>Chronic infections</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&lt;sup&gt;1,6,7&lt;/sup&gt;</td>
<td>Endemic in Africa, Asia, Central and South America</td>
<td>Faecal–oral</td>
<td>Fever, malaise, diarrhoea, nausea, Jaundice, cholestasis</td>
<td>Recovery within 6 months; no chronic form</td>
<td>N/A</td>
<td>Treatment is usually not required</td>
</tr>
<tr>
<td>B&lt;sup&gt;2,6,7&lt;/sup&gt;</td>
<td>Africa, Asia, Central and South America</td>
<td>Percutaneous or permucosal</td>
<td>Dark urine, extreme fatigue, nausea, vomiting and abdominal pain, cholestasis</td>
<td>Cirrhosis, liver failure, hepatocellular carcinoma (HCC)</td>
<td>350 million</td>
<td>Vaccine gives &gt;95% protection. <strong>Acute</strong>: No specific treatment. <strong>Chronic</strong>: Interferon (IFN), nucleos(t)ide analogues</td>
</tr>
<tr>
<td>C&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Africa, central and south-eastern Asia, South America</td>
<td>Percutaneous or permucosal</td>
<td>Asymptomatic (50-90%)</td>
<td>Cirrhosis, liver failure, HCC</td>
<td>130–170 million</td>
<td>Pegylated-IFN + ribavirin (RBV); direct-acting antivirals (DDAs)</td>
</tr>
<tr>
<td>D&lt;sup&gt;4,6,7&lt;/sup&gt;</td>
<td>South America, South Pacific, western Africa, Mediterranean, Middle East and central Asia</td>
<td>Percutaneous or permucosal</td>
<td>Jaundice, anorexia, nausea and vomiting and fever, cirrhosis</td>
<td>Cirrhosis, liver failure, HCC; HBV co- or super-infection; asymptomatic</td>
<td>10 million</td>
<td>HBV vaccine protects against HDV. Otherwise: treatment with IFN</td>
</tr>
<tr>
<td>E&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Endemic in Asia, Middle East, Africa and Central America</td>
<td>Faecal–oral</td>
<td>Jaundice, anorexia, nausea and vomiting and fever</td>
<td>No chronic form</td>
<td>N/A</td>
<td>Treatment is rarely required</td>
</tr>
</tbody>
</table>

Hepatitis C – Impact and Challenges

• **Major public health problem**
  – A leading cause of chronic liver disease\(^1\)
  – Global epidemic with regional variance

• **Uncertainty around transmission**
  – Intravenous or nasal drug use, mother-to-child transmission, medical or surgical procedures, sexual transmission
  – 30% of infections are unexplained\(^2\)

• **Often a ‘silent’ disease**
  – Asymptomatic in 50–90% of cases\(^3\)
  – Over 30% have normal enzymes
  – Screening based on exposure to transmission risk factors\(^4\)

• **Progressive disease**
  – High percentage of patients will develop chronic infection (55–85%)\(^5,6\)

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HCV Is Curable!

- The Goals of HCV treatment are different to those of HBV and HIV!
Patterns of Virologic Response Related to Triple Therapy

The goal of antiviral therapy is to cure hepatitis C via a sustained elimination of the virus. This is achieved if HCV RNA remains negative six months after end of treatment (SVR).

1) Yee et al., 2012, The American Journal of GASTROENTEROLOGY
2) DAA: direct-acting antiviral; PegIFN: peginterferon; RBV: ribavirin
Why is SVR So Important?

SVR Equivalent to Viral Cure

- Nearly 100% of patients who achieve SVR remain undetectable during long-term follow-up\(^1-4\)

<table>
<thead>
<tr>
<th>Duration of Follow-up</th>
<th>Patients With SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.9 yrs (mean)</td>
<td>99(^1)</td>
</tr>
<tr>
<td>3.4 yrs (median)</td>
<td>99(^2)</td>
</tr>
<tr>
<td>3.3 yrs (median)</td>
<td>100(^3)</td>
</tr>
<tr>
<td>5.4 yrs (median)</td>
<td>100(^4)</td>
</tr>
</tbody>
</table>

Improved Efficacy of Treatments for HCV

- **1991**: Standard Interferon (6%)
- **1995**: Ribavirin (16%)
- **1998**: Peginterferon (34%)
- **2001**: PegIFN 12 mo (42%)
- **2002**: PegIFN/R 12 mo (39%)
- **2011**: DAA PegIFN/R/DAA 6–12 mo (75%)

Sustained Response Chart
PEG IFN/r HCV Treatment Guidelines

Evolution of HCV Therapy

The aim will be an interferon-free, oral treatment that eradicates the virus in every patient without side effects!

- Once daily dosing
- Pan-genotype
- No concern about resistance
2011 – A New Era in HCV Therapy

Approval of first specific HCV antivirals (DAA): HCV protease inhibitors

- Triple therapy will become the new standard therapy
- Approved for genotype 1 infected patients
- SVR rates ↑ in treatment-naïve and in treatment-experienced patients

But
- Side effects
- Resistance development
- Complicated treatment algorithm
HCV RNA is THE Key Indicator

- Analysis of HCV RNA levels in plasma or serum is critical for assessing the efficacy of antiviral therapy for chronic hepatitis C virus (HCV) infection.

- The primary goal of anti-HCV therapy is achievement of a sustained virologic response (SVR), traditionally defined as undetectable serum or plasma HCV RNA 24 weeks following completion of treatment.

- The use of on-treatment HCV RNA measurements to guide treatment duration, termed response-guided therapy (RGT), has become a key component of patient management.

- During HCV treatment, a rapid HCV RNA decline may justify a shorter treatment duration without significantly compromising efficacy. Conversely a slow HCV RNA decline may warrant an extended duration of treatment to maximize the chances of achieving SVR, and little or no HCV RNA decline may warrant early treatment cessation due to futility.

_Harrington et al, Hepatology 2012_
**DAA – Clinical Decision Points**  
**Stopping Rules / Truncated Therapy Rules**

**Stop** triple therapy if HCV RNA is...

- $>1000 \text{ IU/mL} \ @ \ wk \ 4 \ or \ wk \ 12 \ (TVR^1)$
- $\geq 100 \text{ IU/mL} \ @ \ wk \ 12 \ (BOC^2)$
- Detectable $@$ wk 24 (TVR & BOC)

**Shorten** therapy by 20/24 wks if HCV RNA is...

- Undetectable $@$ wk 4 and wk 12/24 (TVR / BOC)

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1) TVR: Telaprevir  
2) BOC: Boceprevir
New HCV Drugs
Implications for HCV RNA Measurement

Stop Rules
Measure precisely, accurately, and with high sensitivity
➢ To reduce uncertainty of stopping or continuing therapy

Therapy Duration Rules
Measure with high sensitivity enabling detection of minimal residual viremnia
➢ To provide confidence that the virus is indeed cleared and that therapy can be truncated if HCV RNA is “undetectable”
HCV RNA Assays

HCV RNA assays: Does sensitivity matter?

YES!

In particular for response-guided therapy
## Controversy 1: Sensitivity of HCV RNA Assays

<table>
<thead>
<tr>
<th>Supplier</th>
<th>Assay</th>
<th>Limit of Detection* (IU/ml)</th>
<th>Lower Limit of Quantification* (IU/ml)</th>
<th>Upper Limit of Quantification* (IU/ml)</th>
<th>Reported Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>Abbott RealTime HCV¹</td>
<td>12</td>
<td>12</td>
<td>~9.3/8.8</td>
<td>“Reported value”, detected not detected</td>
</tr>
<tr>
<td>Roche</td>
<td>Roche High-Pure-System/COBAS® TaqMan assay v2 (HPS)²</td>
<td>~9.3/8.8</td>
<td></td>
<td></td>
<td>“Reported value”, detected &lt;25 IU/mL, not quantifiable not detected</td>
</tr>
<tr>
<td>Roche</td>
<td>COBAS® Ampliprep/COBAS® TaqMan® HCV Quantitative Test, version 2.0³</td>
<td>15</td>
<td>43</td>
<td>6.9 x 10⁷</td>
<td>“Reported value” IU/mL, detected &lt;43 IU/mL, not quantifiable not detected</td>
</tr>
<tr>
<td>Roche</td>
<td>COBAS® Viral QuanT® HCV RNA 1.0 (for use on kPCR system)⁵</td>
<td>15</td>
<td>15</td>
<td>10⁸</td>
<td>“Reported value” IU/mL, detected &lt; 15 IU/mL, detected not detected</td>
</tr>
<tr>
<td>Qiagen</td>
<td>artus HCV QS-RGQ⁶</td>
<td>36.2</td>
<td>67.6</td>
<td>1.8 x 10⁷</td>
<td>Not available</td>
</tr>
</tbody>
</table>

* Performance claims as per respective package inserts or websites. 1. Abbott RealTime HCV (LN 4J86; 51-602124/R4); 2. Roche High-Pure-System/COBAS® TaqMan assay v2 (HPS); 3. Roche: COBAS TaqMan HCV, 03543544001-01; 4. COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, version 2.0; 5. Siemens: http://www.medical.siemens.com; 6. Qiagen: artus HCV QS-RGQ, LN 4518366, 1060924EN

Protease inhibitors approval trials were conducted with Roche HPS/COBAS TaqMan assay v2 - a manual assay not commonly used in routine labs. Need to translate cutoffs created with HPS into cutoffs for automated assays.
Simulation of RGT duration based on Week 4 result: HPS vs ART*

At Week 4, 197/261 (75.5%) samples were undetectable by HPS whereas 129/261 (49.4%) were undetectable and 79/261 (30.3%) <12 IU/mL detectable by ART, leading to a different determination of RVR in 68/261 (26.1%) of cases.

PILLAR study data presented at EASL 2012 by C. Sarrazin
RVR, HCV RNA undetectable at Week 4
Evaluation of low end sensitivity

Tab. 1: (A) Results of five different HCV quantification assays in extremely low viremic range of diluted PEI standards at nominal dilution of 25 IU, 10 IU and 5 IU per ml. (B) Performance for 3rd WHO standard dilutions, respectively.

(A) PEI standard

<table>
<thead>
<tr>
<th>Assay</th>
<th>25 IU/ml</th>
<th>10 IU/ml</th>
<th>5 IU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>RealTime HCV</td>
<td>31, 32, 41</td>
<td>&lt;12, &lt;12, &lt;12</td>
<td>&lt;12, &lt;12, nd</td>
</tr>
<tr>
<td>artus HCV QS-RGQ</td>
<td>&lt;36, 91, 98</td>
<td>&lt;36, nd, nd</td>
<td>&lt;36, nd, nd</td>
</tr>
<tr>
<td>Versant kPCR HCV</td>
<td>46, 50, 100</td>
<td>nd, nd, nd</td>
<td>nd, nd, nd</td>
</tr>
<tr>
<td>CAP/CTM.HCV</td>
<td>&lt;43, &lt;43, &lt;43</td>
<td>&lt;43, &lt;43, &lt;43</td>
<td>&lt;43, &lt;43, nd</td>
</tr>
<tr>
<td>CAP/CTM.HCV v2</td>
<td>&lt;15, &lt;15, 21</td>
<td>&lt;15, nd, nd</td>
<td>nd, nd, nd</td>
</tr>
</tbody>
</table>

(B) WHO standard

<table>
<thead>
<tr>
<th>Assay</th>
<th>25 IU/ml</th>
<th>10 IU/ml</th>
<th>5 IU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>RealTime HCV</td>
<td>15, 28, 33</td>
<td>&lt;12, &lt;12, &lt;12</td>
<td>&lt;12, &lt;12, nd</td>
</tr>
<tr>
<td>artus HCV QS-RGQ</td>
<td>185, 150, nd</td>
<td>&lt;36, nd, nd</td>
<td>&lt;36, nd, nd</td>
</tr>
<tr>
<td>Versant kPCR HCV</td>
<td>23, 49, 50</td>
<td>23, &lt;15, &lt;15</td>
<td>&lt;15, nd, nd</td>
</tr>
<tr>
<td>CAP/CTM.HCV</td>
<td>&lt;43, &lt;43, &lt;43</td>
<td>&lt;43, &lt;43, &lt;43</td>
<td>nd, nd, nd</td>
</tr>
<tr>
<td>CAP/CTM.HCV v2</td>
<td>18, &lt;15, nd</td>
<td>nd, nd, nd</td>
<td>nd, nd, nd</td>
</tr>
</tbody>
</table>

* nd = not detected, - = invalid
Case #1

• 55 year old Caucasian female with GT 1 HCV
  – Naïve to therapy
  – IL28B CT
  – Pretreatment viral load 1,400,000
  – F_2 fibrosis

• HCV therapy initiated with Telaprevir Ribavirin and Peginterferon

Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.
Case #1

<table>
<thead>
<tr>
<th>Time Point</th>
<th>HCV RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>1,400,000</td>
</tr>
<tr>
<td>Week 4</td>
<td>Detected/Below Limit Of Quantification (BLOQ)</td>
</tr>
<tr>
<td>Week 12</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Week 24</td>
<td>Undetectable</td>
</tr>
</tbody>
</table>

Is this patient eligible for RGT?

Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.
Assessing eRVR
(extended rapid virologic response)

Telaprevir
• Check HCV RNA at weeks 4 and 12
  – If HCV RNA is undetectable at both time points, patient is eligible for RGT
  – 24 weeks total therapy

Boceprevir
• Check HCV RNA at weeks 8 and 24
  – If HCV RNA is undetectable at both time points, patient is eligible for RGT
  – 28 weeks total therapy for naïve patients
  – 36 weeks total therapy for prior relapsers and partial non-responders

Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.
Detectable/BLOQ ≠ Undetectable?

Clinical Relevance of Detectable but Not Quantifiable Hepatitis C Virus RNA During Boceprevir or Telaprevir Treatment

Patrick R. Harrington, Wen Zeng, and Lisa K. Naeger

• Analyzed boceprevir and telaprevir clinical trial data

• Detectable/BLOQ were reported for 10-20% of all on-treatment HCV RNA measurements

Harrington et al, Hepatology 2012
Detectable/BLOQ ≠ Undetectable!

- Subjects with Detectable/BLOQ at RGT specific time points had ~20% lower SVR rate compared to patients with undetectable HCV RNA
- This patient should receive a total of 48 weeks of therapy for optimum chance at SVR
Case #1 Summary

• **Detectable means Detectable!**
  – Detectable/BLOQ should not be used to make RGT decisions
  – SVR rates ~20% lower when BLOQ/detectable used instead of undetectable

• Current HCV treatment guidelines recommend using assays with LOQ of <25IU/ml and LOD 10-15IU/ml for viral load monitoring

• This recommendation is a critical component of HCV treatment as less sensitive assays in the case of this patient would suggest shortened treatment when this is not beneficial to the patient

Courtesy of Sid Barritt, UNC Hepatology Dept.
### Case # 2

<table>
<thead>
<tr>
<th>Time point</th>
<th>HCV RNA</th>
<th>Lab</th>
<th>LLOQ</th>
<th>LLOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>1,800,000</td>
<td>A</td>
<td>12 IU/mL</td>
<td>7.3 IU/mL</td>
</tr>
<tr>
<td>Week 8</td>
<td>undetectable</td>
<td>B</td>
<td>25 IU/mL</td>
<td>9.3 IU/mL</td>
</tr>
<tr>
<td>Week 24</td>
<td>undetectable</td>
<td>A</td>
<td>12 IU/mL</td>
<td>7.3 IU/mL</td>
</tr>
</tbody>
</table>

- Is this patient eligible for RGT?

Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.
HCV RNA levels and Lab Assays

• Analysis of HCV RNA levels is critical for assessing efficacy of therapy for chronic HCV infection.
• RGT guidelines for boceprevir and telaprevir are based on undetectable viral load and specific time points.
• Protocols for other trials have incorporated secondary endpoints based on achieving <LLOQ viral load rather than an undetectable viral load.

<table>
<thead>
<tr>
<th>Assay Name</th>
<th>LLOQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche COBAS® Amplicor® HCV Test</td>
<td>43 IU/mL</td>
</tr>
<tr>
<td>Roche COBAS® TaqMan® HCV Test, v2.0</td>
<td>25 IU/mL</td>
</tr>
<tr>
<td>Abbott RealTime HCV Assay</td>
<td>12 IU/mL</td>
</tr>
</tbody>
</table>

Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.
Case # 2

- Possible that week 8 HCV RNA assay performed by a less sensitive test may yield a result that would be detectable/BLOQ in another more sensitive assay
- Possible risk for relapse, lower SVR rate as in case #1
- Discussion of risks and benefits with patient

Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.
Case #2 Summary

• Know your lab and HCV RNA assay characteristics
  – Some labs may still use older less sensitive assays
  – Residual viremia at RGT time points may lead to increased relapse rates and reduces SVR

Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.
HCV RNA assays: Does Precision matter?

YES!

*In particular for response-guided therapy*
Controversy 2: Precision Assay Comparison Study

Study Design
Investigate *low end precision, accuracy* and *sensitivity* across different HCV genotypes at clinical decision points of new DAAs comparing

- RealTime HCV
- Roche CAP/CTM HCV 1.0
- Roche CAP/CTM HCV 2.0
- QIAGEN *artus* HCV QS-RGQ
- Siemens HCV kPCR

Naeth et al., ESCV 2012
Precision at clinical decision point

Precision around Boceprevir Stopping Rule\(^4\)

- **HCV (IU/mL)**:
  - 500
  - 400
  - 300
  - 200
  - 100
- **Percentage**:
  - ART: 23%
  - CAP/CTM: 47%

Precision around Telaprevir Stopping Rule\(^5\)

- **HCV (IU/mL)**:
  - 2000
  - 1500
  - 1000
  - 500
- **Percentage**:
  - ART: 17%
  - CAP/CTM: 29%

\((-\) Treatment futility decision point)
HCV panels targeting 700 IU/ml and 80 IU/mL were tested on four separate occasions at six different commercial clinical laboratories.

<table>
<thead>
<tr>
<th>Assay</th>
<th>HCV Target Concentration (IU/mL)</th>
<th>Mean Viral Load (IU/mL)</th>
<th>Range (IU/mL)</th>
<th>Standard Deviation (IU/mL)</th>
<th>% Coefficient of Variation (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott RealTime</td>
<td>80</td>
<td>58</td>
<td>43 - 77</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>700</td>
<td>585</td>
<td>414 - 777</td>
<td>113</td>
<td>19</td>
</tr>
<tr>
<td>Roche CAP/CTM HCV v1</td>
<td>80</td>
<td>131</td>
<td>61 - 278</td>
<td>68</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>700</td>
<td>1617</td>
<td>964 - 3050</td>
<td>678</td>
<td>42</td>
</tr>
</tbody>
</table>

1. Adapted from Lucic et al., abstract at ESCV 2012
Panel precision 100 IU/ml

Fig. 3: Box Plot illustration of inter-assay variation analysis: 10 replicates of each 2 clinical samples (Genotype 1A + 1B) were analysed with all five quantitative HCV assays. Coefficients of variation are illustrated below the bars.
Case #3

• 48 year old Caucasian male with HCV cirrhosis
  – MELD 12
  – No decompensation events
  – Prophylactically listed for liver transplantation
  – Relapser to prior therapy, IL28B CT

• HCV therapy initiated with Telaprevir Ribavirin and Peginterferon

Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.
**Case #3**

<table>
<thead>
<tr>
<th>Time point</th>
<th>HCV RNA</th>
<th>HGB</th>
<th>Platelets</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>2,800,000</td>
<td>13</td>
<td>75,000</td>
<td>RBV 1000, P 180</td>
</tr>
<tr>
<td>Week 1</td>
<td></td>
<td>10</td>
<td>40,000</td>
<td>RBV 600, P 135</td>
</tr>
<tr>
<td>Week 2</td>
<td></td>
<td>9</td>
<td>35,000</td>
<td>RBV 400, P 90</td>
</tr>
<tr>
<td>Week 4</td>
<td>1034</td>
<td>8</td>
<td>35,000</td>
<td>RBV held, P 90</td>
</tr>
</tbody>
</table>

This patient has had >3 log drop in HCV RNA, should we continue?

*Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.*
Case #3

- All medications stopped

- While this patient has had a significant drop in the HCV RNA, viral load remains above the threshold for continuing treatment

- Likely represents protease resistant virus, plus innate poor response to Interferon and Ribavirin

Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.
Case #3

• Importance of adherence to stopping rules
  – Patients who do not respond to 1st generation protease inhibitors carry a dominant strain of protease resistant virus at the time of breakthrough
  – Wild type strain reemerges months after therapy discontinued
  – Return of wild type strain may be an indication that patients may be re-challenged in the future with multidrug cocktails that include protease inhibitors.

Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.
Case #3 Summary

• Stopping rules for futility are important
  – Reduce exposure and expense for patients when chance for SVR is minimal
  – May preserve chance for SVR with future therapies
• Important feature of viral load assay is precision across the full linear range especially around TEL and BOC stopping points

Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.
Clinical & Economic Implications Of A Non-Ideal Test

Any inappropriate decision would waste resources

* Based on a population size of 1000 patients on treatment. Implications of treatment futility such as risk for progression to cirrhosis, 2nd line therapy etc. are not considered. Direct treatment costs until wk 48 based on average European tariffs with estimated weekly costs of 1,000 €. Graph: Abbott
Case # 4

- 60 year old African American female
  - Completed 48 weeks of boceprevir based triple therapy

<table>
<thead>
<tr>
<th>Time Point</th>
<th>HCV RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>400,000 IU/mL</td>
</tr>
<tr>
<td>Week</td>
<td>150 IU/mL</td>
</tr>
<tr>
<td>Week 24</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Week 48</td>
<td>Undetectable</td>
</tr>
</tbody>
</table>

At what time point can we assess SVR?

Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.
Case # 4

- Traditional measure of SVR has been six months (24 weeks) after the completion of therapy.
- New push for faster recognition of cure
  - 12 week assessment of SVR as good as 24 weeks

<table>
<thead>
<tr>
<th>Posttreatment Follow-up</th>
<th>Patients*</th>
<th>SVR†</th>
<th>PPV‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week +4§</td>
<td>252</td>
<td>242</td>
<td>96.0% (93.1-98.1)</td>
</tr>
<tr>
<td>Week +12</td>
<td>409</td>
<td>408</td>
<td>99.7% (99.1-100)</td>
</tr>
<tr>
<td>Week +24</td>
<td>408</td>
<td>408</td>
<td>100%</td>
</tr>
</tbody>
</table>

Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.

Case #4 Summary

• Lesson from Determining SVR at week 12 equivalent to week 24.
  – Patients (and clinical trials) can find out results earlier

Courtesy of Dr. Sid Barritt, UNC Hepatology Dept.
HCV Lifecycle – Lots of Potential “Druggable” Options

Co-Pilot (M12-746) Study: ABT-450/r+ABT-333

Arm 1: Treatment-naïve (N=19) - ABT-450/r 250/100 mg QD + ABT-333 400 mg BID + RBV

Arm 2: Treatment-naïve (N=14) - ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + RBV

Arm 3: Prior P/R non-responders (N=17) - ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + RBV

Follow Up Period

Poordad et al, 47th EASL; Barcelona Spain, April 18-22 2012; Abst 1399
Co-Pilot Study: Virologic Results

Poordad et al, 47th EASL; Barcelona Spain, April 18-22 2012; Abst 1399
GS-7977 ELECTRON - Trial Design

Gane et al., 47th EASL; Barcelona Spain, 2012 Poster # 1113
### GS-7977 ELECTRON Study: Virologic Response

**Patients with HCV RNA < LOD Over Time, n/N (%)**

<table>
<thead>
<tr>
<th></th>
<th>GT 2/3 Treatment-naïve 8 wks (N=10)</th>
<th>GT 1 Null Responders 12 wks (N=10)</th>
<th>GT 1 Treatment-naïve 12 wks (N=25)</th>
<th>GT 2/3 Treatment-experienced 12 wks (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>6/10 (60)</td>
<td>1/10 (10)</td>
<td>7/25 (29)</td>
<td>8/25 (32)</td>
</tr>
<tr>
<td>Week 2</td>
<td>10/10 (100)</td>
<td>7/10 (70)</td>
<td>17/24 (71)</td>
<td>21/25 (84)</td>
</tr>
<tr>
<td>Week 4</td>
<td>10/10 (100)</td>
<td>10/10 (100)</td>
<td>25/25 (100)</td>
<td>25/25 (100)</td>
</tr>
<tr>
<td>EOT</td>
<td>10/10 (100)</td>
<td>9/9 (100)</td>
<td>25/25 (100)</td>
<td>21/21 (100)</td>
</tr>
<tr>
<td>SVR 4</td>
<td>10/10 (100)</td>
<td>1/9 (11)</td>
<td>22/25 (88)</td>
<td>12/15 (80)</td>
</tr>
<tr>
<td>SVR 8</td>
<td>10/10 (100)</td>
<td>1/9 (11)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SVR 12</td>
<td>10/10 (100)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Gane et al., 47th EASL; Barcelona Spain, 2012 Poster # 1113
Summary

- The new HCV drugs represent hope for millions of patients who carry the virus.

- Decisions to stop or continue treatment are crucial in determining the outcome and are guided exclusively by the RNA viral load measurements.

- Early stopping helps avoid toxicity in patients unlikely to achieve SVR; by contrast, continuing treatment for late responders, offers more patients a chance at viral clearance and cure.

- Genotype determination helps to assess a patient’s eligibility for new DAA therapy. Subtype determination of 1a from 1b may be used to predict likelihood of development of resistance.