Retreatment for DAA Failures and Resistance

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Case

62 WM with HCV GT1a and cirrhosis (CPT A5); prior breakthrough on PEG/RBV+TVR. Treatment complicated by severe anemia and neutropenia:

• Week 8: Required transfusion, RBV dose reduction
• Week 12: PEG dose reduction, GCSF
• HCV RNA 127 IU/ml at week 4; viral BT at week 26

• Treatment discontinued
  • Follow-up HCV RNA 2.7 million

Re-treated in a study (12 weeks of SOF/LDV).

• Week 4: HCV RNA <25 IU/mL (detected)
• All subsequent HCV RNA TND (week 6 and on)
• SVR4 f/u: HCV RNA +
Case

Re-re-treated with SOF/LDV for 24wks (no RBV), also in a study.

- HCV RNA UD at week 4
  - undetectable for remainder of course
- SVR4 f/u: AST/ALT 45/67....
  - HCV RNA: 253,000 IU/mL

What to do now?

- Updated labs:
  - PLT 61, Hgb 13.8 g/dL
  - AST/ALT: 59/59, TB 0.7, DB 0.3, ALB 4.1, INR 1.0
  - Cr 1.29 (prior 1.08)
  - HCV RNA 1.2 million

- U/S: Nodular liver, no lesions. 12mm PV, 15cm spleen. No ascites. Non-occlusive R PVT.

- EGD: grade 1 esophageal varices
## HCV Genotypic Resistance Sequencing

### Table: HCV GenoSure® NS3/4A

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Region</th>
<th>Drug Resistance Associated Mutations Detected</th>
<th>Assessment</th>
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</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>Boceprevir</td>
<td>Victrelis</td>
<td>NS3</td>
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<td>NS4A</td>
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<td>NS4A</td>
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### Summary of All Mutations Observed

<table>
<thead>
<tr>
<th>Region</th>
<th>Genotype</th>
<th>Summary of All Mutations Observed</th>
</tr>
</thead>
</table>
Considerations in patients who failed a DAA-based regimen

1. Was initial therapy sub-optimal (or sub-maximal)?
   • IFN+DAA vs. DAA
   • Duration and RBV use?

2. Stage of liver disease/host characteristics

3. Indications of other problems
   • Adherence?
   • Significant drug interactions?
     • Terrault N. #94 AASLD 2015.

4. Immunosuppression?

5. What specific medication classes were used
   • What role dose resistance play?
No problem!

Re-treatment of IFN + PI failures

![Graph showing SVR12 (%) for different treatment durations and regimens.]

Afdahl N. NEJM 2014.
Why give yourself a headache?

- PI failure = PEG/RBV + PI
- Resistance testing results not available
  - Majority did not have baseline testing
- Prior PI failure was associated with a decreased SVR rate
  - OR: 0.4 (0.2-0.9)

Are patients who failed SOF + P/R different?

- 49% failed SOF/P/R
- 29% with cirrhosis
- Viral relapse was in a GT3 female

14/14 SOF/RBV failures achieved SVR12 with SOF/LDV for 12 weeks.


Wyles D. Hepatology 2015.
HCV RESISTANCE
The HCV lifecycle favors resistance development...but not persistence.

**Favors Resistance**

1. High viral turnover rate
   - $10^{12}$ virions/day
2. Error-prone RNA polymerase
   - ~1 error per 10,000 bases
   - Involved twice in replication
3. No overlapping reading frames
4. Moderate rate of infected hepatocyte turnover

**Lack of Persistence**

1. No DNA intermediate
   - Contrast to integrated HIV
   - Contrast to HBV cccDNA
2. No long-lived cellular reservoir known
   - Contrast latently infected HIV + CD4 cells
   - Contrast to transfer of HBV cccDNA in dividing cells
3. There are exceptions!

Resistant variants pre-exist in all patients
Available Resistance Testing (US)

• Ultra-deep (or NGS) vs population (Sanger)
  • What is available:
    1. LabCorp/Monogram Biosciences
       • NGS with 10% detection level reported
    2. Quest Diagnostics
       • RT-PCR with DNA sequencing

• Both assays now available for GT1 (1a and 1b) and GT3

• What matters in the clinic?

http://www.monogrambio.com/content/hcv-ns5a-testing
### Drug Resistance Associated Variants* Detected

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic Name</th>
<th>Region</th>
<th>Drug Resistance Associated Variants* Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir</td>
<td>Daklinza</td>
<td>NS5A</td>
<td>M28V</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>Zepatier</td>
<td>NS5A</td>
<td>M28V</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>Harvoni</td>
<td>NS5A</td>
<td>M28V</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>Viekira Pak</td>
<td>NS5A</td>
<td>M28V</td>
</tr>
</tbody>
</table>

#### Important Definitions

- **Resistance Possible** - Resistance Associated Variants (RAVs) detected that (a) represent naturally-occurring polymorphisms or treatment-emergent variants associated with reductions in sustained virologic response (SVR) rates, (b) emerge during direct-acting antiviral (DAA)-treatment or relapse, and/or (c) may confer reductions in susceptibility based on in vitro data. Refer to prescribing information for specific details regarding the impact of these variants on treatment response in defined patient populations and when administered in combination with other antiviral agents.
- **None/Undetermined** - None; no RAVs detected. Undetermined; variants detected that have a subtle or uncertain impact on DAA-treatment responses.

**Notes:**

- All mutations are reported relative to the HCV genotype/subtype specific reference H77.
- Assessment of drug susceptibility is based on detected mutations and is interpreted using a rules-based algorithm (version 4).
- Naturally-occurring polymorphisms may impact the emergence of resistance, leading to failure of DAA combination therapy.
- Naturally-occurring DAA resistance-associated polymorphisms identified at baseline may impact SVR if the treatment regimen, or adherence, is suboptimal. The impact of these polymorphisms may vary in treatment-naive and treatment-experienced patients and with varying disease states (e.g. non-cirrhotic vs cirrhotic).
- Reduced susceptibility to any one component of a DAA-containing regimen may be overcome by the activity of the other components of the regimen and/or longer treatment duration.
- Treatment emergent RAVs may persist for prolonged periods of time and may impact subsequent treatment regimens.

#### Summary of All Variants Observed

|--------|----------|-----------------------------------------------|

**Comments:** NS5A RAVs at position(s) 28, 30, 31 or 93 DETECTED. If considering an NS5A inhibitor-containing regimen, please refer to the prescribing information, or current guidelines, to determine the appropriate treatment regimen and duration.
## Characteristics of HCV antiviral classes

<table>
<thead>
<tr>
<th>Class</th>
<th>Antiviral Potency</th>
<th>Genotype Activity</th>
<th>Resistance barrier</th>
<th>FDA Approved</th>
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<tbody>
<tr>
<td>NS5B Nucleoside/tide</td>
<td>++ to ++++</td>
<td>1-6</td>
<td>Very High</td>
<td><em>Sofosbuvir</em> (2013)</td>
</tr>
<tr>
<td>NS5B Non-nucleoside</td>
<td>++ to +++</td>
<td>1</td>
<td>Very low</td>
<td><em>Dasabuvir</em> (2014)</td>
</tr>
</tbody>
</table>
Decay of PI resistant variants

91% of nonSVR with resistance

1a: R155K +/- Q80K
1b: D168V

Median (95% CI) time to loss of mutation

- GT1a: 36 (31.7–40.9) weeks
- GT1b: 24 (19.6–36.1) weeks

Proportion of patients with mutations (%)
NS3 Resistance testing- where does it fit?

Baseline:
• *Significant* baseline NS3 RAVs are rare
  • Routine baseline testing not needed
• There is no clear impact of Q80K on SOF+SMV when using approved durations
  • Data are lacking with 24 weeks in cirrhotics

Retreatment:
• Well studied non-PI containing options are available
• Role in the future to determine duration in retreatment with triple DAA regimens?
NS5A Resistance Overview

• Baseline polymorphisms associated with resistance are relatively prevalent (~10%)
  • They impact responses in *select settings*

• Currently available NS5A inhibitors suffer from broad cross-resistance at key positions
  • Q30R, L31M/V, Y93H/N

• NS5A variants persist for prolonged periods

• Selected NS5A RAVs impact re-treatment responses
NS5A resistance terminology

The prevalence of baseline NS5A resistance varies widely in the literature.

• RAPs: Resistance associated polymorphisms
  • ANY non-consensus amino acid at a site associated with resistance to ANY NS5A inhibitor

• Class RAVs: Resistance associated variants
  • Specific amino acid substitutions associated with resistance to ANY NS5A inhibitor

• Drug-specific RAVs:
  • Specific amino acid substitutions associated with resistance to a particular NS5A inhibitor
    • Different fold-change cut-offs have been used (2x, 5x, 10x etc)
Baseline NS5A RAVs: A moving target

### Broad cross-resistance with “early generation” NS5As

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<thead>
<tr>
<th>Fold-change</th>
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<td><strong>LDV</strong></td>
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</tr>
<tr>
<td>M28T</td>
<td>20x</td>
<td>&gt;100x</td>
</tr>
<tr>
<td>Q30R</td>
<td>&gt;100x</td>
<td>&lt;3x</td>
</tr>
<tr>
<td>L31M/V</td>
<td>&gt;100x/ &gt;100x</td>
<td>&lt;10x</td>
</tr>
<tr>
<td>Y93H/N</td>
<td>&gt;1,000x/ &gt;10,000</td>
<td>&lt;10x</td>
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<tr>
<td>L31V</td>
<td>&gt;1000x/ &gt;10,000x</td>
<td>&lt;10x</td>
</tr>
<tr>
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<td>Y93H/N</td>
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<tr>
<td>L31M/V</td>
<td>&gt;100x/ &gt;100x</td>
<td>&lt;3x</td>
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<tr>
<td>Y93H/N</td>
<td>&gt;1,000x/ &gt;10,000x</td>
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<td>L31V</td>
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<td>Y93H/N</td>
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<tr>
<td>Y93H/N</td>
<td>&lt;10x</td>
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Expanded analysis of baseline NS5A RAVs in subjects treated with SOF/LDV

SVR12 to guidelines recommended regimens of LDV/SOF by LDV RAV* status

*LDV RAVs @1% cutoff

Zeuzem S. #91 AASLD 2015.
Impact of baseline NS5A RAVs in patients with cirrhosis treated with SOF/LDV

Impact of subtype and fold-change

**SVR12 (%)**

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<thead>
<tr>
<th></th>
<th>Subtype</th>
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<th>&gt;100x</th>
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<td>1a</td>
<td>No RAVs</td>
<td>98</td>
<td>70</td>
<td>12</td>
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<td></td>
<td>RAVs</td>
<td>97</td>
<td>193</td>
<td>15</td>
</tr>
<tr>
<td>1b</td>
<td>No RAVs</td>
<td>85</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>RAVs</td>
<td>96</td>
<td>100</td>
<td>67</td>
</tr>
</tbody>
</table>

Sarrazin C. #P0773. EASL 2015.
Impact of baseline NS5A RAVs in GT1a patients treated with GZP/EBR

Population Sequencing

- EBR RAVs
  - No RAVS: 414/438 (95%)
  - RAVS: 5/438 (20%)

- NS5A Class RAVs
  - No RAVS: 432/438 (80%)
  - RAVS: 27/438 (65%)

Next Generation Sequencing (1% level)

- EBR RAVs
  - No RAVS: 396/439 (90%)
  - RAVS: 33/439 (7.5%)

- NS5A Class RAVs
  - No RAVS: 289/439 (65%)
  - RAVS: 130/439 (30%)

Regimen: GZP/EBR x 12 weeks

- EBR RAVs
  - SVR12 (%): 98 (405/414), 58 (14/24), 86 (345/352), 98 (389/396), 72 (31/43), 91 (284/316)

- NS5A Class RAVs
  - SVR12 (%): 98 (136/150)

GT1a naïve/relapsers

- EBR RAVs
  - SVR12 (%): 98 (405/414), 58 (14/24), 86 (345/352), 98 (389/396), 72 (31/43), 91 (284/316)

- NS5A Class RAVs
  - SVR12 (%): 98 (136/150)

Rate of selection of NS5A resistance upon virologic failure

- Varies by regimen and duration
  - PI based
    - Vedroprevir + tegobuvir + LDV: >99%
    - EBR/GZP: >90%
    - OBT/r/PTV+DSV: 68%
  - Nucleotide based
    - SOF/LDV: 75%
      - 8 weeks: 65%
  - Nuc-based triple
    - SOF/5816/9857 (≤ 6 weeks): 0% (n=15)
    - SOF + GZR/EBR (≤ 8 weeks): 37% (n=30)
Durability of emergent NS5A RAVs

<table>
<thead>
<tr>
<th>Patients With NS5A RAVs (%)</th>
<th>VF Parent Study</th>
<th>Baseline</th>
<th>FU-12</th>
<th>FU-24</th>
<th>FU-48</th>
<th>FU-96</th>
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<tbody>
<tr>
<td></td>
<td>62/63</td>
<td>58/58</td>
<td>42/43</td>
<td>45/45</td>
<td>52/55</td>
<td>50/58</td>
</tr>
</tbody>
</table>

Wyles D, Dvory-Sobol H. EASL 2015
Are NS5A RAVs associated with retreatment failure? YES!

- **SOF/LDV 8-12wks failures**
  - N=41
  - Combined: 29/41 (71%)
  - No RAVs: 11/11 (100%)
  - RAVs: 18/30 (60%)

- **SVR12 (%)**
  - Q30R or M28T: 100/100 (100%)
  - L31M: 80/80 (100%)
  - Y93H/N: 33/6 (55%)

Lawitz E. #0005 EASL 2015.
Are NS5A RAVs are associated with retreatment failure? Uh...No?

- **SOF/LDV + 9451 +/- 9669 4wks failures**
- **N=34**
- **SOF/LDV**
- **SVR12**

**Combined**
- **97/32**

**No RAVs**
- **100/5**

**RAVs**
- **96/26**

- **2 non-VF excluded**
- **Y93H/N: 8/32**
- **1 failure: L31M + Y93H**
  - >1000x FC in LDV EC<sub>50</sub>

*1 patients failed 6 weeks of initial therapy.
Impact of multiple negative predictors

Retrospective analysis of phase 2/3 studies of SOF + RBV +/− PEG

> 850 patients, genotypes 1, 2 and 3

<table>
<thead>
<tr>
<th>Number of negative predictors</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>94</td>
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<td>4</td>
<td>88</td>
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<tr>
<td>5</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
</tr>
</tbody>
</table>

- Treatment experienced
- Cirrhosis
- HCV RNA
- Male
- >75kg
- IL28B non-CC
- NS5A RAVs

Foster G. EASL 2014.
Demographics in the 2 studies

**Lawitz (N=41)**
- Failed: SOF/LDV 8-12 wks
  - 8 also got GS-9669
  - Regimen SVR: >94%
- Male: 83%
- 1a: 83%
- HCV RNA: 6.2 (4.5-7.4)
- African Amer: 24%
- Non-CC: 93%
- Cirrhosis: 46%
- NS5A RAVs: 73%

**Wilson (N=34)**
- Failed: 4wks LDV/SOF + 9451 +/- 9669
  - Regimen SVR: 20-40%
  - 1 got 6 weeks
- Male: 82%
- 1a: 77%
- HCV RNA: 61% >800,000 IU/ml
- African Amer: 82%
- Non-CC: 91%
- Cirrhosis: 0% (97% F0-2)
- NS5A RAVs: 85%
The impact of RBV?

- Male: 78%
- 1a: 78%
- HCV RNA: 6.4 (+/- 0.8)
- African Amer: 100%
- Non-CC: 100%
- Cirrhosis: 22%
- NS5A RAVs: 78%

N=9

SOF/LDV + RBV

N=9

SVR12

Failure
55 male
GT1a
No cirrhosis
L31M
Triple regimens for re-treatment

- **C-SWIFT Retreatment:**
  - Failed 4, 6 or 8 weeks SOF+GZP/EBR
  - GZP/EBR + SOF + RBV x 12 wks (n=23)
  - 100% SVR12 (including 9/9 with NS3+NS5A RAVs)

- **3D + SOF (±RBV) x 12 wks:**
  - 16/22 failed 3D regimen
  - SVR12 95% (21/22); 19/20 GT1a, 2/2 GT1b
  - Extension to 24wks for 1a with cirrhosis
    - 100% SVR4 (6/6)
Is resistance a unique consideration in DAA failures? **YES.**

1. DAA resistance is frequently selected on failure
2. Resistance mutations to some DAA classes (NS5A) persist for prolonged durations
3. RAVs are associated with retreatment failure
4. Patients failing in clinical practice are likely to have other (multiple) negative predictors

What we don’t know for sure is:

Selection of retreatment therapy based on resistance testing (selection of non-cross resistant regimens) will result in improved treatment success.
DAA failure

Genotypic resistance testing

No NS5A RAVS
- SOF/LDV + RBV 24 weeks
- No Q80K (or other PI RAVs)
  - SOF + SMV + RBV 24 weeks

+ NS5A RAVs (Q30, L31, H58, Y93)
- SOF + SMV + RBV 24 weeks (even if Q80K)

+NS5A RAVs + NS3 RAVs (R155, A156, D168)
- 3D + SOF + RBV
  - SOF + EBR/GZP + RBV
  - LDV/SOF + RBV
- Investigational Triple Regimens
The Future:
Triple-class DAA regimen re-treatment

99% SVR12 (76/77) with RAVs

Single failure: 58 female, GT3 with cirrhosis
- Failed SOF/RBV to SOF/EG/RBV
- Y93H in NS5A prior to triple
- Relapsed at wk 8 post
  - Y93H
  - Q30R

A 2nd single center study of only GT1 (41% NS5A exposed): SOF/VEL/9857+/-RBV for 12 weeks
98% SVR12 with no impact of RBV (24/24 no RBV; 24/25 with RBV)
