HCV Treatment Failure: What Next?
Dr Ashley Brown, Imperial College Healthcare NHS Trust, London

European HIV Hepatitis Co-infection Conference
QEI1 Conference Centre
10th December 2015
<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
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</thead>
<tbody>
<tr>
<td>Ashley Brown</td>
<td>I have received research grants, have acted as an investigator for, or have received speaker honoraria from the following:</td>
</tr>
<tr>
<td></td>
<td>Abbvie, Bristol Myers-Squibb, Gilead, Janssen, Merck</td>
</tr>
</tbody>
</table>

**COMPETING INTEREST OF FINANCIAL VALUE > £1,000:**
The goal of therapy: treat-to-cure

“The primary goal of HCV therapy is to cure the infection.”
- EASL Guidelines 2015

“Currently, there is no data to firmly support retreatment recommendations....”
- EASL Guidelines 2015
Why has treatment failed?

Human Factors

- Adherence issues?
- The wrong drugs??
Why has treatment failed?

Virologic Factors

- Insufficient duration
- Baseline RAVs
- Drug-selected RAVs
Suggested Pathway for HCV Treatment Failure

TREATMENT FAILURE

POST-TREATMENT RAVs?
Suggested Pathway for HCV Treatment Failure

1. **TREATMENT FAILURE**
2. **POST-TREATMENT RAVs?** (Answer: NO)
3. **ADHERENT?**
Pill burden is not a predictor of adherence in short term treatment programmes

Table 2. HIV medication adherence over the first 12 weeks of treatment

<table>
<thead>
<tr>
<th>US Commercial Plans</th>
<th>Cohort 1** 1 pill/day</th>
<th>Cohort 2** 2 pills/day</th>
<th>Cohort 3** 3 pills/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>6,533</td>
<td>496</td>
<td>75</td>
</tr>
<tr>
<td>Adjusted adherence rate*</td>
<td>81.4%</td>
<td>80.0%</td>
<td>80.4%</td>
</tr>
</tbody>
</table>

*Adjusted for age and gender. No statistically significant difference between cohorts.
**Cohort 1: TDF/FTC/EFV; Cohort 2: TDF/FTC+EFV; Cohort 3: TDF+FTC+EFV

Over a short-duration timeframe, pill count does not appear to impact medication adherence in treatment naïve HIV patients
Suggested Pathway for HCV Treatment Failure

TREATMENT FAILURE

POST-TREATMENT RAVs?

NO

ADHERENT?

RETREAT WITH SAME REGIMEN*

NO

* Assuming availability and funding
What is the role of baseline resistance?
Prevalence of Pre-Treatment NS5A RAVs in GT1 patients

NS5A deep sequencing analysis (1% cut-off) on 5397 patients

**NS5A RAV Prevalence by Region**

**GT 1a**

- Q30H/R: 4.9%, 4.1%
- L31M: 3.7%, 4.4%
- Y93H: 2.1%, 2.4%
- Multiple RAVs: 4.8%, 4.4%

**GT 1b**

- L31M/I/V: 8.5%, 9.4%
- Y93H: 13.1%, 3.9%
- Multiple RAVs: 16.1%, 14.1%

Q30H/R, L31M and Y93H RAVs confer >100 fold shift to LDV. Asia Pacific not included due to low number of patients with GT1a (n=27).

Zeuzem, AASLD, 2015, 91

L31M/I/V confer 3-43 fold shift to LDV; Y93H confers >100 fold shift to LDV.
Suggested Pathway for HCV Treatment Failure

TREATMENT FAILURE

POST-TREATMENT RAVs?

NO

ADHERENT?

YES

RETREAT WITH SAME REGIMEN BUT LONGER?*

NO

RETREAT WITH SAME REGIMEN*

* Assuming availability and funding
Same Drugs Longer Duration?
One patient achieved SVR12, but was not subgenotyped; error bars: 95% CI.
Among ION-3 patients with a baseline HCV RNA ≥6 million IU/mL, the relapse rate was 10% with 8-week and 1% with 12-week duration LDV/SOF.
SVR was 83% (suboptimal) in GT1 Naïve non-cirrhotic patients treated with SOF/LDV for 8 weeks and who had baseline NS5A RAV with >100fold

Sarrazin et al, AASLD 2014
Patients Who Failed 8 or 12W LDV/SOF Retreated with LDV/SOF for 24 Weeks

- No NS5B SOF-associated variants (S282T, L159F, V321A) detected at baseline
- Of 12 patients with NS5A RAVs at baseline who failed treatment, NS5B and NS5A variants were detected in 4 and 12 patients, respectively

- LDV/SOF failures* (n=41)

<table>
<thead>
<tr>
<th>GT 1 (n=41)</th>
<th>100% SVR n=11/11</th>
<th>27% No n=11/41*</th>
<th>73% Yes n=30/41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>58 (35-71)</td>
<td>Mean HCV RNA, log_{10} IU/mL (range)</td>
<td>6.2 (4.5-7.4)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>34 (83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>10 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis, n (%)</td>
<td>19 (46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL28B non-CC, n (%)</td>
<td>38 (93)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All 11 had failed 8 weeks of LDV/SOF

LDV/SOF failures* from ION1-3, LONESTAR and TRILOGY-1

Wyles, AASLD, 2014, Oral #235; Lawitz, et al. EASL 2015, O005
Overall 71% of patients achieved SVR12 when retreated with LDV/SOF for 24 weeks.
LDV/SOF for Retreatment of HCV GT1 Previous LDV/SOF Failures

Successful Retreatment of GT1 With LDV/SOF After Initial Short Course of DAAs

• 34 participants with HCV (GT-1) and early-stage liver fibrosis who previously failed 4–6 weeks of LDV/SOF with GS-9669 and/or GS-9451 received LDV/SOF for 12 weeks.
• Prior to retreatment, 29 patients (85%) had NS5A-resistant variants.
• The SVR\textsubscript{12} rate by ITT analysis was 91% (2 patients withdrew and only one relapsed).
Suggested Pathway for HCV Treatment Failure

1. **OTHER DAA CLASSES AVAILABLE?**
   - **YES**
     - **POST-TREATMENT RAVs?**
       - **YES**
         - RETREAT WITH SAME REGIMEN BUT LONGER?*
       - **NO**
         - **ADHERENT?**
           - **NO**
             - RETREAT WITH SAME REGIMEN*
           - **YES**
             - RETREAT WITH SAME REGIMEN BUT LONGER?*

* Assuming availability and funding
Drug Classes

- PROTEASE INHIBITORS
- NS5A INHIBITORS
- NON-NUC POLYMERASE INH
- NUCLEOTIDE POLYMERASE INH
Drug Classes

PROTEASE INHIBITORS

NS5A INHIBITORS

NON-NUC POLYMERASE INH

NUCLEOTIDE POLYMERASE INH

Transport and release

HCV Receptor binding and endocytosis

Fusion and uncoating

(+) RNA

Replication, virion assembly, and egress

Translation and polyprotein processing

Replication, virion assembly, and egress

Suggested Pathway for HCV Treatment Failure

- **RETREAT WITH NEW REGIMEN***
  - **YES**
  - OTHER DAA CLASSES AVAILABLE?
  - **YES**
    - POST-TREATMENT RAVs?
    - **NO**
      - ADHERENT?
      - **YES**
        - RETREAT WITH SAME REGIMEN BUT LONGER?*
      - **NO**
  - **NO**

- **TREATMENT FAILURE**
  - **YES**
    - RETREAT WITH SAME REGIMEN*
  - **NO**

* Assuming availability and funding
Retreatment Using Different Drugs
Currently Available Drugs

**PROTEASE INHIBITORS**
- (Boceprevir)
- (Telaprevir)
- Simeprevir
- Paritaprevir

**NS5A INHIBITORS**
- Ledipasvir
- Daclatasvir
- Ombitasvir

**NON-NUC POLYMERASE INH**
- Dasabuvir

**NUCLEOTIDE POLYMERASE INH**
- Sofosbuvir
Persistence of NS5A RAVs following LDV Treatment

Once NS5A resistance develops, it very infrequently resolves on its own

Wyles et al, EASL 2015; Vienna, Austria. Abstract O059.
Retreatment with SMV+SOF in those who failed an NS5A-Inhibitor containing regimen

Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>54 (43–73)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>13 (81)</td>
</tr>
<tr>
<td>Genotype, n (%)</td>
<td></td>
</tr>
<tr>
<td>GT 1a</td>
<td>11 (69)</td>
</tr>
<tr>
<td>GT 1b</td>
<td>3 (23)</td>
</tr>
<tr>
<td>GT 4</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Severe fibrosis (FS 9.6–12.5 kPa), n (%)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Cirrhosis (FS &gt; 12.5 kPa), n (%)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Previous regimen, n (%)</td>
<td></td>
</tr>
<tr>
<td>DCV+PegIFN+RBV</td>
<td>13 (81)</td>
</tr>
<tr>
<td>DCV+ASV+PegIFN+RBV</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Median baseline HCV RNA, 10^6 IU/mL</td>
<td>1.38</td>
</tr>
<tr>
<td>&gt;800,000 IU/mL, n (%)</td>
<td>14 (88)</td>
</tr>
</tbody>
</table>
Retreatment with SMV+SOF in those who failed an NS5A-Inhibitor containing regimen

- No SAEs, premature D/Cs, or Grade 3/4 laboratory abnormalities
- Two treatment failures
  - One patient with advanced liver disease and one patient previously exposed to a PI

Hezode, AASLD, 2015, 1123
**Baseline Demographics**

<table>
<thead>
<tr>
<th>Patients</th>
<th>n=34</th>
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</thead>
<tbody>
<tr>
<td>Average age, years (range)</td>
<td>59 (49–76)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>28 (82)</td>
</tr>
<tr>
<td>Non-white, n (%)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>GT 1a, n (%)</td>
<td>24 (71)</td>
</tr>
<tr>
<td>IL28B CT/TT, n (%)</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Metavir F3–F4, n (%)</td>
<td>27 (79)</td>
</tr>
<tr>
<td>CPT Class B/C, n (%)</td>
<td>11 (32)</td>
</tr>
<tr>
<td>Post-liver transplant, n (%)</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Median time since last dose of SMV+SOF, weeks (range)</td>
<td>23 (7–55)</td>
</tr>
</tbody>
</table>

**Virologic Response**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>LDV/SOF+RBV 12 weeks</th>
<th>LDV/SOF 12 weeks</th>
<th>LDV/SOF+RBV 24 weeks</th>
<th>LDV/SOF 24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12, %</td>
<td>96</td>
<td>100</td>
<td>67*</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>25/26</td>
<td>5/5</td>
<td>2/3</td>
<td>11/11</td>
<td>7/7</td>
</tr>
</tbody>
</table>

*Only failure was a post-transplant CPT B, MELD 16 patient who was only treated for 12 weeks of LDV/SOF because of insurance issues*

Pungpapong, AASLD, 2015, 1038
LDV/SOF ± RBV for 12-24 Weeks in GT 1 Who Failed SMV+SOF

Interim analysis from 2 hepatology referral centers in Texas, USA

### Baseline Demographics

<table>
<thead>
<tr>
<th>Patients</th>
<th>n=31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>24 (77)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>58 (44–66)</td>
</tr>
<tr>
<td>GT 1a, n (%)</td>
<td>29 (93)</td>
</tr>
<tr>
<td>Compensated cirrhosis, n (%)</td>
<td>15 (48)</td>
</tr>
<tr>
<td>Decompensated cirrhosis, n (%)</td>
<td>10 (32)</td>
</tr>
<tr>
<td>Post-liver transplant, n (%)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>LDV/SOF 12 weeks, n (%)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>LDV/SOF+RBV 12 weeks, n (%)</td>
<td>11 (35)</td>
</tr>
<tr>
<td>LDV/SOF 24 weeks, n (%)</td>
<td>16 (52)</td>
</tr>
<tr>
<td>LDV/SOF+RBV 24 weeks, n (%)</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

### Virologic Response

- **Overall**: 85% SVR12 %
  - 11/13
- **Cirrhotic patients**: 91% SVR12 %
  - 10/11

- 2 patients did not achieve SVR due to relapse
- 31% reported no AEs
- Most common AEs: fatigue, headache, insomnia, nausea, diarrhea
- 1 episode of decompensation with bleeding esophageal varices during treatment (patient on LDV/SOF 24 weeks)

Gonzales, AASLD, 2015, 1146
Retreatment of DAA failure patients with SOF+PegINF/RBV

- 80 GT1 patients who had participated in previous DAA trials of GS-9451 or GS-9256 with or without the non-nucleoside polymerase inhibitor, tegobuvir (TGV), and/or the NS5A inhibitor, ledipasvir (LDV)
- 51% of patients harbored NS3 RAVs, 84% harbored NS5A RAVs, and 28% had NS5B RAVs at time of virologic failure
- All patients treated with 12 weeks Sofosbuvir + P/R
- All patients undetectable at EOTR. 17 patients (21%) relapsed by PTW12 giving overall SVR of 79%

Pol et al, Hepatology. 2015 Jul;62(1):129-34
### Soon to be Licensed Drugs

<table>
<thead>
<tr>
<th>PROTEASE INHIBITORS</th>
<th>NS5A INHIBITORS</th>
<th>NON-NUC POLYMERASE INH</th>
<th>NUCLEOTIDE POLYMERASE INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Boceprevir)</td>
<td>Ledipasvir</td>
<td>Dasabuvir</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>(Telaprevir)</td>
<td>Daclatasvir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Ombitasvir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paritaprevir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grazoprevir</td>
<td>Elbasvir</td>
<td></td>
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<tr>
<td></td>
<td>Velpatasvir</td>
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</tbody>
</table>
Phase 3, Placebo-controlled trial of treatment-naïve GT1,4 and 6 patients.
Cirrhosis allowed. HCC, HIV and HBV coinfection excluded.
54% male, mean age 52.6y, 18% African American
GT1a (50%); GT1b (41%); GT4 (6%); GT6 (3%)
HCV RNA > 800,000 IU/mL 68%
22% cirrhosis
Platelets <100 in 8.1%

All patients with virologic failure (n=12) had baseline HCV RNA >800K IU/mL (genotype 1a [n=9], 1b [n=1], 4 [n=0], 6 [n=2]).

Prevalence and Impact of Baseline NS5A RAVs on Efficacy of GZR/EBR in HCV GT 1a

Population Sequencing

- 98% SVR12
- 95% No RAVs: 414/438
- 5% RAVs: 58 SVR12

Next-Gen Sequencing at 1% ST

- 98% SVR12
- 90% No RAVs: 396/439
- 10% RAVs: 72% SVR12

GZR/EBR in GT 1a TN/Prior Relapsers

- 97% SVR12
- 90% No RAVs: 61/68
- 10% RAVs: 29% SVR12

GZR/EBR in GT 1a PR Non-Responders

- 97% SVR12
- 87% No RAVs: 59/68
- 13% RAVs: 44% SVR12
Effect of Baseline NS5A RAVs on SVR12

TN and prior relapse patients
12 weeks, no RBV
- 98% SVR12
- 284/289
- 66% No RAVs
- 289/439
- 34% RAVs

Prior on-treatment failure
16/18 weeks + RBV
- 100% SVR12
- 38/38
- 73% No RAVs
- 38/52
- 27% RAVs

‡

Thompson, AASLD 2015, 703
C-EDGE: GZR/EBR in Treatment-Naïve, HCV GT1 SVR12 by Baseline RAVs

Genotype 1a

<table>
<thead>
<tr>
<th></th>
<th>No baseline RAVs</th>
<th>Baseline RAVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3 RAVs</td>
<td>58/65</td>
<td>83/86</td>
</tr>
<tr>
<td>NS5A RAVs</td>
<td>133/135</td>
<td>11/19</td>
</tr>
</tbody>
</table>

SVR12 rates with baseline NS5A RAVs: <5-fold potency (90%, 9/10); >5-fold potency (22%, 2/9).

Genotype 1b

<table>
<thead>
<tr>
<th></th>
<th>No baseline RAVs</th>
<th>Baseline RAVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3 RAVs</td>
<td>104/104</td>
<td>24/25</td>
</tr>
<tr>
<td>NS5A RAVs</td>
<td>112/112</td>
<td>17/18</td>
</tr>
</tbody>
</table>

SVR12 (%)

Astral Studies: 12 weeks
Sofosbuvir/Velpatasvir FDC
Suggested Pathway for HCV Treatment Failure

1. RETREAT WITH NEW REGIMEN*
   - YES: OTHER DAA CLASSES AVAILABLE?
     - YES: CLINICAL URGENCY?
     - NO: NO
   - NO: NO

2. TREATMENT FAILURE
   - YES: POST-TREATMENT RAVs?
     - YES: RETREAT WITH SAME REGIMEN*
     - NO: ADHERENT?
       - YES: RETREAT WITH SAME REGIMEN BUT LONGER?*
       - NO: NO
   - NO: NO

* Assuming availability and funding
Suggested Pathway for HCV Treatment Failure

- **RETREAT WITH NEW REGIMEN***
  - **YES**
  - OTHER DAA CLASSES AVAILABLE?
  - **NO**
  - CLINICAL URGENCY?
- **RETREAT WITH SAME REGIMEN***
  - **NO**
- **TREATMENT FAILURE**
  - **YES**
  - POST-TREATMENT RAVs?
- **ADHERENT?**
  - **YES**
  - RETREAT WITH SAME REGIMEN BUT LONGER?*
  - **NO**

* Assuming availability and funding
Suggested Pathway for HCV Treatment Failure

- **RETREAT WITH NEW REGIMEN***
  - [ ] OTHER DAA CLASSES AVAILABLE?
    - **YES**
    - **NO**
  - **NO**
    - CLINICAL URGENCY?
      - **YES**
      - AWAIT NEW TREATMENTS (OR CLINICAL TRIAL)
      - **NO**
    - **NO**
  - **YES**
    - TREATMENT FAILURE
      - POST-TREATMENT RAVs?
        - **YES**
        - **NO**
      - **NO**
        - ADHERENT?
          - **YES**
            - RETREAT WITH SAME REGIMEN BUT LONGER?*
          - **NO**

* Assuming availability and funding
Future Drugs
# Future Drug Pipeline

<table>
<thead>
<tr>
<th>PROTEASE INHIBITORS</th>
<th>NS5A INHIBITORS</th>
<th>NON-NUC POLYMERASE INH</th>
<th>NUCLEOTIDE POLYMERASE INH</th>
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<tr>
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<tr>
<td>Paritaprevir</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Grazoprevir</td>
<td>Elbasvir</td>
<td>Beclabuvir</td>
<td>AL-335</td>
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<td>GS-9857</td>
<td>Odalasvir</td>
<td></td>
<td>MK-3682</td>
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<td>ABT-493</td>
<td>ACH-3102</td>
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<td></td>
<td>MK-8408</td>
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<td></td>
<td>GS-5816</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABT-530</td>
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</tbody>
</table>

**PROTEASE INHIBITORS**

**NS5A INHIBITORS**

**NON-NUC POLYMERASE INH**

**NUCLEOTIDE POLYMERASE INH**
GZR, grazoprevir (NS3/4A inhibitor); EBR, elbasvir (NS5A inhibitor).

Lawitz, AASLD, 2015, LB-12

**Triple Therapy as the Ultimate Rescue?**

<table>
<thead>
<tr>
<th></th>
<th>n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>22 (88)</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>54 (23-66)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>25 (100)</td>
</tr>
<tr>
<td>IL28B CC, n (%)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Previous treatment failure, n 4 / 6 / 8 week treatment</td>
<td>17 / 7 / 1</td>
</tr>
<tr>
<td>GT 1a, n (%)</td>
<td>22 (88)</td>
</tr>
<tr>
<td>Cirrhosis, n (%)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Mean baseline viral load, log_{10} IU/mL</td>
<td>6.19</td>
</tr>
<tr>
<td>Baseline NS5A RAVs, n (%)</td>
<td>20 (80)</td>
</tr>
<tr>
<td>Baseline NS3 RAVs, n (%)</td>
<td>13 (52)</td>
</tr>
</tbody>
</table>
SOF + GZV/EBV+RBV for 12 Weeks in GT1 Patients Who Failed 4, 6 or 8 Weeks GZV/EBVDA Therapy

**SVR12 by baseline RAVs, mFAS**

- Overall: 23/23 *
- With Baseline NS5A RAVs: 100
- With Baseline NS3 RAVs: 100
- With Both Baseline NS5A and NS3 RAVs: 9/9

**Safety Summary**

- Patients: SOF + GZR/EBR+ RBV x 12 weeks n=25
- ≥ 1 AE, n (%): 13 (52)
- SAE, n (%): 1 (4)
- Drug-related AE, n (%): 9 (36)

*Excludes 2 patients lost to follow-up at Day 3 and Treatment Week 4

**Most common AEs >5%**

- Rash: 2 (8)
- Fatigue: 2 (8)
- Nausea: 2 (8)
- UTI: 2 (8)

**NS3 RAVs:** V36M (1/22), Q80K (12/22), S122G (2/22), D168E (1/22), and I170V (1/22)
THANK YOU

RETREAT WITH NEW REGIMEN*

OTHER DAA CLASSES AVAILABLE?

CLINICAL URGENCY?

AWAIT NEW TREATMENTS (OR CLINICAL TRIAL)

TREATMENT FAILURE

POST-TREATMENT RAVs?

ADHERENT?

RETREAT WITH SAME REGIMEN*

RETREAT WITH SAME REGIMEN BUT LONGER?*

* Assuming availability and funding