Difficult to treat patients: do they still exist?

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ESCMID Study Group for Viral Hepatitis (ESGVH)

ESCMID post Graduate course, Elimination of hepatitis: are we ready?
Ljubljana, September 27-28, 2019
**difficult**  [dif-i-kult, -kult]  SHOW IPA 🎧

**SYNONYMS | EXAMPLES | WORD ORIGIN**

**adjective**

1. not easily or readily done; requiring much labor, skill, or planning to be performed successfully; hard:
   a difficult job.

2. hard to understand or solve:
   a difficult problem.

3. hard to deal with or get on with:
   a difficult pupil.

4. hard to please or satisfy:
   a difficult employer.

5. hard to persuade or induce; stubborn:
   a difficult old man.

6. disadvantageous; trying; hampering:
   The operation was performed under the most difficult conditions.
Difficult to treat

it’s a matter of perspective

the pill

OR

the patient
HCV treatment

enormous progress has been made
Cure rate with 1st generation DAAs combinations

- > 90-95%
- Suboptimal for G3, and for decompensated cirrhosis
- Complex regimen for non specialist prescribers
  - Depending on genotype
  - 8, 12, 24 weeks
  - +/- RBV
- Risk of failure in case of baseline polymorphism or acquired RASs
2nd generation DAA combinations: pangenotypic and panfibrotypic

- **SOFOSBUVIR / VELPATASVIR**
  - 1 caps daily, 12 weeks
  - > 95-97% SVR

- **GLECAPREVIR / PIBRENTASVIR**
  - 3 caps daily, 8-12 weeks
  - (except G3 pretreated: 16 weeks)

- **SOFOSBUVIR / VELPATASVIR / VOXILAPREVIR**
  - 1 caps daily, 12 weeks
  - > 95-97% SVR
**EASL Recommendations on Treatment of Hepatitis C 2018**

**Baseline assessment**
- Proof of HCV replication (+/- genotype)
- APRI or FIB-4 for liver disease severity
- Assessment of drug-drug interactions

**SVR12**
- is dispensable in the simplified treatment strategy

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Changing the system
everybody can treat HCV

- Multi-center phase-4 trial

- nurse, GP or specialist
  - 3h training session

- 600 patients treated with Harvoni
  - 96% Afro-American
  - 82% naive
  - 20% cirrhotic

<table>
<thead>
<tr>
<th>Provider Type</th>
<th>Provider</th>
<th>SVR Rate</th>
<th>Patients With SVR/Total Patients, n/N</th>
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<tbody>
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<td>NPs</td>
<td>NP 1</td>
<td>0.77</td>
<td>33/43</td>
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<td></td>
<td>NP 2</td>
<td>1.00</td>
<td>12/12</td>
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<td>PCP 4</td>
<td>0.88</td>
<td>21/24</td>
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<td>32/36</td>
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<td>Specialists</td>
<td>Specialist 1</td>
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<td>0.89</td>
<td>34/38</td>
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<td>Specialist 4</td>
<td>0.76</td>
<td>13/17</td>
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<td>Specialist 5</td>
<td>0.94</td>
<td>35/37</td>
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<tr>
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<td>Specialist 6</td>
<td>0.82</td>
<td>64/78</td>
</tr>
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</table>

Does it remain difficult to treat patient?

- A few patients needing a specialized advice

- Still children (lack of data)
- Chronic renal disease
- Drug-drug interactions
- Adherence problems
- DAA-failure
- CP-B cirrhotic
Decompensated Cirrhosis: addition of ribavirin needed

- 267 patients G1-6, decompensated cirrhosis (CP-B)
- Sofosbuvir + Velpatasvir (ASTRAL 4)
- Randomly assigned 1:1:1
  - SOF/VEL x 12 weeks
  - SOF/VEL + ribavirin x 12 weeks
  - SOF/VEL x 24 weeks
- Common AE: fatigue (29%), nausea (23%), headache (22%), anemia (31%)

SVR 83%, 86% without RBV vs 94% with RBV

HCV patients with advanced liver fibrosis and decompensated cirrhosis: real life DAA effectiveness

- 213 cirrhotic GT4-patients
  - Tt naïve (59.6%), experienced (40.4%)
  - Metavir F3 (n = 30), F4, n = 135), decompensated cirrhosis (n = 48)
  - prior DAA failure were excluded

- LDV/SOF +/- RBV
  - 12 weeks or 24 weeks
  - RBV (600-1200mg) dosed by physician discretion

**Results**

Overall, SVR rates 92.5%
93.3% for F3,
93.3% for compensated cirrhosis,
89.6% for decompensated cirrhosis (p=0.68)

No difference in SVR12 rates between 12 vs 24 weeks (90.9% and 92.6%, respectively; P = 0.586).
Prior treatment failure

• Retreatment strategy depends on initial regimen

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
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<tbody>
<tr>
<td>After failure of PEG-IFNα + RBV, SOF + PEG-IFNα/RBV or SOF + RBV</td>
<td>A</td>
<td>1</td>
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<tr>
<td>• Retreat according to recommendations for TE patients, by HCV genotype</td>
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<tr>
<td>HCV resistance testing after failure of any DAA-based regimen (excluding regimens with SOF as the only DAA) is a useful guide to retreatment</td>
<td>B</td>
<td>2</td>
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<tr>
<td>After failure of DAA (PI and/or NS5A inhibitor)-containing regimen</td>
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<tr>
<td>• First-line retreatment</td>
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<tr>
<td>– SOF/VEL/VOX for 12 weeks (without cirrhosis/with compensated cirrhosis)</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>– SOF/VEL + RBV* for 24 weeks (decompensated cirrhosis)</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>• Patients with predictors of poor response, SOF + GLE/PIB for 12 weeks</td>
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<td></td>
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<tr>
<td>– Advanced liver disease</td>
<td>B</td>
<td>2</td>
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<tr>
<td>– Multiple courses of DAA-based treatment</td>
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<td>– Complex NS5A RAS profile</td>
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<tr>
<td>• Very difficult-to-cure patients:‡ SOF/VEL/VOX + RBV or SOF + GLE/PIB + RBV for 12 weeks or for 16 or 24 weeks</td>
<td>C</td>
<td>2</td>
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</table>
Retreatment after DAA failure: Sofosbuvir/velpatasvir/voxilaprevir

- Fixed-dose combination of a polymerase inhibitor, an NS5A inhibitor, and a protease inhibitor
- Important interactions to consider
- Several AE: headache, fatigue, diarrhea, nausea, fatigue, diarrhea, and nausea

SOFOSBUVIR: NS5b inhibitor
VELPATASVIR: NS5a inhibitor
VOXILAPREVIR: NS3 inhibitor

Patients after DAA failure:
- n = 263 POLARIS-1
- n = 182 POLARIS-4

SVR12:
- G1: 12 weeks, 96%
- G2: 12 weeks, 97%

Retreatment after DAA failure: real-life Italian study of sofosbuvir/velpatasvir/voxilaprevir

- 179 Italian patients with previous DAA failure
- Excellent effectiveness of SOF/VEL/VOX: SVR ITT: 91%, SVR PP: 96%
- Cirrhosis (p=0.05) and HCC (p=0.02) were features associated with treatment failure
- Frequent adverse events: fatigue (6%), hyperbilirubinemia (6%), anemia (4%).

Retreatment after DAA failure: real-life Spanish study of sofosbuvir/velpatasvir/voxilaprevir

- 179 Spanish patients with previous DAA failure (mainly to SOF/NS5A)
- Overall SVR: 95%
- SVR was lower in cirrhosis (89%, p=0.05) and G3 (80%, p<0.001)
- Patients with GT3 infection and cirrhosis had the lowest SVR12 rate (69%).

*Llaneras J et al. J Hepatol, J Hepatol. 2019 Jun 14*
Chronic kidney disease: algorithm for using DAA

HCV-infected CKD patients

- eGFR < 30 ml/min
  - All genotypes
    - Glecaprevir/pibrentasvir
      - No dosage adjustment
  - Genotype 1-4
    - Glecaprevir/pibrentasvir
    - No dosage adjustment
    - Elbasvir/grazoprevir 12 w*
      - No dosage adjustment
- eGFR > 30 ml/min
  - Same regimen to general population
    - No dosage adjustment
    *naive for G4
Efficacy of DAA in adolescents

**SOF/LDV**

*12 weeks*

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<tr>
<th>Patients (%)</th>
<th>Total</th>
<th>SVR12, %</th>
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<tr>
<td>Tous</td>
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<tr>
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<tr>
<td>G2</td>
<td>100</td>
<td>37/37</td>
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<td>G3</td>
<td>100</td>
<td>3/3</td>
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<td>G4</td>
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3 lost to FU

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**GLE/PIB**

*8 weeks or 16 weeks (G3 pretreated)*

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<tr>
<th>Patients (%)</th>
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<th>SVR12, %</th>
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<tr>
<td>G1</td>
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<td>G2</td>
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<td>G3</td>
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<td>G4</td>
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Pharmacokinetics of GLE/PIB in adolescents

Similar AUC in teenagers and adults

**GLE**

- Teenagers: 4380
- Adults: 4800

**PIB**

- Teenagers: 1440
- Adults: 1430

*Jonas MM, Etats-Unis, AASLD 2018, Abs. 2379 updated*
Lack of data for young children

- study underway of GLE/PIB in 3-12 years children with a granules formulation
Drug-drug interactions

DAAs can act as inhibitors and/or inducers of metabolic enzymes (CYP3A4) and of transporters. They can increase toxicity or decrease effectiveness of coadministered drugs and *vice versa* => comediations may influence the choice of DAA

www.hep-druginteractions.org
# Drug-drug interactions

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Drug</th>
<th>SOF</th>
<th>LDV/SOF</th>
<th>SOF/VEL</th>
<th>GLE/PIB</th>
<th>SOF/VEL/VOX</th>
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<td>Pravastatin</td>
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<td>Cardiovascular drugs</td>
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**Key**
- ![Plus Sign](Plus Sign): No clinically significant interaction expected
- ![Circle](Circle): Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring
- ![Triangle](Triangle): These drugs should not be co-administered.

*IPP: Omeprazole 20 mg simultaneously or before SOF/VEL + food and 4 h before SOF/VEL/VOX*
Non-adherence

• Resistance not an issue in adherent patients

• In non adherent patients, efficacy although compromised may be still obtained
  – Recent IVDU people treated with sofosbuvir/velpatasvir
  – Overall, 32% (n = 33) were considered non-adherent (<90% adherence).
  – SVR was similar among adherent and non-adherent populations (94% vs. 94%, P = 0.944).

Financial regulations

- In some countries financial restrictions exist
  - type of medication
  - institution where patients reside (e.g. prison)
In conclusion

- The treatment landscape has made HCV treatment easy

- A sum of different characteristics make a patient difficult to treat
  - prior treatment failure with RAS
  - decompensated cirrhosis
  - drug-drug interactions
  - non-adherence
  - renal failure
  - financial regulations

- Number of these patients decline over time
### SMART-C: Efficacy and Safety

- VF: 2 (1.6%) standard vs 6 (2.4%) simplified
- Adherence > 95%: 98% standard vs 96% simplified

#### Treatment Emergent AEs, n (%)

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<th>Standard (n = 127)</th>
<th>Simplified (n = 253)</th>
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<tbody>
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<td>AEs</td>
<td>70 (55)</td>
<td>133 (53)</td>
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<tr>
<td>- Grade 1/2</td>
<td>69 (54)</td>
<td>131 (52)</td>
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<tr>
<td>- Grade 3</td>
<td>1 (0.8)</td>
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<td>- Grade 4</td>
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<td>Common AEs (&gt; 5%)</td>
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<tr>
<td>- Fatigue</td>
<td>30 (14)</td>
<td>52 (15)</td>
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<td>- Headache</td>
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<td>- Nausea</td>
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<td>11 (4)</td>
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<td>- On treatment</td>
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<tr>
<td>- Total</td>
<td>8 (6)</td>
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**ITT**

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<tbody>
<tr>
<td>Standard</td>
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<td>Simplified</td>
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<tr>
<td>SVR12 (%)</td>
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(Decompensated) cirrhosis

Recommendations

- IFN-free regimens are the only options in HCV-monoinfected and in HIV-coinfected patients with decompensated (Child-Pugh B or C) cirrhosis, with or without an indication for liver transplantation, and in patients after liver transplantation because of their virological efficacy, ease of use, safety and tolerability (A1).

- Protease inhibitor-containing regimens are contraindicated in patients with decompensated (Child-Pugh B or C) cirrhosis (A1).