The European Hepcare project

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Even in the era of DAAs, ~47,000 patients would fail to achieve SVR in Europe

<table>
<thead>
<tr>
<th>Country</th>
<th>France</th>
<th>Germany</th>
<th>Italy</th>
<th>Spain</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR (%)</td>
<td>14,411 (14.1%)</td>
<td>3,596 (3.9%)</td>
<td>14,022 (6.7%)</td>
<td>9,023 (5.7%)</td>
<td>9,484 (10.0%)</td>
</tr>
<tr>
<td>NS5A (%)</td>
<td>83,019 (81.0%)</td>
<td>69,771 (75.7%)</td>
<td>158,881 (76.4%)</td>
<td>136,107 (86.7%)</td>
<td>77,785 (81.9%)</td>
</tr>
<tr>
<td>Non-NS5A (%)</td>
<td>5,125 (5.0%)</td>
<td>18,799 (20.4%)</td>
<td>35,014 (16.8%)</td>
<td>11,850 (7.5%)</td>
<td>7,702 (8.1%)</td>
</tr>
<tr>
<td>Treatment failure (%)</td>
<td>13,226 (12.9%)</td>
<td>9,291 (10.1%)</td>
<td>23,224 (11.2%)</td>
<td>15,193 (9.7%)</td>
<td>9,999 (10.5%)</td>
</tr>
</tbody>
</table>

Among treatment failures

<table>
<thead>
<tr>
<th>Failure Type</th>
<th>France</th>
<th>Germany</th>
<th>Italy</th>
<th>Spain</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR (%)</td>
<td>8,015 (60.6%)</td>
<td>1,369 (14.7%)</td>
<td>5,759 (24.8%)</td>
<td>4,864 (32.0%)</td>
<td>3,990 (39.9%)</td>
</tr>
<tr>
<td>NS5A (%)</td>
<td>4,322 (32.7%)</td>
<td>4,126 (44.4%)</td>
<td>9,381 (40.4%)</td>
<td>7,900 (52.0%)</td>
<td>3,861 (38.6%)</td>
</tr>
<tr>
<td>Non-NS5A (%)</td>
<td>889 (6.7%)</td>
<td>3,796 (40.9%)</td>
<td>8,084 (34.8%)</td>
<td>2,429 (16.0%)</td>
<td>2,148 (21.5%)</td>
</tr>
<tr>
<td>Cirrhotic (%)</td>
<td>6,408 (48.5%)</td>
<td>4,426 (47.6%)</td>
<td>14,722 (63.4%)</td>
<td>7,586 (49.9%)</td>
<td>3,201 (32.0%)</td>
</tr>
<tr>
<td>Genotype 1 (%)</td>
<td>9,281 (70.2%)</td>
<td>4,641 (50.0%)</td>
<td>16,353 (70.4%)</td>
<td>11,150 (73.4%)</td>
<td>4,578 (45.8%)</td>
</tr>
<tr>
<td>Genotype 2 (%)</td>
<td>716 (5.4%)</td>
<td>649 (7.0%)</td>
<td>5,161 (22.2%)</td>
<td>436 (2.9%)</td>
<td>466 (4.7%)</td>
</tr>
<tr>
<td>Genotype 3 (%)</td>
<td>2,087 (15.8%)</td>
<td>3,672 (39.5%)</td>
<td>867 (3.7%)</td>
<td>2,988 (19.7%)</td>
<td>4,582 (45.8%)</td>
</tr>
<tr>
<td>Genotype 4-6 (%)</td>
<td>1,142 (8.6%)</td>
<td>329 (3.5%)</td>
<td>843 (3.6%)</td>
<td>619 (4.1%)</td>
<td>373 (3.7%)</td>
</tr>
</tbody>
</table>

Chhatwal J et al., EASL 2017 poster #FRI-233
DAA-Failing patients: WHO are you?

- Liver status
- HCV Genotype and Subtype
- Willingness to be treated
- HCV-RNA
- Treatment experience
- Comorbidities
- Resistance

Limited failure/retreatment studies with real-life data
And posters ...

- **Abstract 47.** Comparison of genetic variability and resistance profile among DAA-naïve and DAA-failed HCV 3 infected patients in Italy. *Barbaliscia S.*
- **Abstract 58.** HCV inter-subtype 2k/1b recombinant detected in a DAA treated patient in Italy. *Paolucci S.*
- **Abstract 59.** Prevalence of NS5A resistance associated variants in patients experienced a virological failure. *Delucis S.*
- **Abstract 61.** Inadequate daclatasvir blood levels in a liver transplantation recipient, treated with sofosbuvir + daclatasvir in association with ursodeoxycholic acid: a case report. *Bussini L.*
- **Abstract 77.** Resistance-associated substitutions among HCV1b virus populations in patients who failed DAA based regimens. *Pavia G.*
- **Abstract 78.** High and unpredictable prevalence of resistance in all HCV genotypes at DAA failure may affect the retreatment options and decrease cure rates. *Di Maio V.C.*
- **Abstract 79.** Frequent de novo generation of HCV3a resistance-associated substitutions in Spain. *Vrancken B.*
Real-life experience from Italian VIRONET-C network: 67% of PI-failures and 92% of NS5A-failures were associated with RASs emergence

310 patients who experienced a virologic failure to a currently recommended DAA IFN-free regimen and with available resistance test at failure were analyzed by population sequencing.

![Bar chart showing prevalence of RASs at failure and No RASs at failure for different viral proteins: NS3 (N=133, 66.9%), NS5A (N=198, 91.9%), NS5B NI (N=261, 75.5%), NS5B NNI (N=47, 59.6%).]

NI, Nucleotide inhibitor; NNI Non-Nucleoside Inhibitor

Di Maio VC et al., EHHRW 2017
The Spanish Gehep004 cohort had similar experience

- 289 patients failing first line IFN-free DAA

<table>
<thead>
<tr>
<th></th>
<th>SOF-SIM±RBV</th>
<th>SOF-LDV±RBV</th>
<th>SOF-DCV±RBV</th>
<th>3D/2D±RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failed (n)</td>
<td>56</td>
<td>113</td>
<td>55</td>
<td>43</td>
</tr>
<tr>
<td>With RASs (%)</td>
<td>59% (NS3)</td>
<td>65% NS5A</td>
<td>80% NS5A</td>
<td>69% NS5A</td>
</tr>
<tr>
<td></td>
<td>NS3</td>
<td>NS5A</td>
<td>NS5A</td>
<td>NS5A</td>
</tr>
<tr>
<td></td>
<td>3% S282T</td>
<td></td>
<td>37% NS3</td>
<td>14% ALL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retreated (n)</td>
<td>47</td>
<td>54</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Reached W12 (n)</td>
<td>38</td>
<td>32</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Reached SVR12</td>
<td>34 90%</td>
<td>28 88%</td>
<td>13 72%</td>
<td>2 66%</td>
</tr>
</tbody>
</table>

AB Perez, F García et al., EHHRW 2017
Efficacy of **NS5A-retreatment** is reduced by baseline presence of **NS5A-RASs** (natural or derived by NS5Ai-exp)

\[ P = 0.015 \]

- **No NS5A RASs**: 85.5% SVR
- **Only 1 NS5A RAS**: 66.7% SVR
- **More than 1 NS5A RAS**: 42.9% SVR

Only 3/7 patients with Y93H/C RASs reached SVR.

Double NS5A RASs reduced SVR rates to 50% even in GT-1b patients.

P-value was calculated by Fisher exact test.

NS5Ai, NS5A inhibitor; RAS, resistance associated substitution; SVR, sustained viral response

_Cento V et al., EHHRW 2017_
Understanding more about RASs may help us learn why failure occurred, and may allow optimization of retreatment regimens.

- Occurrence of resistance associated DAA treatment failure
- Mutations patterns associated with DAA treatment failure
  - Type
  - Number of RASs
  - Multiclass resistance
Collaboration. Is it the new innovation?

ey.com/transactions #BetterQuestions
HepCare

Hepatitis C antiviral Therapy Registry

A joint study organized by the European Society for Antiviral Research among European participants
HepCare

- International multicenter study
  - Clinical cases of failure

- Since 2014, 14 Countries joined HepCare.
  - 18 individual study sites
  - 1 National collaborative network: GEHEP-004 cohort [Spain]

- Central Database at International Health institute in Luxembourg

- Part of ESAR
  - Sister of the SPREAD database
European society for translational antiretroviral research - ESAR

- More than 33 countries

- Combines the efforts of virologists, clinicians and epidemiologists

- Extensive experience with collaboration
  - SPREAD (HIV)
  - CAPRE (HBV)
Benefits of contributing

Part of joint publications

- **Letter to the editor: Pre-exposure prophylaxis for HIV in Europe: The need for resistance surveillance**
  C van Tienen, D van de Vijver, T Noori, A Sönnerborg, C Boucher. *Eurosurveillance, Volume 22, Issue 11, 16 March 2017*

- **HIV-1 transmission between MSM and heterosexuals, and increasing proportions of circulating recombinant forms in the Nordic Countries.**

- **The global spread of HIV-1 subtype B epidemic**

- **Transmission of HIV drug resistance and the predicted effect on current first-line regimens in Europe.**

- **Combined Analysis of the Prevalence of Drug-Resistant Hepatitis B Virus in Antiviral Therapy-Experienced Patients in Europe (CAPRE).**
Benefits of contributing

• Submit your own research question
  ▪ Access to HepCare data

• Use HepCare data as a reference

• Contribute into better patient care
Governance

• Submission does not affect ownership

• Permission will be requested when new research question is submitted

• We encourage to publish your own data first
HepCare inclusion criteria

• > 18 years old

• HCV infection

• Failure/relapse on a DAA regimen

• Sequence available at DAA failure
  • And possibly at DAA baseline
How to submit

http://www.esar-society.eu/
How to submit

• Web-based submission form

• For login
  ▪ s.popping@erasmusmc.nl
THERAPY AT TIME OF FAILURE:

Start date of current HCV therapy: YYYY-MM-DD
Stop date of current HCV therapy: YYYY-MM-DD
Viral rebound at week no: 
Specification of triple therapy:

- Ribavirine
- Peginteron or Pegasey
- Telaprevir
- Boceprevir
- Sofosbuvir
- Simeprevir
- Vaniprevir
- Adefovir
- Asunaprevir
- Sofaprevir
- Daclatasvir
- Ledipasvir
- Dasabuvir (Exviera)
- Ombitasvir, Paritaprevir & Ritonavir (ViekiraX)
- Grazoprevir
- Elbasvir

Outcome: 
Co-medications:

- Anxiolytics/sedatives
- Antiarrhythmics
- Anticonvulsants/antipsychotics
- Antimicrobials

Co-medications comments:

Please specify the prescribed regimen at time of therapy failure.

Week no after therapy start
Please specify the clinical outcome
Please specify if relevant co-medications was prescribed during therapy (multiple selections possible, scrollable list).

PAST THERAPY:

add a past therapy

CO-INFECTION STATUS

HIV status: Unknown
HBV status: Unknown
CD4 at time of start current HCV therapy:
CD4 at time of failure current HCV therapy:

At time of start of current HCV therapy
At time of start of current HCV therapy

submit patient
How to submit

• Web-based submission form

• For login
  ▪ s.popping@erasmusmc.nl

• Larger dataset?
  ▪ data dump is available
HepCare collaboration

**France**
Hopital Cochin

**Italy**
University of Rome Tor Vergata

**Israel**
Virology laboratory and national HIV reference laboratory

**Luxembourg**
Luxembourg Institute of Health

**Netherlands:**
University Medical Centre Utrecht
Erasmus Medical Center
Rijnstate Arnhem
Bernhoven hospital Uden
Nijmegen & University Medical Centre Nijmegen

**Norway**
Norwegian Institute of Public Health

**Poland**
Hospital for infectious diseases Warschauw

**Romania**
Carol Davila University of Medicine and Pharmacy

**Russia**
D.I. Ivanovsky Institute of Virology

**Slovenia**
University of Ljublana & Slovenia AIDS reference

**Spain**
Hospital San Cecilio, Granada

**Sweden**
Karolinska Institute

**Turkey**
Kocaeli University & Medical Faculty
Turkish national public health institution

**United Kingdom**
Public health Wales Microbiology Cardiff
ICVC charitable trust
HepCare Coordinating structure

**Coordinating committee**
- Annemarie Wensing MD, PhD
- Carlo Federico Perno, MD, PhD
- Carole Devaux, MD, PhD
- Charles Boucher, MD, PhD
- Federico Garcia, MD, PhD
- Francesca Ceccherini-Silberstein, PhD
- Joop Arends, MD, PhD

**Study coordinators**
- Stephanie Popping, MD
- Valeria Cento, MD, PhD
- Federico Garcia, MD, PhD

**Statistical analysis**
- David van de Vijver, PhD
Closing remarks

• A combined European effort is essential to gain more insights into the clinical correlates and mechanisms of DAA failure

• Hepcare is the DAA Failure registry database provided by ESAR

• Contribution leads to joint publication and does not affect data ownership

WANNA JOIN???
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fegarcia@ugr.es