EASL-ILC 2017: Viral Hepatitis

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Conflicts of Interest

Honoraria for consulting or speaking (last 5 years):
  Abbott, Abvie, Biolex, BMS, Boehringer Ingelheim, Eiger, Falk Foundation,
  Gilead, ITS, JJ/Janssen-Cilag, Medgenics, Merck/Schering-Plough, Novartis,
  Roche, Roche Diagnostics, Siemens, Transgene, ViiV

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  Abbott, Abbvie, BMS, Falk Foundation, Gilead, Merck, Novartis, Roche,
  Roche Diagnostics, Siemens

Selection of abstracts is biased by personal interest!
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Fabien Zoulim

Mounia Heddad-Masson (EASL office)

and all presenters providing slides!
Hepatitis A
Hepatitis A

- Acute hepatitis, no chronicity
- Vaccine provides long-term protection, almost no vaccine non-responder
- Change in HAV epidemiology

Importance of HAV infections for acute-on-chronic liver failure?
Importance of HAV infection for acute-on-chronic liver failure?

Poovorawan et al., Abstract Thu-138
- 1,481 patients with acute hepatitis A in Thailand (347 hospitals)
  - Analysis of all-cause mortality

<table>
<thead>
<tr>
<th>Factors (n)</th>
<th>30-day mortality (%)</th>
<th>Adjusted Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (1,481)</td>
<td>2.2</td>
<td>-</td>
</tr>
<tr>
<td>Age ≥ 60 years (136)</td>
<td>10.3</td>
<td>6.36</td>
</tr>
<tr>
<td>Cirrhosis (29)</td>
<td>24.1</td>
<td>8.12</td>
</tr>
<tr>
<td>Alcoholic liver diseases (17)</td>
<td>17.6</td>
<td>1.46</td>
</tr>
<tr>
<td>Chronic hepatitis B (17)</td>
<td>11.7</td>
<td>5.83</td>
</tr>
<tr>
<td>Chronic hepatitis C (5)</td>
<td>20</td>
<td>21.11</td>
</tr>
</tbody>
</table>

➢ Still high mortality rate for HAV infections in Thailand, in particular in patients with chronic liver disease
Hepatitis A

- Acute hepatitis, no chronicity
- Vaccine provides long-term protection, almost no vaccine non-responder
- Change in HAV epidemiology

Importance of HAV infections for acute-on-chronic liver failure!

Possible role of HAV and HEV infections for the development of AIH (Taubert et al., LBP-532)
Hepatitis E
Hepatitis E

- Acute hepatitis, chronicity in immunocompromised patients (also during treatment with tyrosine kinase inhibitors)  
  Komolmit et al., SAT-137  
  Protin et al., THU-140

- Severe courses in patients with chronic liver disease  
  Fraga-Christinet et al., SAT-298

- Clinical courses differ between HEV genotypes  
  Sayed et al., THU-130

- HEV is mainly a zoonosis in Europe but infections by blood transfusions are possible (e.g. Germany 1:896 donations HEV-RNA(+))  
  Westhölter et al., PS-110

- Ribavirin is a treatment option, treatment failure may occur (in particular during ibrutinib therapy?)  
  Tjwa et al., THU-323  
  Protin et al., THU-140

- HEV is discussed as a cause for extrahepatic symptoms  
  Pischke et al., J Hepatol 2017
Role of HEV in acute non-traumatic neurological injury

Webb, Dalton et al., PS-103:
- Prospective HEV screening of patients with neurological injury (non-traumatic)

```
Den Bosch, the Netherlands n= 83
Toulouse, France n= 164
Cornwall and Plymouth, UK n=217

Patients with acute non-traumatic neurological injury tested for HEV (n=464)

IgM+, IgG + PCR+ n=3
IgM-, IgG- PCR +ve n=2
IgM+, IgG- PCR +ve n=2
IgM+, IgG+ PCR -ve n=4
IgM-ve, IgG+ PCR -ve n=152
IgM-ve, IgG-ve PCR -ve n=302

Current HEV infection
Recent HEV Infection
Distant HEV infection
Never Infected with HEV
```
### Role of HEV in acute non-traumatic neurological injury

#### Jones et al., PS-104:
- HEV-associated neuralgic amyotrophy has a different phenotype than HEV-neg. NA:
  - bilateral;
  - more neurol. Damage
  - involvement outside brachial plexus

<table>
<thead>
<tr>
<th>Acute neurological event</th>
<th>Number tested (n=)</th>
<th>HEV infection n= (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuralgic amyotrophy</td>
<td>5</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>11</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>7</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>7</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cranial Nerve palsies</td>
<td>31</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Seizure(s)</td>
<td>44</td>
<td>3* (7%)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>170</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>68</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Migraine/headaches</td>
<td>51</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>12</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Myelitis</td>
<td>14</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>25</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>28</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

- 2.4% of acute neurology patients have evidence for HEV infection

Webb, Dalton et al., PS-103:
- Prospective HEV screening of patients with neurological injury (non-traumatic)
Extrahepatic manifestations of HEV infection

• Extrahepatic HEV replication
  
  Drave et al., J Viral Hepatitis 2016
  EASL ILC-2017: Qu et al., FRI-138

• T cell cross-reactivity
  
  Soon et al., THU-313
  (Al-Ayoubi et al., THU-285)

Wedemeyer & Cornberg, Liver International 2016
Pischke et al., Journal of Hepatology 2017
Hepatitis E: ILC-2017

- Robust tools and models to study HEV virology and immunity
  
  *e.g. Sayed et al, THU-130*van der Garde et a., FRI-290,

- New data on epidemiology and natural history

- HEV may cause neurological symptoms, specifically neuralgic amyotrophy

- New treatment options are needed for ribavirin treatment failures
  
  *e.g. NUC 2CMC Qu et al., FRI-138*
Hepatitis B
Clinical Practice Guidelines

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection

European Association for the Study of the Liver

Chair: Pietro Lampertico

Panel members:
Kosh Agarwal, Thomas Berg, Maria Buti, Harry L.A. Janssen, George Papatheodoridis, Fabien Zoulim; EASL Governing Board representative: Frank Tacke

Reviewers:
EASL Governing Board, Maurizia Brunetto, Henry Chan, Markus Cornberg
## Natural history of HBV - New nomenclature

<table>
<thead>
<tr>
<th>HBeAg status</th>
<th>HBsAg</th>
<th>HBeAg</th>
<th>HBV DNA</th>
<th>ALT</th>
<th>Liver disease</th>
<th>Old terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg positive</td>
<td>High</td>
<td>Positive</td>
<td>&gt;10E7 IU/mL</td>
<td>Normal</td>
<td>None/minimal</td>
<td>Immune tolerant</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>High/Intermediate</td>
<td>Positive</td>
<td>10E4-10E7 IU/mL</td>
<td>Elevated</td>
<td>Moderate/severe</td>
<td>Immune reactive HBeAg positive</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>Low</td>
<td>Negative</td>
<td>&lt;2,000 IU/mL°°</td>
<td>Normal</td>
<td>None</td>
<td>Inactive carrier</td>
</tr>
<tr>
<td>HBeAg positive</td>
<td>Intermediate</td>
<td>Negative</td>
<td>&gt;2,000 IU/mL</td>
<td>Elevated*</td>
<td>Moderate/severe</td>
<td>HBeAg negative Chronic hepatitis</td>
</tr>
</tbody>
</table>

*Persistently or intermittently

°° HBV-DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis
Hepatitis B

TDF $\rightarrow$ TAF

(\textit{tenofovir disoproxil fumarate} $\rightarrow$ \textit{tenofovir alafenamide})

Week 48 Data:
Buti et al., Lancet Gastroenterol & Hepatol 2016; 1: 196-206 (HBeAg-negative)
TAF: Week 96 data and switching from TDF

Brunetto et al., PS-042 & Argawal et al., FRI-153: Week 96 data
- HBV-DNA <29 IU/ml 90% (HBeAg-negative) and 73% (HBeAg-positive)
- Non-inferior to TDF

Chan et al., PS-041: Switch from TDF to TAF after week 96

Switching:
- Improvement in ALT normalization
- Improvement in bone density
- Improvement in GFR
### Indications for selecting ETV or TAF over TDF*

| 1. Age >60 year                      |
| 2. Bone disease                     |
| Chronic steroid use or use of other medications that worsen bone density |
| History of fragility fracture       |
| Osteoporosis                        |
| 3. Renal alteration**              |
| eGFR <60 min/ml/1.73 m²             |
| Albuminuria >30 mg or moderate dipstick proteinuria |
| Low phosphate (<2.5 mg/dl)          |
| Hemodialysis                        |

* TAF should be preferred to ETV in patients with previous exposure to nucleoside analogues.

** ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) 15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis.
Hepatitis B

Besifovir Phase 3 Study

Novel nucleotide (guanosine monophosphate)
**Besifovir phase 3 study**

Ahn et al., GS-017: Week 48 data
- 193 patients in Korea
- Randomized trial vs. TDF
- Addition of L-carnitine required

**Virolologic Response Rate**

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>Besifovir VR (n,%)</th>
<th>Tenofovir VR (n,%)</th>
<th>One sided 97.5% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>VR (%)</td>
<td></td>
<td>76 (80.85)</td>
<td>79 (84.95)</td>
<td>-0.149, ∞</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>94</td>
<td>93</td>
<td></td>
</tr>
</tbody>
</table>

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Hepatitis B

NUC-discontinuation
DARING-B: Discontinuation of ETV or TDF

Papatheodoridis et al., PS 043: Prospective trial in Greece
- 60 patients; ETV/TDF for ≥ 4 years and HBV DNA undetectable ≥ 3 years
Hepatitis B

New drugs to achieve HBV cure

“functional cure”, HBsAg loss, HBs seroconversion, ...
TARGETS FOR HBV “Cure”

- Therapeutic vaccination
- TLR Agonists
- Checkpoint Inhibitors
- Bispecific Antibodies
- T-cell transfer

Entry inhibitors
- Myrcludex

cccDNA Inhibition (formation, degradation)
- CRISP/CAS9

Core Protein modulators
- CPAMs

HBsAg „Release“ Inhibitors
- Inhibition SVP formation

Inhibit Protein Translation
- siRNA

H. Wedemeyer 4-2017  EASL-ILC Viral Hepatitis
Fabien Zoulim, and David Durantel Cold Spring Harb Perspect Med 2015;5:a021501
TARGETS FOR HBV “Cure”

- Entry inhibitors: Myrcludex
  - Ding et al., PS-046

- cccDNA Inhibition (formation, degradation): CRISP/CAS9
  - Donker et al., SAT-174

- Core Protein modulators: CPAMs
  - Bazinet et al., THU-154-6

Other Targets:
- Therapeutic vaccination
- TLR Agonists
- Checkpoint Inhibitors
- Bispecific Antibodies
- T-cell transfer

Induction of antiviral effectors: e.g., APOBEC3A/B

Inhibitors:
- HBsAg "Release" Inhibitors
- Inhibition of SVP formation

Additional References:
- Fabien Zoulim, and David Durantel Cold Spring Harb Perspect Med 2015;5:a021501
- Ding et al., PS-046
- Boni et al., PS-050
- Wisskirchen et al, PS-051
- Schuch et al., PS-052
- Fisciaro et al, PS-053
- Gane et al., PS-044
- Yuen et al., PS-045
- Gane et al., THU-176
- Streinu-Cercel et al., SAT-155
- Donker et al., SAT-174
Hepatitis D
Hepatitis D (delta)

- Most severe form of chronic viral hepatitis
  - possibly less aggressive in African patients
  - also higher risk for HCC development

- HDAg shows high variability
  Reduced HBV quasispecies complexity

- PEG-IFNa is effective in only 20-25% of patients
  Viral dominance patterns associated with response

Clinical and virological characteristics of hepatitis D worldwide?
Alternative antiviral treatment options?
Heterogeneity of hepatitis delta world-wide: the HDIN network

Wranke et al., THU-157:
- The Hepatitis Delta International Network (HDIN)
- 1579 anti-HDV+ or HDV-RNA+ patients from 15 countries

Giersch et al., SAT-175: HDV-G3 leads to higher infection rates in mouse models
Shirazi et al., SAT-154: HDV in Israel (6.5% prevalence)
Novel treatment options for HDV infection

<table>
<thead>
<tr>
<th>Novel antiviral strategies against HDV in clinical development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entry inhibitors</strong></td>
</tr>
<tr>
<td>• Sodium taurocholate co-transporting polypeptide (NTCP)</td>
</tr>
<tr>
<td>Drug: Myrcludex B</td>
</tr>
<tr>
<td>Structure/function: Myristoylated lipopeptide obtaining 47 amino acids of the pre S1 domain of L-HBsAg</td>
</tr>
<tr>
<td>Clinical Phase: Phase II</td>
</tr>
<tr>
<td><strong>Prenylation inhibitors</strong></td>
</tr>
<tr>
<td>• Farnesyl or geranylgeranyl prenyl lipids</td>
</tr>
<tr>
<td>Drug: Lonafarnib</td>
</tr>
<tr>
<td>Structure/function: Inhibitor of an essential step in viral propagation and assembly</td>
</tr>
<tr>
<td>Clinical Phase: Phase II</td>
</tr>
<tr>
<td><strong>Nucleic acid polymers</strong></td>
</tr>
<tr>
<td>• Amphipathic alpha-helices in class I surface glycoproteins</td>
</tr>
<tr>
<td>Drug: REP 2139-Ca</td>
</tr>
<tr>
<td>Structure/function: Blocks release of HBsAg particles; entry and post-entry antiviral activity</td>
</tr>
<tr>
<td>Clinical Phase: Phase II</td>
</tr>
</tbody>
</table>

- Buchmann et al., Thu-158: kinase inhibitors with activity against HDV
- Donkers et al., SAT-174: NTCP inhibitors (e.g. rosiglitazone)
- Bazinet et al., REP-2139 long-term follow-up; LBP-507
Lonafarnib for HDV infection

- Final step in HDV replication involves prenylation (i.e. farnesylation):
  Farnesyl transferase is a host enzyme which can be targeted by drugs
- Lonafarnib for 28 days induced a dose-dependent HDV-RNA decline

_EASL-ILC 2017:_
Wedemeyer et al., PS-039: → Lonafarnib dose escalation, treatment 24 weeks
Yurdaydin et al., GS-008: → Lonafarnib dose finding, 12-24 weeks
Koh et al., LPB-519: → Lonafarnib once daily dosing, 24 weeks
Yurdaydin et al., THU-161: → post-treatment HDV RNA clearance

_Koh et al., Lancet Infect. Dis. 2015; 15: 1167-74_
Lonafarnib for HDV infection
LOWR-HDV-4 (PS-039)

Log HDV-RNA IU / mL

Mean decline after 24 weeks (ITT):
-1.7 log IU/mL (SD ± 1.5)

% with > 1 log decline: 9/15 (60%)
% with > 2 log decline: 4/15 (27%)

Pt 14: HDV-RNA < LLOQ @ Week 24
Pt 3: HDV-RNA undetectable @ Week 24

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Lonafarnib for HDV infection
LOWR-HDV-4 (PS-039)

Week 48:
% with > 2 log decline: 3/15 (20%)
Lonafarnib for HDV infection

- Antiviral efficacy confirmed for up to 24 weeks
- GI side effects are dose-limiting
- Off-treatment viral control is possible in some patients (can be associated with hepatitis flares)
- Longer therapies/combination therapies may be needed

**EASL-ILC 2017:**
- Wedemeyer et al., PS-039: → Lonafarnib dose escalation, treatment 24 weeks
- Yurdaydin et al., GS-008: → Lonafarnib dose finding, 12-24 weeks
- Koh et al., LPB-519: → Lonafarnib once daily dosing, 24 weeks
- Yurdaydin et al., THU-161: → post-treatment HDV RNA clearance
Hepatitis C
Direct Acting Antivirals against HCV

**Protease-Inhibitors „...previrs“**
- Paritaprevir/r
- Grazoprevir
- Glecaprevir
- Simeprevir

**NS5A-Inhibitors „...asvirs“**
- Sofosbuvir
- Daclatasvir
- Ledipasvir
- Velpatasvir

**Polymerase-Inhibitors „...buvirs“**
- Sofosbuvir
- Velpatasvir

**Non-Nuc**
- Sofosbuvir + RBV

**Nucleos(t)ide**
- Paritaprevir/r
- Grazoprevir
- Glecaprevir
- Simeprevir

**General**
- Ombitasvir
- Dasabuvir
- Elbasvir
- Pibrentasvir
- Velpatasvir
- Uprifosbuvir
- Ruzasvir
- AL-335
- Asunaprevir
- Velpatasvir
- Odalasvir
- Uprifosbuvir
- AL-335
Direct Acting Antivirals against HCV

Protease-Inhibitors „...previrs“
- Grazoprevir
- Simeprevir

Polymerase-Inhibitors „...buvirs“
- Glecaprevir
- Pibrentasvir
- Voxilaprevir
- Grazoprevir
- Unrifosbuvir
- Odalasvir
- Simeprevir
- Omalasvir
- AL-335

NS5A-Inhibitors „...asvirs“
- Sofosbuvir
- Daclatasvir
- Ledipasvir
- Paritaprevir/r Ombitasvir Dasabuvir
- Asunaprevir Daclatasvir
- Grazoprevir Elbasvir
- Glecaprevir Pibrentasvir

Non-Nucs
- Sofosbuvir + RBV

Nucleos(t)ide
- Grazoprevir
- Elbasvir
- Velpatasvir
- Velpatasvir
- Ombitasvir
- Ombitasvir
- Dasabuvir
- Dasabuvir
- Pibrentasvir
- Pibrentasvir
- Sofosbuvir
- Sofosbuvir
- Omalasvir
- Omalasvir
- Odalasvir
- Odalasvir

“Integrated analysis”
- Grazoprevir
- Paritaprevir/r Ombitasvir Dasabuvir
- Asunaprevir Daclatasvir
- Grazoprevir Elbasvir
- Glecaprevir Pibrentasvir
- Grazoprevir Unrifosbuvir Ruzasvir
- Grazoprevir Unrifosbuvir Ruzasvir
- Grazoprevir Unrifosbuvir Ruzasvir
HCV treatment ILC-2017: Phase 3 studies

Forns et al., GS-005:
- glecaprevir/pibrentasvir in GT 1,2,4,5,6 cirrhosis (n=146) (Expedition-1); **SVR: 145/146**

Forster et al., GS-006:
- GT 3 (Endurance-3)
  - glecaprevir/pibrentasvir 12 weeks: **SVR 95% (222/233)**
  - sofosbuvir/daclatasvir 12 weeks: **SVR 97% (111/115)**
  - glecaprevir/pibrentasvir 8 weeks: **SVR 95% (149/157)**

Chayama et al., FRI-262 and FRI-262:
- glecaprevir/pibrentasvir in Japanese patients with GT 1 & 2 (Certain 1&2 studies): **SVR 100%**

Wei et al., FRI-266
- elbasvir/grazoprevir in GT1,4,6 (C-CORAL) (Asia, Russia, Australia; n=250), 12 weeks
  - **SVR 92.8% (GT1b 98.9%; GT6 62.9%)**

Reau et al., LBO-03
- glecaprevir/pibrentasvir in liver or renal transplant patients (Magellan-2): **SVR 98%**
Hepatitis C

Efficacy and safety of approved regimens in “real-world” cohorts
HCV treatment ILC-2017: cohort studies/registries

- TRIO Network: 7,550 patients; e.g. Flamm et al., SAT-279
- HCV TARGET: >10,000 patients; e.g. Sulkowski et al., SAT-229
- French HEPATHER and ANRS cohorts: >5,000 patients; e.g. Salmon et al. PS-131
- German Hepatitis C Registry: >10,000 patients; e.g. Deterding et al. PS-096
- Spanish registry Hepa-C: >6000 patients; e.g. Badia Aranda et al., THU-275
- Italian PITER platform: 3,936 patients; e.g. Kondili et al., FRI-280
- RESIST-HCV (Sicily): >5,000 patients; e.g. Cacciola et al., FRI-228
- Scottish HCV Clinical Database: nation-wide; e.g. Innes et al., PS-035
- ... and many more registries/cohorts (e.g. Egypt, VA, etc.)
HCV treatment ILC-2017: Real-world Velpatasvir/Sofosbuvir

Curry et al., PS-102:
- sofosbuvir/velpatasvir in GT2-6 (TRIO Network) (n>600); SVR: GT2 97%, GT3 97%, GT4-6 91%

Vermehren et al., PS-155:
- GT3 treatment according to baseline RASs with SOF/DAC or SOF/VEL

Khalili et al., SAT-222:
- sofosbuvir/velpatasvir in GT1-6 (HCV-TARGET Study)

Buggisch et al., SAT-254:
- sofosbuvir/velpatasvir, single center Germany

Christensen et al., SAT-275:
- sofosbuvir/velpatasvir, German GECCO (n=165 started therapy)
Elbasvir/Grazoprevir experience in the VA healthcare system

Kramer, Puenpatom et al., PS-095:
- 2,436 patients (evaluable population) starting EBR/GZR between 2/2016 and 8/2016

- SVR 95.6% (EP) and 97% (PP)
- Similar high SVR rates in
  - pts. with history of alcohol abuse
  - pts. with history of drug abuse
  - cirrhosis (n=808)
  - CKD stage 4-5 (n=407)
  - HIV infection (n=74)
  - GT4 (n=64)
  - Afr. Americ (n=1400)
  - Hispanics (n=81)

SVR according to prior treatments

- Prior LDV/SOF: 82.9%
- Prior PrOD: 88.6%
- Prior SOF/SIM/BOC/TEL: 93.3%
- IFN +/- RBV: 96.5%
EASL HCV Advisor

www.hcvadvisor.com
Hepatitis C

Antiviral treatment of patients with HCV-related lymphoproliferative disorders and cyroglobulinemia
### HCV-clearance improves extrahepatic manifestations

**Venezia et al., PS-100:**
- HCV treated in Torino, 67 patients, all achieved SVR
- 44 pts. with lymphoproliferative diseases; 32 cyrogobulinemia (5 pts both)
- Mixed cryoglobulinemia: 77% improvement of symptoms, in particular vasculitis
- B-NHL group: 52% maintained complete regression; 39% maintained stable disease

**Saadoun et al., PS-099:**
- HCV cyrogobulinemia-vasculitis (41 pts both); treated with SOF/DAC
- SVR 12: 100%
- 37/41 (90.2%) complete clinical response
- Improvement in kidney function and skin ulcer
Hepatitis C

Antiviral treatment of children
Ledipasvir/Sofosbuvir (half dose) is effective and safe in children (6-11 years)

Murray et al., PS-101:
- Children aged 6-11 years
- Ledipasvir/sofosbuvir (45/200mg) for 12 weeks (n=87) or 24 weeks (n=3)

- SVR 99% (1 relapse in 1 GT1a patient with cirrhosis)
- 1 SAE (not related)
Hepatitis C

Antiviral treatment in HBV co-infection
Liu et al., PS-098:
- Ledipasvir/sofosbuvir in HBsAg+/HCV-RNA+ patients (n=111)
- no current HBV treatment, 99% HBeAg-negative
- HBV-DNA undetectable 33%; Mean baseline HBV-DNA 2.1 log10 IU/ml

- HCV-SVR: 100%
- HBV DNA increase in 63%
- Two patients started HBV therapy
- Factors associated with HBV↑ + ALT >2xULN (n=5):
  - baseline ALT
  - HBV-DNA

No patient had AEs of jaundice, liver decompensation, liver failure or liver transplant
Hepatitis C

HCC risk and IFN-free antiviral therapy
HCCs still occur after HCV clearance

*Journal of Hepatology October 2016*

- Reig et al., earlier and more frequent recurrence
- Pol et al., 0.73 HCC/100 person months, no increased incidence
- Conti et al., de-novo HCC 3.16%
- Cheung et al., de-novo HCC 5.4% in SVR
- Kozbial et al., de-novo HCC 5.2% in SVR

**de novo incidence vs. recurrence!**
IFN-free clearance of HCC could affect HCC immune surveillance

Owusu-Sekyere et al., GS-03:
➢ Role of HCC-specific T cells in patients with cirrhosis receiving IFN-free HCV therapy

HCC-specific T cells are detectable in patients with HCV cirrhosis w/o HCC

HCC-specific T cells are weak in pts. who develop HCC after DAA therapy

HCC-specific T cells decline during IFN-free therapy
HCC risk and HCV clearance: HCV-induced epigenetic changes persist despite HCV clearance

Jühling, Hamdane et al., PS-033:
- Genome-wide ChIP-Seq mapping of HCV-induced epigenetic changes
- Cell culture and patient samples
Hepatitis C

HCC risk and IFN-free antiviral therapy

de novo HCC incidence

IFN-free SVR does not alter the short-term HCC risk in HCV cirrhosis

- Calvaruso et al., PS-038:
- Waziry et al., PS-160
- Innes et al., PS-035

- Mettke et al., THU-081
- Ji et al., PS-037
- Korenega et al., PS-036
**IFN-free SVR does not alter the short-term HCC risk in HCV cirrhosis**

Mettke, Schlevogt et al., THU-081:
- 158 cirrhotic HCV patients Hannover Medical School who started DAA therapy after 1/2014

**IFN-free SVR vs. untreated historical control**

- Factors associated with HCC:
  - higher MELD scores
  - higher AFP levels
- HCC incidence:
  - 2.9 / 100 person years vs.
  - 4.5 / 100 person years (control)

HCC-free survival analysis shows:
- IFN-free SVR group vs. untreated control group
- p = .39
SVR reduces the HCC risk in pts. with HCV cirrhosis receiving DAA therapy

Calvaruso et al., PS-038:
- 2466 patients in the RESIST HCV-cohort who started DAA between 3/2015 and 7/2016

**SVR vs. no-SVR**

- **Factors associated with HCC:**
  - Low albumin
  - Low platelet counts
  - No SVR

- Risk of HCC in SVR patients remains proportional to the stage of liver disease

---

**Table:**

<table>
<thead>
<tr>
<th>Time</th>
<th>Events, N. (%)</th>
<th>Cumulative Rate (Kaplan–Meier estimates x 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>24 (1.0)</td>
<td>1.0%</td>
</tr>
<tr>
<td>12 months</td>
<td>59 (2.4)</td>
<td>2.7%</td>
</tr>
<tr>
<td>18 months</td>
<td>78 (2.9)</td>
<td>4.1%</td>
</tr>
<tr>
<td>24 months</td>
<td>78 (3.1)</td>
<td>7.4%</td>
</tr>
</tbody>
</table>
No evidence for higher risk of HCC recurrence

Innes et al., PS-035:
- Scottish HCV clinical database: 857 patients with cirrhosis treated with DAA vs. SVR after IFN-containing therapies

- Patients treated with DAA were
  - older
  - lower platelet counts
  - more often Child B/C

- HCC Association (univariate):
  - DAA therapy
  - Age
  - Child-Pugh & platelets
  - treatment experienced

Association between IFN-free versus IFN-containing therapy and HCC occurrence

- Hazard ratio for DAA therapy: 2.48
- Hazard ratio for Child-Pugh & platelets: 1.15
Hepatitis C

HCC risk and IFN-free antiviral therapy

HCC recurrence
More aggressive pattern of HCC recurrence after IFN-free therapy

Reig et al., PS-031:
- Follow-up of the J Hepatol 2016 paper
- 77 HCC/HCV patients with complete response to HCC therapy
- HCV therapy initiated in all patients

- 31.2% HCC recurrence
- More aggressive pattern and faster tumor growth
No evidence for higher risk of HCC recurrence

Waziry et al., PS-160:
- Systematic review, metanalysis & meta-regression
No evidence for higher risk of HCC recurrence

Waziry et al., PS-160:
- Systematic review, metanalysis & meta-regression

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted RR</th>
<th>Adjusted RR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average follow-up</td>
<td>0.86</td>
<td>0.79</td>
<td>0.55, 1.15</td>
<td>0.19</td>
</tr>
<tr>
<td>Average age</td>
<td>1.11</td>
<td>1.11</td>
<td>0.96, 1.27</td>
<td>0.14</td>
</tr>
<tr>
<td>Treatment</td>
<td>1.36</td>
<td>0.62</td>
<td>0.11, 3.45</td>
<td>0.56</td>
</tr>
</tbody>
</table>
Hepatitis C

Treatment of DAA failures
Treatment of DAA failure patients

Protease-Inhibitors „...previrs“
- Glecaprevir
- Pibrentasvir
- Voxilaprevir
- Sofosbuvir
- Velpatasvir
- Grazoprevir
- Uprifosbuvir
- Ruzasvir

NS5A-Inhibitors „...asvirs“
- Glecaprevir
- Pibrentasvir

Polymerase-Inhibitors „...buvirs“
- Grazoprevir
- Uprifosbuvir
- Ruzasvir

Non-Nucleosides (Non-Nucs)
- Non-Nucleoside

Nucleos(t)ide
Poordad et al., PS-156:
- Magellan-1, Part 2: 91 patients;
  30% PI failure; 37% NS5A failure;
  33% PI+NS5A failure
- 30% cirrhotic
- 12 weeks: SVR 89% (39/44)
- 16 weeks: SVR 91% (43/47)
Treatment of DAA failure patients

Sarrazin et al., THU-248:
- Integrated analysis of Polaris-1 and Polaris-4 study
- No impact of baseline RASs on virological responses in DAA-experienced patients

<table>
<thead>
<tr>
<th></th>
<th>SOF/VEL/VOX 12 Weeks</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>POLARIS-1 (N = 260)</td>
</tr>
<tr>
<td>No VOX and/or VEL RASs</td>
<td>90/93 (97%)</td>
</tr>
<tr>
<td>Any VOX and/or VEL RASs</td>
<td>151/155 (97%)</td>
</tr>
<tr>
<td>NS3 VOX RASs</td>
<td>3/3 (100%)</td>
</tr>
<tr>
<td>R155any</td>
<td>3/3 (100%)</td>
</tr>
<tr>
<td>A156G</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>D/Q168any</td>
<td>13/13 (100%)</td>
</tr>
<tr>
<td>NS5A VEL RASs</td>
<td>143/147 (97%)</td>
</tr>
<tr>
<td>Y93any</td>
<td>63/66 (95%)</td>
</tr>
<tr>
<td>A/L/Q/R30any</td>
<td>86/89 (97%)</td>
</tr>
</tbody>
</table>
Treatment of DAA failure patients

Wedemeyer et al., PS-159:
- C-SURGE: 94 patients; 76% LDV/SOF failure; 24% EBR/GZR failure
- 43% cirrhotic
- 84% NS5A RASs; 65% NS3 RASs; 55% Dual RASs

![Graph showing SVR12 (% with HCV RNA <15 IU/mL; 95% CI)]
Hepatitis C

Is HCV elimination possible?
Effects of elimination programs?
Projected impact of HCV elimination program in Georgia

Walker et al., PS-125:
- Projected impact (model)

Georgia: HCV elimination program launched 2015

- Target: 90% reduction in prevalence by 2020
- >27,000 pts. treated by the end of 2016

Impact on mortality

- Treat 40000/year
- Current Treatment + Target F3
- Current Treatment + Target Cirrhosis
- Current Treatment + No PWID
- Maintain Current Treatment
- Treat 12000/year + Target PWID
- Treat 12000/year
- No treatment

Reduction in mortality 2015 to 2020
Prison hepatitis programs should be part of elimination programs

McDonald et al., PS-126:
➢ Treatment of HCV infection in the Prison Setting in Victoria, Australia

- Nurse-led
  - 2 full-time nurse specialists
  - protocol-driven assessment & management
  - portable FibroScan
  - delivers care locally to each prison
    - minimizes prisoner movement
  - state-wide service – central medical record (J-Care)

- Supervising hepatologists
  - 2 part-time hepatologists
  - F2F and via tele-medicine

```
Assessment
N=1180

Eligible
N=718

DAA started
N=633

SVR12 time-point
N=244

Not eligible for treatment*
Waiting for treatment
Not yet at SVR12
```
See you in Paris!

Prof. Tom Hemming Karlsen

Prof. Frank Tacke