HCV in 2018

14th International Workshop on Co-infection: HIV, Hepatitis and Liver Disease, 16 - 18 May 2018, Seville, Spain.

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Disclosure: JKR

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• Research grants from Dt. Leberstiftung, DZIF, NEAT ID.
Viral hepatitis is responsible for approximately 1.45 million deaths/yr

Stanaway et al. Lancet 2016
Incidence:
1.75 million new infections / year
(Unsafe health care and injection drug use)

Prevalence:
71 million infected, all regions

Sources – WHO (Center for Disease Analysis)
Burden of HIV/HCV co-infection

37 million HIV infected

2.3 million co-infected with HCV

- North America: ~1.6 million (~320,000)
- Latin America (South & Central America, Caribbean): ~1.8 million (~180,000)
- Middle East & North Africa: ~1 million (~104,000)
- South, West, East & Central Africa: ~26 million (~430,000)
- Eastern Europe & Central Asia: ~1.5 million (~608,000)
- East Asia: ~820,000 (~190,000)
- South & South-East Asia: 3.1 million (~290,000)
- Western Pacific: ~740,000 (~115,000)


IDU: injecting drug user; MSM: men who have sex with men
CASCADE: 20% OF 71 MILLION DIAGNOSED, 1.1 MILLION STARTED TREATMENT IN 2015

CASCADE of care

Sources – WHO (Center for Disease Analysis)
## Access to HCV Therapy in Western Countries

<table>
<thead>
<tr>
<th></th>
<th>Germany</th>
<th>Spain</th>
<th>Italy</th>
<th>France</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>National Plan</strong></td>
<td>No</td>
<td>Yes</td>
<td>No (soon)</td>
<td>No</td>
<td>No (soon)</td>
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<tr>
<td><strong>Screening program</strong></td>
<td>No</td>
<td>Yes</td>
<td>Soon</td>
<td>No</td>
<td>No</td>
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<tr>
<td><strong>Program to improve access to Trt</strong></td>
<td>No (local)</td>
<td>Yes (Prison, PWID)</td>
<td>No</td>
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<tr>
<td><strong>Treatment restrictions</strong></td>
<td>No</td>
<td>No (2017)</td>
<td>No</td>
<td>No (2017)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Nb HCV Patients</strong></td>
<td>200,000</td>
<td>172-218,000</td>
<td>&gt;300,000</td>
<td>230,000</td>
<td>125,000</td>
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<tr>
<td><strong>Nb patients treated so far with DAAs</strong></td>
<td>55,000</td>
<td>81,643</td>
<td>109,408</td>
<td>91,764</td>
<td>25,000</td>
</tr>
<tr>
<td><strong>Nb patients treated in</strong></td>
<td>13,200</td>
<td>29,732</td>
<td>45,201</td>
<td>14960 (2016)</td>
<td></td>
</tr>
</tbody>
</table>

*2016/2017*
Marked reduction in the prevalence of HCV among PWID during 2nd year of the Treatment as Prevention (TraP HepC) programme in Iceland

» Nationwide treatment programme initiated Jan 2016, aiming for elimination of CHC infection as a public health threat. Estimated 800–1000 HCV-infected individuals in Iceland

» Vogur Addiction Hospital, a key sentinel site where most PWID in Iceland seek treatment; provides an opportunity to monitor trends in HCV prevalence among PWID

HCV PCR positive PWID at Vogur Hospital 2015–17

- After 2 years of TrapHep C, 80–85% of all patients evaluated or initiated on DAA treatment
- HCV prevalence among PWID:
  - 2015: 42.6% — among those admitted for addiction treatment prior to TraP HepC
  - 2017: 11.6% — representing a 73% reduction (p<0.001)

• Conclusion:
  - A major scale-up in HCV treatment all patient groups has been successfully initiated in Iceland
  - This has already translated into a significant reduction in prevalence among PWID
  - Key population, should be the focus of treatment scale-up to curtail spread of HCV

Runarsdottir V, et al. ILC 2018, #1705 (PS-095)
Hepatitis C care cascade as of April 30, 2017

- **Aim:** to assess progress towards 90-95-95 targets after 2 years of a national elimination programme

- **Methods:**
  - The proportion engaged in stages of care was quantified from total estimated number of HCV-infected individuals
  - Data on diagnosis, treatment and cure were extracted from national hepatitis C elimination programme treatment databases (28 April 2015 through 30 April 2017)
  - SVR was calculated using both per-protocol and mITT analysis

- **Results:**
  - Efficacy analysis included 25,359 persons:
    - 24,758 persons with complete SVR data
    - 601 persons who discontinued treatment
  - Total SVR rate:
    - Per-protocol: 98.0% (24,273/24,758)
    - mITT: 95.7% (24,273/25,359) in mITT
  - SVR rate
    - 79.5% for SOF-based regimen
    - 98.5% for LDV/SOF

- **Conclusions:**
  - Georgian hepatitis C treatment model ensures high cure rates already exceeding 2020 target with LDV/SOF and without newer-generation DAAs
  - Scaling-up testing and diagnosis, along with effective linkage-to-care services are needed to achieve elimination

*At the time of analysis, 24,758 patients were assessed for SVR
Tsertsvadze T, et al. ILC 2018, #4804 (PS-096)
Current approaches to HCV screening

Symptomatic testing

Testing of at-risk patients


LFT: liver function test
Current approaches to HCV screening

Symptomatic testing

Too late!

Testing of at-risk patients

Intervene before disease progresses


LFT: liver function test
Milestones in the treatment of HCV Genotype 1 infection

**Cyclophilin A inhibitor**
- Inhibition of cyclophilin A reduces HCV replication

**NS3 inhibitor**
- Inhibits activity of NS3 protease
- Prevents processing of HCV proteins required for replication

**NS5A inhibitor**
- Inhibits activity of NS5A, a multifunctional protein
- Prevents viral replication

**NS5B inhibitor(s)**
- Inhibits NS5B RNA replicase
- Prevents replication of viral genome

**PEG-IFN lambda**
- Type III pegylated interferon
- Expression of receptor is more limited than Alfa, should lead to improved tolerability and safety

**HCV life cycle**
- PEG-IFN lambda
- Endocytosis
- Uncoating
- RNA replication
- Virion assembly
- Maturation
- NS4A, NS4B
- ER Lumen
- Cytoplasm
- Liver cell

HCV DAAs

5' UTR → Core → E1 → E2 → p7 → NS2 → NS3 → NS4B → NS5A → NS5B → 3' UTR

Protease

Ribavirin

Telaprevir
Boceprevir
Simeprevir
Paritaprevir
Asunaprevir
Grazoprevir
Glecaprevir
Voxilaprevir

NS3 Protease-Inhibitor

Daclatasvir
Ledipasvir
Velpatasvir
Ombitasvir
Elbasvir
Pibrentasvir
Ruzasvir

NS5A-Inhibitor

Sofosbuvir
VX-135
IDX21437
ACH-3422

NS5B NUC Inhibitor

Dasabuvir
Beclabuvir
Uprifosbuvir

NS5B Non-NUC Inhibitor

Polymerase

-previr
-asvir
-buvir
The Evolution of HCV Care – The Short and Simple Truth?


- The IFN era
- Early era of DAAs
- 1st-generation DAA era
- Pan-genotypic era

- 1984
- 2011
- 2014
- 2016

- Short: 8-12 weeks
- Simple: Minimal pre-testing required
- Safe: Minimal monitoring
### Effective for Genotype 1,(2),3,4,5,6
- **Sofosbuvir + Daclatasvir ± Ribavirin**
  - Genotype 1, 2, 3, 4
- **Sofosbuvir/Ledipasvir ± Ribavirin**
  - Genotype 1, (3), 4, 5, 6
- **Sofosbuvir/Velpatasvir ± Ribavirin**
  - Genotype 1, 2, 3, 4, 5, 6
- **Glecaprevir/Pibrentasvir**
  - Genotype 1, 2, 3, 4, 5, 6
- **Sofosbuvir/Velpatasvir/Voxilaprevir**
  - Genotype 1, 2, 3, 4, 5, 6

### Effective for Genotype 1 and 4
- **Sofosbuvir + Simeprevir ± Ribavirin**
  - Genotype 1, 4
- **Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir ± Ribavirin**
  - Genotype 1
- **Ombitasvir/Paritaprevir/Ritonavir + Ribavirin**
  - Genotype 4
- **Grazoprevir/Elbasvir ± Ribavirin**
  - Genotype 1, 4

**HCV Therapy 2017/2018**

8–24 Weeks Therapy

>95% sustained virological response
All Patients Are Now Prioritized for Treatment including TN NC

AASLD\(^1\)  
Last updated November 2017

WHO\(^2\)  
Last updated April 2017

EASL\(^3\)

Treatment is indicated for:

- All patients with HCV infection must be considered for therapy, including treatment-naïve patients and individuals who failed to achieve SVR after prior treatment (A1).

All patients are now prioritized for treatment including TN NC

1. AASLD recommendations for testing, managing and treating hepatitis C. Available at: http://www.hcvguidelines.org/full-report-view (accessed January 2018);
Goal of Therapy
(2018 EASL guidelines)

- The goal of therapy is to cure HCV infection, in order to:
  (i) prevent the complications of HCV-related liver and extra-hepatic diseases, including hepatic necro-inflammation, fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe extra-hepatic manifestations and death; (ii) improve quality of life and remove stigma; and (iii) prevent onward transmission of HCV (A1).

- The endpoint of therapy is undetectable HCV RNA in serum or plasma by a sensitive assay (lower limit of detection ≤15 IU/ml) 12 weeks (SVR12) or 24 weeks (SVR24) after the end of treatment (A1).
Pre-therapeutic assessment (2018 EASL guidelines)

**Recommendations**

- The contribution of comorbidities to the progression of liver disease must be evaluated and appropriate corrective measures implemented (A1).
- Liver disease severity must be assessed prior to therapy (A1).
- Patients with cirrhosis must be identified, as their treatment regimen must be adjusted and post-treatment surveillance for HCC is mandatory (A1).
- Post-treatment surveillance for HCC must also be performed in patients with advanced fibrosis (METAVIR score F3) (B1).

- Fibrosis stage must be assessed by non-invasive methods initially, with liver biopsy reserved for cases where there is uncertainty or potential additional aetiologies (A1).
- Renal function (creatinine/estimated glomerular filtration rate [eGFR]) should be ascertained (A1).
- Extra-hepatic manifestations of HCV infection should be identified in case of symptoms (A1).
- HBV and HAV vaccination should be proposed to patients who are not protected (A1).
EASL practice guidelines 2018

Recommendations

- IFN-free, ribavirin-free, DAA-based regimens must be used in HCV-infected patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis, including “treatment-naïve” patients (defined as patients who have never been treated for their HCV infection) and “treatment-experienced“ patients (defined as patients who were previously treated with pegylated IFN-α and ribavirin; or pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirin), because of their virological efficacy, ease of use, safety and tolerability (A1).

- The same IFN-free, ribavirin-free treatment regimens should be used in HIV-coinfected patients as in patients without HIV infection, as the virological results of therapy are identical. Treatment alterations or dose adjustments should be performed in case of interactions with antiretroviral drugs (A1).

- Whenever possible (same treatment duration, equivalent SVR rates), combination regimens comprising two drugs are preferred to triple combination regimens, in order to minimize the risk of side effects and drug-drug interactions (B1).
**Recommendation**

- Simplified, pangenotypic anti-HCV treatment recommendations are now possible, thanks to the approval of highly efficacious, safe and well-tolerated pangenotypic anti-HCV drug regimens (B1).

- Pre-treatment assessment can be limited to proof of HCV replication (presence of HCV RNA or of HCV core antigen in serum or plasma) and the assessment of the presence or absence of cirrhosis by means of a simple non-invasive marker (such as FIB-4 or APRI) that determines whether the patient needs post-treatment follow-up (B1).

- Treatment-naïve and treatment-experienced patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis can be treated with either the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, or the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks without testing genotype (B1).
EASL practice guidelines 2018

- If cirrhosis can be reliably excluded by means of a non-invasive marker in treatment-naïve patients, the combination of glecaprevir and pibrentasvir can be administered for 8 weeks only (A1).
- Generic drugs can be used, provided that quality controls are met and guaranteed by the provider (A1).
- Possible drug-drug interactions should be carefully checked and dose modifications implemented when necessary (A1).
- Given the high SVR12 rates expected with these regimens across all groups of patients if adherent, checking SVR12 12 weeks after the end of treatment is dispensable (B1).
Check for DDIs between HCV and comedications!

- **Drug interactions**
  - http://drugchecker.aol.com
  - http://hcvdruginfo.ca

- **List of CYP substrates, inhibitors, inducers**
  - http://medicine.iupui.edu/clinpharm/ddIs

- **HIV drug interactions**
  - http://www.hiv-druginteractions.org
  - http://www.hep-druginteractions.org

Khoo S. 15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, May 2014 [oral presentation].
### Drug-drug interactions: HCV DAAs and HIV ARTs

<table>
<thead>
<tr>
<th></th>
<th>SOF</th>
<th>LDV/SOF</th>
<th>SOF/VEL</th>
<th>OBV/PTV/r + DSV</th>
<th>GZR/EBR</th>
<th>SOF/VEL/VOX</th>
<th>GLE/PIB</th>
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<tbody>
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<td><strong>NNRTIs</strong></td>
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<tr>
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</tr>
</tbody>
</table>

- ♦: No clinically significant interaction expected
- ◼: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring
- ●: These drugs should not be co-administered

*Known or anticipated increase in tenofovir concentrations in regimens containing tenofovir disoproxil fumarate. Caution and frequent renal monitoring.

**ART**: antiretroviral therapy; **NRTI**: nucleoside reverse-transcriptase inhibitor; **NNRTI**: non-nucleoside reverse-transcriptase inhibitor.
# Drug-drug interactions: HCV DAAs and HIV ARTs

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<thead>
<tr>
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<th>SOF</th>
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<th>SOF/VEL/VOX</th>
<th>GLE/PIB</th>
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<td><strong>Protease inhibitors</strong></td>
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<tr>
<td>Atazanavir/ritonavir</td>
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<td>◆*</td>
<td>◆*</td>
<td>◼</td>
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<td>◼</td>
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<tr>
<td>Atazanavir/cobicistat</td>
<td>◆</td>
<td>◆*</td>
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<td>Darunavir/cobicistat</td>
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<td>◆*</td>
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<td>□</td>
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<td>Lopinavir/ritonavir</td>
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<td>◆*</td>
<td>◆*</td>
<td>◼</td>
<td>□</td>
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<td><strong>Entry/integrase inhibitors</strong></td>
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<tr>
<td>Elvitegravir/cobicistat/emtricitabine/TDF</td>
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<td>◆*</td>
<td>◼</td>
<td>◼</td>
<td>□</td>
<td>◼</td>
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<tr>
<td>Elvitegravir/cobicistat/emtricitabine/TAF</td>
<td>◆</td>
<td>◼</td>
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<tr>
<td>Raltegravir</td>
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<td>□</td>
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</tbody>
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EASL. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.026 [Epub ahead of print]
TRIO - Effect of PPI on SVR: Predictors of Response By PPI Type and Dose

Afdhal N, et al. 51st EASL; Barcelona, Spain; April 13-17, 2016. Abst. LBP519.
Sustained Virologic Response is associated with a reduction in liver-related mortality and HCC

Ten-year cumulative incidence of liver-related mortality or transplantation in HCV patients (n=530) was also calculated in the European/Canadian study within five large tertiary hospitals. All patients had received an interferon-based regimen between 1990 and 2003.

Survival after SVR

3- Survival according to fibrosis at baseline

<table>
<thead>
<tr>
<th></th>
<th>Survival</th>
<th>5 years</th>
<th>10 years</th>
<th>15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td></td>
<td>96.8%</td>
<td>90.4%</td>
<td>80.1%</td>
</tr>
<tr>
<td>F0F1</td>
<td></td>
<td>97.4%</td>
<td>93.1%</td>
<td>87%</td>
</tr>
<tr>
<td>≥ F2</td>
<td></td>
<td>93.2%</td>
<td>83.4%</td>
<td>65.4%</td>
</tr>
</tbody>
</table>

- F0F1
- ≥ F2

4- Survival according to treatment

<table>
<thead>
<tr>
<th></th>
<th>Survival</th>
<th>5 years</th>
<th>10 years</th>
<th>15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0F1 fibrosis</td>
<td>SVR</td>
<td>98.1%</td>
<td>95.7%</td>
<td>92.5%</td>
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<tr>
<td></td>
<td>Treatment failure</td>
<td>97.9%</td>
<td>91.8%</td>
<td>81.8%</td>
</tr>
<tr>
<td></td>
<td>Not treated</td>
<td>96%</td>
<td>91.5%</td>
<td>87.5%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Survival</th>
<th>5 years</th>
<th>10 years</th>
<th>15 years</th>
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<td>≥ F2 fibrosis</td>
<td>SVR</td>
<td>98.7%</td>
<td>97.6%</td>
<td>83%</td>
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<tr>
<td></td>
<td>Treatment failure</td>
<td>93.4%</td>
<td>79.7%</td>
<td>62.6%</td>
</tr>
<tr>
<td></td>
<td>Not treated</td>
<td>78.3%</td>
<td>62.4%</td>
<td>37.6%</td>
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</table>
Compensated HCV-related cirrhotic patients with SVR showed lower incidence of Major Adverse Cardiovascular Events (MACE)

Cumulative Incidence of MACE (%)

\[ P = 0.036 \]

Time (months)

<table>
<thead>
<tr>
<th>Incidence</th>
<th>1yr</th>
<th>2yrs</th>
<th>3yrs</th>
<th>4yrs</th>
<th>5yrs</th>
<th>6yrs</th>
<th>7yrs</th>
<th>8yrs</th>
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<tbody>
<tr>
<td>Non-SVR</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>1.1</td>
<td>2.8</td>
<td>4.3</td>
<td>6.0</td>
<td>6.8</td>
<td>8.7</td>
<td>11.4</td>
<td>15.2</td>
</tr>
<tr>
<td>[95%CI]</td>
<td>[0.6:2.1]</td>
<td>[1.8:4.2]</td>
<td>[3.0:6.1]</td>
<td>[4.4:8.2]</td>
<td>[5.0:9.2]</td>
<td>[6.4:11.8]</td>
<td>[8.2:15.7]</td>
<td>[10.5:21.8]</td>
</tr>
<tr>
<td>SVR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>0.7</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>[95%CI]</td>
<td>[0.2:2.9]</td>
<td>[0.8:6.4]</td>
<td>[0.8:6.4]</td>
<td>[0.8:6.4]</td>
<td>[0.8:6.4]</td>
<td>[0.8:6.4]</td>
<td>[0.8:6.4]</td>
<td>[0.8:6.4]</td>
</tr>
</tbody>
</table>

Cacoub P et al. EASL 2017
Disease outcomes after DAA-induced SVR: Data from the RESIST-HCV Cohort

- Cohort: 4468 patients treated with DAAs (March 2015–Dec 2016), followed for a median of 73 weeks

<table>
<thead>
<tr>
<th>63 patients died during the follow-up</th>
<th>Chronic hepatitis</th>
<th>Child–Pugh A cirrhosis</th>
<th>Child–Pugh B cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall death, n (%)</td>
<td>7 (0.7)</td>
<td>32 (1.0)</td>
<td>24 (6.3)</td>
</tr>
<tr>
<td>Liver-related death, n (%)</td>
<td>0</td>
<td>17 (0.5)</td>
<td>14 (3.7)</td>
</tr>
<tr>
<td>Cardiovascular death, n (%)</td>
<td>5 (0.5)</td>
<td>6 (0.2)</td>
<td>8 (2.1)</td>
</tr>
<tr>
<td>Other causes, n (%)</td>
<td>2 (0.2)</td>
<td>9 (0.3)</td>
<td>2 (0.5)</td>
</tr>
</tbody>
</table>

Liver mortality in 3095 patients with Child–Pugh A (mITT)

CV mortality in 4468 patients (mITT)

- Conclusions:
  - Patients with Child–Pugh A cirrhosis and SVR to DAAs have a better outcome than non-SVR patients
  - Patients with Child–Pugh B cirrhosis retain significant risk of liver events and death even after HCV eradication
  - Deaths linked to CV diseases seem to be reduced after viral eradication regardless of fibrosis stage

*Multivariate Cox regression
Calvaruso V, et al. ILC 2018, #4253 (PS-149)
ASTRAL-1, -2, -3: SOF/VEL for 12 Weeks in GT1–6 Treatment-Naive and -Experienced* Patients with and without Cirrhosis

- SVR12 (%)
- GT1: 98/323 (2 relapse, 1 D/C, 2 LTFU)
- GT2: 99/237 (1 D/C)
- GT4: 100/116 (1 death)
- GT5: 97/34 (34/35)
- GT6: 100/41
- GT3: 95/264 (11 relapse, 2 LTFU)

12 weeks

- D/C, discontinued; LTFU, lost to follow-up.
- * Patients treated with pegIFN/RBV ± PI or IFN ± RBV.

Study Design/Key Eligibility Criteria

- Randomized, open-label study in GT 3 patients with compensated cirrhosis conducted at 29 sites in Spain
- Inclusion criteria
  - Treatment naïve and treatment experienced, including patients with NS3/4 PI or NS5B inhibitor treatment experience
  - Patients with HIV coinfection were eligible
- Patients were stratified by treatment experience

Buti M, et al. EASL 2018; PS-035
## Results: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>SOF/VEL 12 Weeks n=101</th>
<th>SOF/VEL + RBV 12 Weeks n=103</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (range)</td>
<td>51 (31–70)</td>
<td>51 (31–85)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>75 (74)</td>
<td>87 (85)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>84 (83)</td>
<td>95 (92)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (range)</td>
<td>27 (18–40)</td>
<td>27 (18–47)</td>
</tr>
<tr>
<td>Treatment experienced, n (%)</td>
<td>27 (27)</td>
<td>28 (27)</td>
</tr>
<tr>
<td>HIV coinfection, n (%)</td>
<td>16 (16)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>IL28B CC, n (%)</td>
<td>64 (63)</td>
<td>53 (52)</td>
</tr>
<tr>
<td>Mean HCV RNA, log_{10} IU/mL (range)</td>
<td>6.2 (4.0–7.5)</td>
<td>6.3 (4.8–7.5)</td>
</tr>
</tbody>
</table>

- All patients had GT 3 HCV infection and cirrhosis

Buti M, et al. EASL 2018; PS-035
Results: SVR12 by Prior Treatment

Treatment Naïve
n=149

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SOF/VEL</th>
<th>SOF/VEL + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve</td>
<td>66/74</td>
<td>72/75</td>
</tr>
<tr>
<td></td>
<td>4 relapses 1 nonresponder 1 D/C due to AE 2 LTFU</td>
<td>1 relapse 2 LTFU</td>
</tr>
<tr>
<td>Exper.</td>
<td>96</td>
<td>96</td>
</tr>
</tbody>
</table>

Treatment Experienced
n=55

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SOF/VEL</th>
<th>SOF/VEL + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exper.</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>1 relapse</td>
<td>1 relapse</td>
</tr>
</tbody>
</table>

Error bars represent 95% confidence intervals.

Buti M, et al. EASL 2018; PS-035
### Integrated Efficacy Analysis: G/P for 8 Weeks in GT1–6
Treatment-Naive and -Experienced* Patients without Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>GT1</th>
<th>GT2</th>
<th>GT3 †</th>
<th>GT4</th>
<th>GT5</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTT</td>
<td>98</td>
<td>99</td>
<td>98</td>
<td>95</td>
<td>95</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>mITT</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>97</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

- **Overall:** 2 BT 7 RL 5 D/C 1 LTFU 7 LTFU
- **GT1:** 1 BT 2 D/C 1 LTFU
- **GT2:** 2 RL 2 D/C
- **GT3 †:** 1 BT 5 RL 4 LTFU
- **GT4:** 1 D/C 2 LTFU
- **GT5:** 2 2 2 2 13 13
- **GT6:** 12 †

**SVR rates were high, regardless of baseline patient or viral characteristics**

BT, breakthrough; mITT, modified intent-to-treat.

* Includes patients with prior SOF use (8-week G/P, n = 7); † One GT6 patient initially with missing SVR12 data is excluded from this analysis; ‡ All GT3 patients were treatment naive.

Bernstein D, et al. ACG 2017 (oral presentation).
Integrated Efficacy Analysis: G/P for 12 Weeks in GT1–6 Treatment-Naive Patients with Cirrhosis

### Pan-genotypic Regimens Safety Profiles

<table>
<thead>
<tr>
<th></th>
<th>G/P Integrated safety analysis</th>
<th>SOF/VEL Integrated ASTRAL studies</th>
<th>SOF/VEL/VOX POLARIS-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No cirrhosis (n = 1977)</td>
<td>Cirrhosis (n = 288)</td>
<td>± Cirrhosis (n = 1035)</td>
</tr>
<tr>
<td>SAE</td>
<td>31 (2)</td>
<td>17 (6)</td>
<td>23 (2)</td>
</tr>
<tr>
<td>D/C due to AE</td>
<td>8 (&lt; 1)</td>
<td>0</td>
<td>2 (&lt; 1)</td>
</tr>
<tr>
<td>AEs occurring in ≥ 10% of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>363 (18)</td>
<td>58 (20)</td>
<td>296 (29)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>272 (14)</td>
<td>47 (16)</td>
<td>217 (21)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nausea</td>
<td>–</td>
<td>–</td>
<td>135 (13)</td>
</tr>
</tbody>
</table>

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Retreatment of HCV infection in patients who failed GLE/PIB: MAGELLAN-3 study

Objective: ongoing study to evaluate efficacy and safety of 12 or 16 weeks of GLE/PIB + SOF + RBV in patients who previously failed GLE/PIB treatment

Study design:

- **Results:**
  - 30% cirrhosis, 26% failed PI and/or NS5Ai before GLE/PIB treatment failure, and 65% had ≥2 NS5A RASs at baseline
  - One GT 1a cirrhotic patient with prior experience of SOF/LDV relapsed
  - 100% (14/14) SVR12 in GT 3 patients
  - No D/Cs and no DAA-related SAEs

- **Conclusion:**
  - Preliminary analysis shows retreatment with GLE/PIB + SOF + RBV yields a high SVR12 rate in HCV-infected patients who have experienced virological failure following GLE/PIB treatment

*Either treatment or combination received before treatment with GLE/PIB

Summary

» All treatment-naïve and experienced HCV patients should be considered for all oral DAA therapy.

» The benefit of SVR goes way beyond improved outcome of underlying liver disease.

» Drug-drug interactions need to be considered prior to starting HCV therapy.

» All patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc.

» The main challenge in the DAA era is the implementation of improved screening programs and linking newly diagnosed treatment-naïve patients into HCV care.
Thank you