Best of HCV from EASL 2014

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Best of HCV from EASL 2014

• Candidacy for Treatment of HCV Patients: The Clinical Experience from Kaiser Permanente

• The New Treatment Regimens for HCV

• Assessment of Patient-related Outcomes During HCV treatment
Comorbid Conditions Associated With Decision-Making Regarding Treating or Not Treating Chronic Hepatitis C in a Large U.S. Health Maintenance Organization

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Methods

• Study Design
  – A retrospective study using the database of Kaiser Permanente, Southern California, a large Health Maintenance Organization including 3.5 – 4 million members

• Inclusion Criteria
  – ≥ 18 years old with a diagnosis code or a positive lab test result for HCV RNA from January 1, 2002 through December 31, 2012
  – ≥ 6 months continuous membership plus drug benefit prior to HCV treatment
  – Index date was defined as the date of the first treatment course or first chronic HCV diagnosis

Nyberg, L. et al. EASL 2014, Abstract #O67
Identification of comorbid illnesses representing relative or absolute contraindications to HCV treatment with interferon-based therapy were determined by diagnosis codes and/or lab tests for:

- Comorbid illness identified in the study: cancer, anemia, autoimmune disorder, renal dysfunction, thrombocytopenia, diabetes, HIV, CVD, psychosis/bipolar disorder, depression, severe lung disease, substance abuse, Hepatitis B, MELD ≥ 12

Multivariate logistic regression was used to determine predictors of treatment vs non-treatment
Entire Population (Patients with a diagnosis code or positive lab test for HCV)
- N=51,984 patients
- 7,945 patients (15%) of this population received treatment

Study Population (After applying inclusion/exclusion criteria)
- N=32,283 patients
- 5,533 patients (17%) in the study population received treatment
Entire Population (Patients with a diagnosis code or positive lab test for HCV)

- N=51,984 patients
- 7,945 patients (15%) of this population received treatment

Study Population (After applying inclusion/exclusion criteria)

- N= 32,283 patients
- 5,533 patients (17%) in the study population received treatment
Study Population
N=32,283

With at least 1 Significant Comorbid Illness
N=16,186 (50%)

Not Treated
N=13,702 (85%)

Treated
N=2,484 (15%)

Results

The patients with at least 1 significant comorbid illness

...
0% (16,186/32,283) of the study population had at least one significant comorbid illness.
- 15% (2,484/16,186) were treated
- 85% (13,702/16,186) were not treated
In multivariate logistic regression analysis, factors associated with receiving treatment included younger age (age<65), male gender, presence of hemorrhage, HIV co-infection, and a history of liver transplantation (P = 0.0012 to <0.0001).
Factors Associated with NOT Receiving Treatment

In multivariate logistic regression analysis, factors associated with not receiving treatment for HCV included presence of anemia, autoimmune disorders, renal dysfunction, CVD, psychosis/bipolar, substance abuse, severe lung disease and MELD>12 (P = 0.0195 to <0.0001)
In this large database representing a real world population, only 15-17% of those identified with HCV were treated with interferon-based regimens. 2% of the total study population were likely interferon ineligible or intolerant. 0% had no apparent contraindications to interferon-based therapy. 0% had comorbid conditions representing relative or absolute contraindications to interferon-based therapy. New, interferon-free regimens may offer new treatment options for this group.
Candidacy for Treatment of HCV Patients: The Clinical Experience from Kaiser Permanente

The New Treatment Regimens for HCV

Assessment of Patient-related Outcomes During CV treatment
Simeprevir Plus Sofosbuvir With/Without Ribavirin in HCV Genotype-1 Prior Null-responder / Treatment-naïve Patients (COSMOS Study): Primary Endpoint (SVR12) Results in Patients With METAVIR F3-4 (Cohort 2)

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Osmos Study Design: Randomised, Multicentre, Open-label Trial

- **Aim:**
  - Stratified by treatment history, HCV GT 1a/1b
  - Primary endpoint: SVR12
  - Secondary endpoints: RVR, on-treatment failure, relapse rate, safety and tolerability

- **Randomised:** 2:1:2:1

- **Arm 1:** SMV + SOF + RBV (Post-treatment follow-up)
- **Arm 2:** SMV + SOF (Post-treatment follow-up)
- **Arm 3:** SMV + SOF + RBV (Post-treatment follow-up)
- **Arm 4:** SMV + SOF (Post-treatment follow-up)

**Dosage:**
- SMV 150 mg QD + SOF 400 mg QD±RBV 1000/1200 mg/day (BID)

**Aim:**
- Short 1: METAVIR F0-F2, prior null responders
- Short 2: METAVIR F3-F4, prior null responders or treatment-naïve
- Stratified by treatment history, HCV GT 1a/1b

**Note:**
- SMV, smegosin; SOF, sofosbuvir; RBV, ribavirin; RVR, rapid virologic response; imprevir; QD, once daily; GT, genotype; BID, twice daily; BID, twice daily; GT, genotype; QD, once daily; RBV, ribavirin; RVR, rapid virologic response; imprevir; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after end of treatment.
OSMOS Cohort 2: SVR12 – Primary Endpoint (Treated population)

SVR12: sustained virologic response 12 weeks after end of treatment
Non-VF: Non-virologic failure
Relapse

Proportion of patients (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>24 weeks</th>
<th>12 weeks</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMV/SOF + RBV</td>
<td>28/30</td>
<td>16/16</td>
<td>25/27</td>
</tr>
<tr>
<td>SMV/SOF</td>
<td>2/30</td>
<td>2/27</td>
<td>1/14</td>
</tr>
<tr>
<td>SMV/SOF ± RBV</td>
<td>3/87</td>
<td>13/14</td>
<td>82/87</td>
</tr>
</tbody>
</table>

7% 7% 7%
20 40 60 80 100

SMV/SOF + RBV SMV/SOF SMV/SOF
Proportion of patients (%)
OSMOS Cohort 2: Conclusions

SMV/SOF QD led to SVR12 rates of 93-100% (ITT) in HCV GT 1 infected treatment-naïve and prior null-responder patients with METAVIR F3-4.

SVR12 rates were high, regardless of baseline characteristics:
- HCV GT 1 subtype, Q80K polymorphism, METAVIR score, IL28B GT, prior treatment history

SMV/SOF QD +/- RBV was safe and well tolerated. Two Phase 3 trials investigating SMV/SOF without RBV are ongoing (OPTIMIST-1 and -2)

Phenotype; ITT, Intent-to-treat; QD, once daily; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR12, virologic response 12 weeks after end of treatment.
SAPPHIRE I: Phase 3 Placebo-Controlled Study Of Interferon-Free, 12-Week Regimen Of ABT-450/r/ABT-267, ABT-333, And Ribavirin In 631 Treatment-Naïve Adults With Hepatitis C Virus Genotype 1
APPHIRE-I: Placebo-Controlled Design

- Double-Blind Treatment Period
- Open-Label Treatment Period
- 3D + RBV (n=473)
- Placebo (n=158)
- 3D + RBV
- 48-Week Follow-Up

Week 0 | Week 12 | Week 24 | Week 60 | Week 72

Primary Analysis: SVR12

D: co-formulated ABT-450/r/ombitasvir, 150 mg/100 mg/25 mg QD; dasabuvir, 1000 mg BID
RBV: 1000-1200 mg daily according to body weight (<75 kg and >75 kg, respectively)
## APPHIRE-I: Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>3D + RBV (N=473)</th>
<th>Placebo (N=158)</th>
</tr>
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<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>271 (57.3)</td>
<td>73 (46.2)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
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<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>428 (90.5)</td>
<td>144 (91.1)</td>
</tr>
<tr>
<td>Black</td>
<td>26 (5.5)</td>
<td>8 (5.1)</td>
</tr>
<tr>
<td>Hispanic/Latino ethnicity, n (%)</td>
<td>27 (5.7)</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>52.0 (18.0-70.0)</td>
<td>52.0 (21.0-70.0)</td>
</tr>
<tr>
<td>Median BMI, kg/m² (range)</td>
<td>25.2 (18.0-38.4)</td>
<td>25.5 (18.5-39.4)</td>
</tr>
<tr>
<td>Genotype stage, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>0-F1</td>
<td>363 (76.7)</td>
<td>116 (73.4)</td>
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<tr>
<td>2</td>
<td>70 (14.8)</td>
<td>27 (17.1)</td>
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<tr>
<td>3</td>
<td>40 (8.5)</td>
<td>15 (9.5)</td>
</tr>
<tr>
<td>4</td>
<td></td>
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</tr>
<tr>
<td>BB non-CC genotype, n (%)</td>
<td>329 (69.6)</td>
<td>108 (68.4)</td>
</tr>
<tr>
<td>subtype, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>322 (68.1)</td>
<td>105 (66.5)</td>
</tr>
<tr>
<td>b</td>
<td>151 (31.9)</td>
<td>53 (33.5)</td>
</tr>
<tr>
<td>Median HCV RNA, log_{10} IU/mL (range)</td>
<td>6.51 (3.58-7.60)</td>
<td>6.64 (3.71-7.51)</td>
</tr>
</tbody>
</table>

Genotype and subtype were assessed using the Versant HCV Genotype Inno-LiPA Assay, v2.0.
APPHIRE-I Results: ITT SVR12 Rates (Superiority to Calculated Placebo Rate)
SAPPHIRE-I: Conclusions

The ITT SVR12 rate was 96.2% (455/473) for treatment-naïve GT1-infected patients receiving 12 weeks of co-formulated ABT-450/r/ombitasvir + dasabuvir + RBV.

The regimen was generally well-tolerated, with a low rate of study drug discontinuation due to AE(s) (0.6%).
All-Oral Dual Therapy With Daclatasvir And Asunaprevir
In Patients With HCV Genotype 1b Infection: Phase 3
Study Results
Primary endpoint: proportion of DCV + ASV-treated patients with SVR\textsubscript{12} patients infected with HCV genotype 1b

Treatment-naive
Nonresponders: prior null or partial response to pegIFN/RBV
Interferon-ineligible/intolerant (treatment-naive or -experienced) due to
- Depression
- Anemia/neutropenia
- Compensated advanced fibrosis/cirrhosis (F3/F4) with thrombocytopenia

<table>
<thead>
<tr>
<th>Randomization</th>
<th>DCV 60 mg QD + ASV 100 mg BID 24 weeks (N = 203)\textsuperscript{a}</th>
<th>Follow up 24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive</td>
<td>DCV-PBO + ASV-PBO 12 weeks (N = 102)</td>
<td>Enter another study: DCV + ASV 24 weeks</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>DCV + ASV 24 weeks (N = 205)</td>
<td>Follow up 24 weeks</td>
</tr>
<tr>
<td>Tolerable/intolerant</td>
<td>DCV + ASV 24 weeks (N = 235)</td>
<td>Follow up 24 weeks</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Excludes 2 patients inadvertently assigned, instead of randomized, to DCV + ASV; patients were excluded from efficacy analyses but both achieved SVR\textsubscript{12}
### Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment-naive DCV + ASV (N = 205)</th>
<th>Treatment-naive Placebo (N = 102)</th>
<th>Nonresponder&lt;sup&gt;a&lt;/sup&gt; (N = 205)</th>
<th>Ineligible/intolerant&lt;sup&gt;b&lt;/sup&gt; (N = 235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median years</td>
<td>55</td>
<td>54</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>(%)</td>
<td>101 (49)</td>
<td>54 (53)</td>
<td>111 (54)</td>
<td>98 (42)</td>
</tr>
<tr>
<td>Median age</td>
<td>135 (66)</td>
<td>59 (58)</td>
<td>148 (72)</td>
<td>169 (72)</td>
</tr>
<tr>
<td>(%)</td>
<td>14 (7)</td>
<td>8 (8)</td>
<td>10 (5)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Abnormal ALT</td>
<td>52 (25)</td>
<td>33 (32)</td>
<td>45 (22)</td>
<td>56 (24)</td>
</tr>
<tr>
<td>(%)</td>
<td>52 (25)</td>
<td>26 (25)</td>
<td>27 (13)</td>
<td>48 (20)</td>
</tr>
<tr>
<td>3,000 log&lt;sub&gt;10&lt;/sub&gt; IU/mL</td>
<td>53 (26)</td>
<td>26 (25)</td>
<td>27 (13)</td>
<td>48 (20)</td>
</tr>
<tr>
<td>1,000 log&lt;sub&gt;10&lt;/sub&gt; IU/mL</td>
<td>152 (74)</td>
<td>76 (75)</td>
<td>178 (87)</td>
<td>187 (80)</td>
</tr>
<tr>
<td>Cirrhosis, n (%)</td>
<td>33 (16)</td>
<td>16 (16)</td>
<td>63 (31)</td>
<td>111 (47)</td>
</tr>
<tr>
<td>Genotype, n (%)</td>
<td>76 (37)</td>
<td>N/A</td>
<td>29 (14)</td>
<td>82 (35)</td>
</tr>
<tr>
<td>CC</td>
<td>129 (63)</td>
<td>N/A</td>
<td>173 (84)</td>
<td>143 (61)</td>
</tr>
</tbody>
</table>

<sup>a</sup>119 (58%) null responders, 84 (41%) partial responders, and 2 (1%) relapsers.

<sup>b</sup>71 (30%) patients with depression, 87 (37%) with anemia/neutropenia, and 77 (33%) with compensated advanced cirrhosis with thrombocytopenia (6 with advanced fibrosis [F3], 70 with cirrhosis [F4], and 1 not reported).
SVR$_{12}$ rates documented on or after posttreatment Week 12
- Treatment-naive: 91%
- Nonresponders: 82%
- Ineligible/intolerant: 83%
All-oral DCV + ASV therapy achieved SVR$_{12}$ rates up to 1% in treatment-naive, 82% in nonresponder, and 3% in ineligible/intolerant patients with genotype 1b.

- SVR$_{12}$ rates were similar in non-cirrhotic (85%) and cirrhotic (84%) patients.
- No differences by age, gender, race, $IL28B$ genotype, or prior IFN/RBV treatment experience.

CV + ASV was generally safe and well tolerated.

- Only 2% of patients discontinued treatment due to adverse events.

CV is being further evaluated in all-oral combinations in multiple patient populations of high unmet need.
Safety and Efficacy of the All-oral Regimen of MK-5172/MK-8742 + Ribavirin in Treatment-naïve, Non-cirrhotic Patients With Hepatitis C Virus Genotype 1 Infection: The C-WORTHY Study


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To assess the efficacy/safety of an 8- to 12-week regimen of MK-5172 + K-8742 ± weight-based ribavirin in treatment-naïve, noncirrhotic patients with HCV G1 infection

**Key inclusion/exclusion criteria:**
- Treatment-naïve patients ≥ 18 years old with chronic HCV G1a or G1b infection
- Liver biopsy or noninvasive test (METAVIR F0-F3)
- Minimum baseline hemoglobin: 12 g/dL (females) or 13 g/dL (males)
- HIV and hepatitis B virus negative
- Alanine aminotransferase (ALT) as aspartate aminotransferase (AST) <350 IU/L
Sustained virologic response; TW = treatment week.
WORTHY (A+B) – Overall Efficacy (SVR$_{4-24}$)*
Intention-to-Treat (Nonvirologic Discontinuation = Failure)

- 8 weeks with RBV
- 12 weeks with RBV
- 12 weeks (no RBV)

Treatment Week 4
- 8 weeks with RBV: 100%
- 12 weeks with RBV: 96%
- 12 weeks (no RBV): 94%

End of Treatment
- 8 weeks with RBV: 95%
- 12 weeks with RBV: 96%
- 12 weeks (no RBV): 98%

SVR$_{4-24}$
- 8 weeks with RBV: 83%
- 12 weeks with RBV: 94%
- 12 weeks (no RBV): 98%

Note: 100% of patients have completed SVR$_{24}$; Part B: 8-week arm, 93% of patients have completed SVR$_{8}$; 12-week arms, 100% of patients have completed SVR$_{8}$; 2 patients (Part A), 2 patients (Part B) discontinued early and are counted as failures.
**Summary**

**Efficacy**
- MK-5172/MK8742 once daily with or without RBV for 12 weeks is highly efficacious with a SVR of 94%-98%
- MK-5172/MK-8742 + RBV for 8 weeks in patients with HCV G1a infection had an SVR4/8 of 83%
- Most common type of virologic failure was relapse after a treatment duration of 8 weeks

**Safety**
- All treatment regimens were generally safe and well-tolerated
- There were no early discontinuations due to drug-related AEs
- No grade 3 or 4 laboratory abnormalities
dipasvir/Sofosbuvir With and Without Ribavirin for 8 Weeks Compared to Ledipasvir/Sofosbuvir for 12 Weeks in Treatment-Naïve Noncirrhotic Genotype-1 HCV-Infected Patients: The Phase 3 ION-3 Study

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Virginia Mason Medical Center, Seattle, WA, USA; ²Henry Ford Health System, Detroit, MI, USA; Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, PA, USA; ⁴University of California Davis Medical Center, Sacramento, CA, USA; ⁵North Shore University Hospital, Manhasset, NY, USA; ⁶Gilead Sciences, Inc., Foster City, CA; ⁷Division of Gastroenterology and Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA; ⁸Scripps Clinic, La Jolla, CA; ⁹Indianapolis Gastroenterology Research Foundation, Indianapolis, IN, USA; ¹⁰University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
Background and Aims

1 Treatment-Naïve (ION-3)

DV/SOF ± RBV for 8 weeks and LDV/SOF for 12 weeks demonstrated high SVR rates in the Phase LONESTAR study in treatment-naïve HCV patients without cirrhosis.

To evaluate whether LDV/SOF for 8 weeks is effective for HCV treatment-naïve, non-cirrhotic, GT patients or if RBV or a longer treatment duration of 12 weeks is required to achieve high SVR rate.
Treat 1 treatment-naïve patients without cirrhosis
Inclusion criteria
- No upper age or BMI limit
- Opiate substitution therapy allowed
47 patients randomized 1:1:1 across three arms
Randomized by HCV subtype (1a or 1b)
Results: Non-Inferiority Comparison

1 Treatment-Naïve (ION-3)

SVR12 (%)

- LDV/SOF: 94 (202/215)
- LDV/SOF + RBV: 93 (201/216)
- LDV/SOF: 95 (206/216)

8 Weeks

12 Weeks

*Numbers represent 95% confidence intervals.*
Conclusions

1 Treatment-Naïve (ION-3)

LDV/SOF ± RBV for 8 or 12 weeks results in high VR12 rates

no difference in efficacy among the groups was observed

host and viral factors traditionally associated with lower VR rates did not affect SVR12 rates

LDV/SOF ± RBV was safe and well tolerated

- RBV contributed to a higher incidence of AEs and laboratory abnormalities

an 8 week LDV/SOF treatment regimen is a safe and effective treatment for treatment-naïve non-cirrhotic patients with HCV GT 1 infection

by K, et al. NEJM In Press
ledipasvir (LDV) and Sofosbuvir (SOF) Combination Improves Patient-Reported Outcomes (PRO) During Treatment of Chronic Hepatitis C (CH-C) Patients: Results From the ION-1 Clinical Trial

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Background

Interferon-based treatment for chronic hepatitis C (CH-C) causes substantial side effects that negatively impact patient-reported outcomes (PROs). The use of ribavirin (RBV) is associated with additional burden on PROs. Merger of interferon- and ribavirin-free regimens are expected to result in less if any adverse events and, therefore, better PROs in patients undergoing anti-CV treatment.
to assess patient reported outcome of CH-C patients treated with sofosbuvir and ledipasvir (LDV+SOF) with or without ribavirin in the 12 weeks arms of ION-1 clinical trial
N-1 Multicenter Phase 3 Clinical Trial

31 HCV genotype 1 treatment-naïve patients in 12 weeks arm of the study

Clinical data: 52±11 years old, 59% male, 16% cirrhotic, 56% from USA

Patient-reported outcome (PRO) questionnaires were completed at baseline, during and post-treatment: SF-36, FACIT-F, CLDQ-HCV, WPAI:SHP

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<th>0</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>24</th>
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<tr>
<td>400 mg + LDV 90 mg + RBV 1000/1200 mg daily</td>
<td>n=217</td>
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<tr>
<td>400 mg + LDV 90 mg daily</td>
<td>n=214</td>
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Follow-Up Week 12

PROs PROs PROs PROs PROs PROs PROs

Treatment-related anemia: 74.2% in LDV+SOF+RBV, 7.0% in LDV+SOF (<0.01)

SVR rate: 97.2% in LDV+SOF+RBV, 98.6% in LDV+SOF (p=NS)

-treatment and post-treatment HCV RNA viral load results were blinded to patients and investigators
Scores in Patients Treated With Ledipasvir and Sofosbuvir With or Without Ribavirin: Treatment Week 12

- SF-36: physical HRQL
- SF-36: mental HRQL
- FACIT-F: fatigue
- FACIT-F: total well-being
- CLDQ-HCV; total HRQL
- Work productivity
- Activity other than work

Values represent differences between treatment regimens

- not significant (p>0.05)
- p=0.0006
- p=0.053
- p=<0.0001
- p=<0.0017
Changes in PRO Scores From Baseline to Treatment Week 12

- Values represent differences between treatment regimens
- *p* ≤ 0.05 for the difference from baseline
Conclusions

Treatment-naïve genotype 1 CH-C patients receiving sofosbuvir+ledipasvir have similar SVR and superior PROs compared to patients receiving the same regimen with added ribavirin. The RBV-free regimen is associated with improved PRO scores during treatment and after achieving VR-12.
During this year’s EASL meeting (ILC-2014, London, England), exciting data regarding a number of new regimens to treat HCV were presented.

The data presented showed that these regimens have high efficacy, improved safety, and shorter duration of treatment.

Furthermore, some of these regimens can clearly improve patient reported outcomes such as fatigue and HRQL.