Hepatitis Debrief
The Liver Meeting 2019
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Bethesda, Maryland
Overview

HBV
- Natural history
- Novel therapies to achieve functional cure
- Prevention
  - Vaccination
  - Screening
- Co-infection with HDV

HCV
- Models of elimination
  - Treatment
  - Vaccination
- Therapy
  - Unique populations
  - Challenging populations
- Benefits of SVR
- Organ transplantation
Steatohepatitis Worsens HBV Liver Injury

Liver biopsies from 420 adults enrolled in North American cohort study scored for inflammation, fibrosis and NAFLD

Fibrosis stage by severity of NAFLD

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Unadjusted Risk Ratio (95%CI)</th>
<th>P</th>
<th>Adjusted Risk Ratio (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No steatosis</td>
<td>249</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steatosis</td>
<td>71</td>
<td>0.6 (0.3, 1.1)</td>
<td>0.003</td>
<td>0.5 (0.3, 0.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Steatohepatitis</td>
<td>55</td>
<td>1.7 (1.1, 2.5)</td>
<td></td>
<td>1.6 (1.1, 2.4)</td>
<td></td>
</tr>
<tr>
<td>Age, per 10 years</td>
<td>375</td>
<td>1.1 (1.0, 1.3)</td>
<td>0.1</td>
<td>1.2 (1.1, 1.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Sex (versus Female) Male</td>
<td>141</td>
<td>1.7 (1.1, 2.6)</td>
<td>0.02</td>
<td>1.4 (1.0, 2.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>HBV DNA, per log10 IU/mL</td>
<td>375</td>
<td>1.1 (1.0, 1.2)</td>
<td>0.02</td>
<td>1.2 (1.1, 1.3)</td>
<td>0.004</td>
</tr>
<tr>
<td>ALT, per log2 U/L</td>
<td>342</td>
<td>1.3 (1.2, 1.5)</td>
<td>&lt;0.001</td>
<td>1.3 (1.1, 1.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Implications for clinical practice: Important to screen and manage metabolic abnormalities to prevent liver disease progression

Khalili et al Abstract 0162
Is There a Difference in HCC Risk between Tenofovir and Entecavir?

ANRS CO22 Cohort: 1960 (all races) HBeAg+/− patients who received tenofovir (1075) or entecavir (885) followed-up for a mean of in 45 months.

Log-rank, P=0.321

TDF 0.086

ETV 0.077

PAGE-B Cohort: 1935 Caucasian adults HBeAg +/- with or without compensated cirrhosis on ETV (n=772) or TDF (n=1163)

No difference in HCC risk between tenofovir and entecavir.

Pol et al Abstract 0197

Papatheodoredis et al Abstract 0454
Association Between Anti-Platelet Therapy and HCC Risk

Retrospective cohort study in patients receiving entecavir or tenofovir for ≥6 months

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Multivariable analysis^</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted HR</td>
</tr>
<tr>
<td>Antiplatelet#</td>
<td>0.83</td>
</tr>
<tr>
<td>Aspirin monotherapy#</td>
<td>Referent</td>
</tr>
<tr>
<td>Non-user#</td>
<td>1.12</td>
</tr>
<tr>
<td>DAPT#</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Implications for clinical practice: Provocative findings, need further confirmation
NA-Induced HBsAg Loss is Durable

Retrospective analysis of patients who stopped or continued NA after HBsAg loss
Evaluated incidence of HBsAg sero-reversion and HCC

Implications for clinical practice: HBsAg loss is a durable and safe endpoint for stopping therapy

Kim et al Abstract 0198
Switch or Add-on Peginterferon to NA Therapy

**Implications for clinical practice:** Little benefit to add-on or sequential approach to induce HBsAg loss

**Primary endpoint**
- HBeAg loss at week 72
- Reduction in qHBsAg>1log

**Farag et al Abstract 0195**
HBV Lifecycle and Many Drug Targets

**Entry Inhibitors**
- Myrcludex
- Cyclosporine
- Ezetimibe

**Immunodulators**
- TLR 7 and 9 agonists
- T-cell vaccines
- PD-1/PD-L1 blockade

**Core inhibitors**
- Heteroaryldihydropyrimidines
- Phenylpropenamides
- Sulfamoyl benzamides
- Aminothiazole

**RT Pol Inhibitors**
- Nucleotide analogues
- Non-Nuc analogues
- RNaseH inhibitors

**HBSAg release Inhibitor**
- NAP

**cccDNA silencing**

**Inhibit viral transcripts by:**
- siRNA
- Antisense oligonucleotides
- Ribozymes
Pathways to Achieving Functional Cure

Inhibit Viral Replication
- Virions (HBV DNA)
- +/- CpAM
- +/- RNAi
- +/- Entry inhibitor
- +/- cccDNA inhibitor

Lower Viral Antigen Burden
- HBeAg
- HBsAg

Boost Immune Response
- NK cells
- T cells
- B cells
- Macrophages
- PD-1; PDL1
- Lymphotoxin B
- T Cell reprogramming
- Therapeutic vaccine
Core Assembly Modulator (CAM) JNJ-0440

Two cohorts of 10 treatment-naïve HBeAg +/- patients randomized to JNJ-0440 or placebo x 28 days

Efficacy

<table>
<thead>
<tr>
<th></th>
<th>750 mg QD</th>
<th>750 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in HBV DNA vs. BL log_{10} IU/mL</td>
<td>-3.2</td>
<td>-3.3</td>
</tr>
<tr>
<td>Mean change in HBV RNA vs. BL log_{10} copies/mL</td>
<td>-2.0</td>
<td>-2.6</td>
</tr>
</tbody>
</table>

- Mean change in HBeAg vs. BL log_{10} IU/mL -0.2
- No relevant changes in HBsAg levels

Safety

No treatment discontinuations-serious AEs

Potent inhibition of viral replication ?functional cure
GSK3389404 (antisense oligonucleotide) in NUC Suppressed Patients

Phase 2a, multicenter, randomized, double-blind, placebo-controlled study in HBeAg+-, n=66

Mean change from baseline in HBsAg (log$_{10}$ IU/mL) over time by treatment group

Table 1. Summary of AEs

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=10)</th>
<th>30 mg weekly (N=6)</th>
<th>60 mg weekly (N=20)</th>
<th>120 mg weekly (N=15)</th>
<th>120 mg bi-weekly (N=15)</th>
<th>Total GSK3389404 (N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AEs, n (%)</td>
<td>8 (80)</td>
<td>3 (50)</td>
<td>15 (75)</td>
<td>11 (73)</td>
<td>8 (53)</td>
<td>37 (66)</td>
</tr>
<tr>
<td>Mild (Grade 1)</td>
<td>2 (20)</td>
<td>2 (33)</td>
<td>7 (35)</td>
<td>4 (27)</td>
<td>4 (27)</td>
<td>17 (30)</td>
</tr>
<tr>
<td>Moderate (Grade 2)</td>
<td>4 (40)</td>
<td>0</td>
<td>8 (40)</td>
<td>6 (40)</td>
<td>2 (13)</td>
<td>16 (29)</td>
</tr>
<tr>
<td>Severe (Grade 3)</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
<td>1 (7)</td>
<td>2 (13)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Potentially life-threatening (Grade 4)</td>
<td>2 (20)*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related AEs, n (%)</td>
<td>4 (40)</td>
<td>3 (50)</td>
<td>10 (50)</td>
<td>8 (53)</td>
<td>7 (47)</td>
<td>28 (50)</td>
</tr>
<tr>
<td>Serious AEs, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (7)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>AEs leading to study withdrawal or treatment discontinuation, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (7)*</td>
<td>1 (2)</td>
<td></td>
</tr>
</tbody>
</table>

*Both Grade 4 lab abnormality of creatine kinase increase attributed to physical activity. *Grade 1 pruritus on the neck.

Proof of principle that antisense oligonucleotides can decrease HBsAg levels

Yuen et al Abstract 0695
Toll-Like Receptor 8 Agonist (TLR8) GS-9688 in NA Suppressed Patients

Gane et al Abstract 0697

- HBsAg loss in 2 HBeAg- patients (one from each treatment arm at Weeks 24, 48)
- HBeAg loss in 1 patient (Week 24)
- Dose-dependent increases in serum cytokines observed in GS-9688 treatment groups

Promising approach, await further studies
Therapeutic HBV Vaccine

- NASVAC: contains HBsAg and HBcAg
- Administered intranasally 10 times, bi-weekly to NA-suppressed patients and inactive carriers

Efficacy
- ~3/4 had 20% decline in HBsAg
- ~1/3 developed anti-HBs
- 2 patients in each group lost HBsAg

Promising immune therapy for achieving functional cure

Yoshida et al Abstract 0088
### Dual Therapy CAM (ABI-H0731) plus NA

- **Study 202**
  - **HBeAg+ Rx-naive**
  - **ETV + Pbo (n=12)**
  - **ETV + 731 300 mg (n=13)**

  **Double blind**
  
- **Study 201**
  - **HBeAg+ On NA suppressive therapy**
  - **NA + Pbo (n=18)**
  - **NA + 731 300 mg (n=29)**

  **Double blind**

#### Study 202

- Superior reductions in DNA/pgRNA

#### Deeper HBV DNA and HBV RNA suppression with combination. Await data on HBeAg and HBsAg loss

#### Study 201

- Higher % of patients with DNA TND and pgRNA <35 IU/mL

- Among HBeAg positive patients, rapid reductions in HBV pgRNA levels by Week 6 were observed only in patients treated with ABI-H0731 + ETV

Sulkowski et al Abstract LP1
Triple Therapy: RNAi + CAM + NA

HBeAg+ n=4 / HBeAg- n=8, NA-naïve n=5 / experienced n= 7, All 12 Asian

- Three 200 mg JNJ-3989 subcutaneous doses on Days 1, 29 and 57
- Oral JNJ-6379 250 mg once daily for 12 weeks (until Day 85)
- Started or already on ETV or TDF treatment on Day 1 to beyond the end of JNJ-6379 dosing
- Response rates similar between HBeAg+ and HBeAg-

HBsAg

JNJ-6379 (CAM-N) once-daily treatment

JNJ-3989 (RNAi) monthly dosing

Log_{10} HBsAg change from Day 1 (Mean±SEM)

HBV DNA

HBV DNA

JNJ-6379 (CAM-N) once-daily treatment

JNJ-3989 (RNAi) monthly dosing

HBV DNA LLOQ

HBsAg

qHBsAg

Day

Mean (SEM) HBsAg (IU/mL)

0 5000 10000 15000

0 1 8 15 29 43 57 71 85 113

Day

Log_{10} qHBsAg

0 -0.5 -1.0 -1.5 -2.0

Triple therapy resulted in marked decline in HBsAg levels …?Functional cure

Yuen et al Abstract LP4
### Trivalent HBV Vaccine Superior to Monovalent Vaccine

<table>
<thead>
<tr>
<th>Population</th>
<th>Engerix-B® N</th>
<th>SPR (%)</th>
<th>Sci-B-Vac™ N</th>
<th>SPR (%)</th>
<th>Difference in SPR (%) [95% Confidence Interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>723</td>
<td>76.5%</td>
<td>718</td>
<td>91.4%</td>
<td>14.9% [11.2%, 18.6%]</td>
</tr>
<tr>
<td>18-44 years</td>
<td>135</td>
<td>91.1%</td>
<td>125</td>
<td>99.2%</td>
<td>8.1% [3.4%, 14.2%]</td>
</tr>
<tr>
<td>45-64 years</td>
<td>322</td>
<td>80.1%</td>
<td>325</td>
<td>94.8%</td>
<td>14.7% [9.8%, 19.8%]</td>
</tr>
<tr>
<td>65+ years</td>
<td>266</td>
<td>64.7%</td>
<td>268</td>
<td>83.6%</td>
<td>18.9% [11.6%, 26.1%]</td>
</tr>
<tr>
<td>Men</td>
<td>269</td>
<td>69.5%</td>
<td>282</td>
<td>86.9%</td>
<td>17.4% [10.6%, 24.2%]</td>
</tr>
<tr>
<td>Women</td>
<td>454</td>
<td>80.6%</td>
<td>436</td>
<td>94.3%</td>
<td>13.7% [9.5%, 18.0%]</td>
</tr>
<tr>
<td>Diabetics</td>
<td>60</td>
<td>58.3%</td>
<td>54</td>
<td>83.3%</td>
<td>25.0% [8.4%, 40.4%]</td>
</tr>
<tr>
<td>Obese (BMI &gt; 30)</td>
<td>254</td>
<td>68.1%</td>
<td>269</td>
<td>89.2%</td>
<td>21.1% [14.3%, 28.0%]</td>
</tr>
<tr>
<td>Non-Obese (BMI ≤ 30)</td>
<td>469</td>
<td>81.0%</td>
<td>449</td>
<td>92.7%</td>
<td>11.6% [7.4%, 16.0%]</td>
</tr>
<tr>
<td>Current Smokers</td>
<td>95</td>
<td>70.5%</td>
<td>92</td>
<td>85.9%</td>
<td>15.3% [3.5%, 27.0%]</td>
</tr>
</tbody>
</table>

Promising HBV vaccine with higher response rates in difficult to vaccinate populations

Favors Engerix-B®    Favors Sci-B-Vac™

Langley et al Abstract LP13
Impact of Regular Follow-up on Liver Cancer Mortality in Patients with Chronic Hepatitis B

National Health Insurance Cohort Study in Korea

Compliant patients (every 3 to 6 months)
- N = 94,781 (22.9%)

"No-shows"
- N = 79,333 (19.1%)

Liver cancer
- More curative treatments (23.1% vs. 15.1%)

Risk of death from HCC
- -44%
  HR 0.561
  (95% CI 0.500-0.631)

Implications for clinical practice: Reinforce need to screen patients with chronic hepatitis B

Shim et al Abstract 0159
Bulevirtide (Myrcludex B) plus Peginterferon alfa-2a or Tenofovir for Delta Hepatitis

30 HBeAg-neg CHB/CHD patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median HDV RNA reduction [log]</th>
<th>Undetectable HDV RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFNα</td>
<td>-1.29</td>
<td>13.3%</td>
</tr>
<tr>
<td>10mg BLV q.d. + PEG-IFNα</td>
<td>-6.09</td>
<td>86.7%</td>
</tr>
</tbody>
</table>

Virological response: week 48

Promising results; May require long-term administration

Wedemeyer et al Abstract 0085
Lonafarnib, Ritonavir and Peginterferon Lambda for Delta Hepatitis

Phase 2a, open-label, prospective treatment trial x 24 weeks

Efficacy
• At the end of therapy (n=19), median HDV RNA decline was 3.4 log IU/mL (p<0.0001)
  10/19 (53%) patients achieved HDV RNA undetectable or below LLOQ in serum

Safety
• GI symptoms most common AEs
• Hyperbilirubinemia
• Dose reduction occurred in 3 patients
• Discontinuation of therapy occurred in 4 patients

Promising results, await longer follow-up

HDV RNA Change from Baseline To End of Therapy

Koh et al Abstract L08
HBV Summary

• Steatohepatitis worsens HBV liver disease
• Many promising therapeutic approaches to achieve functional cure
  • Combination therapy will be needed
  • Optimal combination unknown
• HCC surveillance reduces HCC mortality
• Antiplatelet therapy may lower HCC risk in NA-suppressed patients
• More effective vaccine for difficult to vaccinate populations
• Promising therapies for delta virus
Overview

HBV
- Natural history
- Therapy
  - Current
  - Novel therapy
- Prevention
  - Screening
  - Vaccination
- Co-infection with HDV

HCV
- Models of elimination
  - Treatment
  - Vaccination
- Therapy
  - Unique populations
  - Challenging populations
- Benefits of SVR
  - Organ transplantation
Feasibility of Treating PWIDs in Public Health Setting

Primary care providers trained to provide care using standard algorithm

- 3477 PWIDs initiated treatment
- 7% cirrhosis
- SVR_{12} was achieved in 91% in a modified ITT analysis
- Treatment interruptions were common and reduced SVR rate to 78%

Decentralized care of PWIDs using DAA regimens is safe and effective even those with cirrhosis.

Dhiman et al Abstract 0165
Schmidbauer Abstract 1561; Sulkowski1554; Nallapeta 1589
Reinfection Rate After Curative Therapy

Population-based cohort study estimated HCV reinfection rates among all DAA-treated individuals in British Columbia, Canada.

Total participants | 5,702
Total reinfections, n | 64
Follow-up time, person-years (PY) | 4,834.5 PY

### ReinfecXon rate/100 PY
- **All:** 1.28
- **PWID:** 2.36

Cumulative incidence curve by IDU history

<table>
<thead>
<tr>
<th>Variable</th>
<th>All AdjHR (95% CI)</th>
<th>PWID AdjHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth cohort ≥ 1975 (ref: &lt; 1965)</td>
<td>3.81 (2.01-7.23)</td>
<td>4.69 (2.07-10.62)</td>
</tr>
<tr>
<td>Male (Ref: Female)</td>
<td>1.47 (0.83-2.59)</td>
<td>4.2 (1.59-11.08)</td>
</tr>
<tr>
<td>PWID (Ref: No)</td>
<td>3.28 (1.37-7.87)</td>
<td>3.28 (1.37-7.87)</td>
</tr>
<tr>
<td>OAT, Regular use, (ref: non-user)</td>
<td>NE/0 re-infections</td>
<td>NE/0 re-infections</td>
</tr>
<tr>
<td>OAT, Non-regular use, (ref: non-user)</td>
<td>2.09 (1.43-3.00)</td>
<td>2.09 (1.43-3.00)</td>
</tr>
<tr>
<td>Illicit opioid use history (ref: no)</td>
<td>1.65 (0.72-3.81)</td>
<td>1.65 (0.72-3.81)</td>
</tr>
<tr>
<td>Major mental illness (ref: no)</td>
<td>1.46 (0.83-2.57)</td>
<td>1.78 (0.79-4.02)</td>
</tr>
<tr>
<td>HIV Co-infection (Ref: No)</td>
<td>1.69 (0.94-3.02)</td>
<td>1.86 (0.92-3.75)</td>
</tr>
<tr>
<td>Antipsychotic treatment (Ref: No)</td>
<td>0.92 (0.5-1.67)</td>
<td>0.55 (0.27-1.12)</td>
</tr>
</tbody>
</table>

**Implications for clinical practice:** Consider opioid agonist therapy before and after HCV treatment in PWIDs.

PWIDs have a ~3-fold higher reinfection rate that non-PWIDs

Janjua et al Abstract 0282 Grebely 1584
HCV Vaccine to Prevent HCV Infection

Double blind, randomized, placebo controlled phase I/II trial of prime (chimpanzee derived Adenovirus: ChAd3) /boost (modified vaccinia virus Ankara) HCV vaccine among actively using PWIDs

- **Incidence of Infection**
- **Peak HCV RNA levels**
- **Immunogenicity**

**Infection**
- Probability of infection (%)

**Peak HCV RNA levels**
- 1,078,092 IU/mL
- 193,795 IU/mL
- p = 0.01

**Immunogenicity**
- IFN-g Elispot

Demonstrated feasibility of vaccine studies among PWIDs. More efforts are needed on vaccine development.

Page et al Abstract LP17
Pangenotypic Therapy for Children: Glecaprevir /Pibrentasvir (G/P)

Safety and efficacy of the pediatric formulation of G/P for 8 weeks in children aged 3-<12 years, n=81, GTs 1-6

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight Range</th>
<th>Dose (GLE + PIB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 2 (9-&lt;12 years)</td>
<td>≥30 to &lt;45 kg</td>
<td>250 mg + 100 mg</td>
</tr>
<tr>
<td>Cohort 3 (6-&lt;9 years)</td>
<td>≥20 to &lt;30 kg</td>
<td>200 mg + 80 mg</td>
</tr>
<tr>
<td>Cohort 4 (3-&lt;6 years)</td>
<td>≥12 to &lt;20 kg</td>
<td>150 mg + 60 mg</td>
</tr>
</tbody>
</table>

Safety

<table>
<thead>
<tr>
<th>Treatment-emergent Adverse event (AE), n (%)</th>
<th>Total N = 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>33 (69)</td>
</tr>
<tr>
<td>Any AE with a reasonable possibility of being related to G/P</td>
<td>13 (27)</td>
</tr>
<tr>
<td>Any AE with a Grade 3 or higher</td>
<td>0</td>
</tr>
<tr>
<td>Any AE leading to treatment discontinuation</td>
<td>0</td>
</tr>
<tr>
<td>AEs in ≥10% of all patients</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td></td>
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<tr>
<td>Upper abdominal pain</td>
<td></td>
</tr>
</tbody>
</table>

Efficacy

Overall 96%  Cohort 2 94%  Cohort 3 100%  Cohort 4 94%

Jonas et al Abstract 1551
Pangenotypic Therapy for Children with CHC

204 children, 70% Caucasian, genotypes 1-4 & 6, no cirrhosis

Aged 6–11 Years (n=102)
SOF + VEL 200mg + 50 mg x 12 weeks

Aged 12–17 Years (n=102)
SOF + VEL 400mg + 100 mg x 12 weeks

Study ongoing in children 3–<6 years

Implications for clinical practice: In the near future we should have a safe and effective, pangenotypic regimen for children 3 year or older

Jonas et al Abstract 0748
Short Course Therapy for Compensated Cirrhosis and HCV GT 3

61 treatment-naïve patients with GT3 and compensated cirrhosis received glecaprevir/pibrentasvir x 8 weeks

- 1 patient relapsed
- NS5A RASs: A30K was present at 4.8% at 2% and 15% NGS detection thresholds
  Y93H was present at 8.1% and 6.5% using a detection threshold of 2% or 15%
- All GT3-infected patients with A30K or Y93H at baseline achieved SVR12

Implications for clinical practice: Effective short duration therapy approved for previously difficult to treat population

Brown et al Abstract LP9
# Impact of SVR on Liver-related Mortality

VA database of CHC patients  
Treated patients propensity score matched untreated controls

<table>
<thead>
<tr>
<th>Liver-related deaths</th>
<th>N</th>
<th>Rate/100PY (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV+ treated</td>
<td>1057</td>
<td>0.68 (0.64,0.72)</td>
<td>--</td>
</tr>
<tr>
<td>HCV+ untreated</td>
<td>1921</td>
<td>1.29 (1.23,1.35)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Among those treated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By treatment response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR achieved</td>
<td>127</td>
<td>0.14 (0.12,0.17)</td>
<td>--</td>
</tr>
<tr>
<td>SVR not achieved</td>
<td>930</td>
<td>1.40 (1.31,1.49)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>By treatment regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG/RBV treated</td>
<td>963</td>
<td>0.76 (0.72,0.81)</td>
<td>--</td>
</tr>
<tr>
<td>DAA treated</td>
<td>73</td>
<td>0.31 (0.24,0.38)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>By regimen and SVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG/RBV SVR achieved</td>
<td>84</td>
<td>0.13 (0.10,0.16)</td>
<td>--</td>
</tr>
<tr>
<td>PEG/RBV SVR not achieved</td>
<td>879</td>
<td>1.44 (1.35,1.54)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DAA SVR achieved</td>
<td>40</td>
<td>0.20 (0.14,0.27)</td>
<td>0.02</td>
</tr>
<tr>
<td>DAA SVR not achieved</td>
<td>33</td>
<td>0.81 (0.54,1.09)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Further evidence of the benefits of SVR

Butt et al Abstract 0039
Impact of SVR on Extra-Hepatic Outcomes

Chronic Hepatitis Cohort 15,999 HCV patients under routine care at four US health care systems

Extra-hepatic benefits to SVR

- SVR was associated with significantly reduced risk of ACS, regardless of treatment type.
- IFN SVR was associated with a significantly lower risk of ACS than DAA SVR.

**Acute Coronary Syndromes**

- Untreated
- DAA SVR
- IFN SVR

**End Stage Renal Disease**

- Untreated
- DAA SVR
- IFN SVR

**Ischemic Stroke**

- Untreated
- IFN SVR
- DAA SVR

- SVR associated with significantly reduced risk of ischemic stroke, regardless of treatment type.

Li et al Abstract 0037
SVR Improves HCC Survival

Multi-national, propensity score matched analysis of impact of HCV eradication on HCC survival

### All-cause Mortality

<table>
<thead>
<tr>
<th>Type of Mortality</th>
<th>HCV treatment status</th>
<th>Adjusted HR* (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause</td>
<td>Untreated for HCV</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>SVR</td>
<td>0.37 (0.16-0.83)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

### Liver-related Mortality

<table>
<thead>
<tr>
<th>Type of Mortality</th>
<th>HCV treatment status</th>
<th>Adjusted HR* (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver-related</td>
<td>Untreated for HCV</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>SVR</td>
<td>0.34 (0.13-0.88)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Implications for clinical practice: HCC patients who are candidates for HCC therapy should also be considered for DAA therapy.

Dang et al Abstract 0040
Use of HCV-Seropositive Donors in HCV-Seronegative Liver Transplant Recipients

Retrospective analysis of 24 HCV-seropositive to HCV-seronegative Liver transplants (10 NAT neg; 14 NAT+)

- Viremic documented within 5 days after LT
- Mean pre-treatment viral load 24,955,159 IU/ml (range 3,230 to 97,500,000)
- Median time to start DAA treatment 27.5 days (range 6-67)
  - G/P x 12 weeks,
  - Sof/Vel x 12 weeks,
  - SOF/LDV+/-RBV x 12-24 weeks
- All achieved SVR12

Implication for Clinical Practice: LT using grafts from HCV-viremic donors to HCV negative recipients had excellent short-term outcomes

Wijarnpreecha et al Abstract 0003
Short Duration, Prophylactic Therapy to Prevent Post-transplant HCV Infection from HCV-Infected Donors to HCV-Uninfected Recipients

10 HCV D+/R- kidney transplants

Outcome
- 5/10 never had detectable HCV RNA
- 5/10 low level (peak 161 IU/mL) first week
- 9/9 achieved SVR

Safety
- No AEs related to DAA prophylaxis
- No deaths, graft failures or rejections
- No significant elevations in AST, ALT, or bilirubin

Implications for clinical practice: Short duration prophylactic therapy appears effective at preventing post-transplant infection from HCV Donor+ to -recipients

Durand et al Abstract 0042
Pre-emptive Combination DAA and Entry Blocker Therapy to Prevent Post-transplant HCV Infection from HCV-Infected Donors to HCV-Uninfected Recipients

Ezetimibe (HCV entry blocker) + Glecaprevir/Pibrentasvir given 1 dose before and for 7 days post-transplant to prevent HCV infection from 16 HCV+ organ donors to 25 HCV-negative recipients 12 lung, 8 kidney, 1 K-P, 4 heart

Outcome
• 9 had quantifiable HCV RNA (max 2.96 log IU/mL)
• 9 had HCV RNA that was detectable but <LLOQ (15 IU/mL)
• 7 never had detectable viremia
• All HCV RNA negative at last F/U
• Donor VL was the only predictor of transient post-transplant viremia

Safety
• Reversible ALT and CK elevations with no other safety concerns

Implications for clinical practice: Pre-emptive Ezetimibe + glecaprevir/pibrentasvir for 7 days, prevented or rapidly cured post-transplant HCV infection

Feld et al Abstract 0038
HCV Summary

• Feasible to treat PWIDs. Overcoming adherence issues is a challenge

• Treatment
  • Pangentypic regimens will be available for children
  • Short course pangentypic therapy available for treatment-naïve compensated cirrhotics

• Multiple benefits of SVR
  • Lower liver-related mortality
  • Lower cardiovascular and renal outcomes
  • Improved survival after HCC treatment

• Pre-emptive 7-28 day therapy appears to prevent or cure HCV infection post-transplant