What’s new in Hepatology
AASLD 2016

CWN Spearman

C Kassianides
What’s new in Hepatology? AASLD 2016

CWN SPEARMAN

Hepatitis C

Alcoholic liver disease

Cholestatic Liver Disease
• Primary biliary Cholangitis
• Primary Sclerosing cholangitis

Cirrhosis

C KASSIANIDES

Hepatitis B

NASH
HEPATITIS C
Hepatitis C : ERA of DAAs

• **CURE is now possible for : SVR >90%**
  - Treatment naïve, experienced and cirrhotic patients
  - HIV/HCV co-infection
  - Liver transplant patients

• **SVR improves prognosis of non-cirrhotic and cirrhotic HCV pts**
  - Concerns re HCC and Hepatitis B reactivation on DAA therapy
  - Re-infection risks must be addressed: harm reduction programmes

• **SVR improves both all-cause and liver-related mortality**

• **All patients with chronic hepatitis C are candidates for Rx**

• **Prioritise patients with :**
  - Advanced fibrosis or cirrhosis
  - HIV/HBV co-infection
  - Extrahepatic manifestations
  - Transplant patients
SVR and Prevention of Diabetes/Insulin Resistance

SVR reduced the rate of de novo insulin resistance evaluated 2 years later

SVR reduces the incidence of type 2 diabetes* by ~60%

N=2842, mean follow-up 6.3 years

Cumulative development rate of T2DM (%)

P < 0.001

Period of follow-up post-SVR

SVR (N = 1175)

Non-SVR (N = 1667)

<table>
<thead>
<tr>
<th>Overall</th>
<th>HCV 1/4</th>
<th>HCV 2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>7% 17%</td>
<td>8% 16%</td>
<td>7% 20%</td>
</tr>
</tbody>
</table>

N=384, 71% non-advanced fibrosis
HOMA-IR done pre and 24 mos post-treatment

Aghemo A. Hepatology. 2012; 56:1681-7

*Independent of age, cirrhosis and prediabetes at baseline

Treatment Associated with Reduced Rates of Renal and Cardiovascular Outcomes

- Population-based cohort from Taiwan, HCV treated (n=12,384) with SVR compared to propensity matched untreated HCV controls (N=24,768)

<table>
<thead>
<tr>
<th></th>
<th>95% CI</th>
<th>aHR</th>
<th></th>
<th>95% CI</th>
<th>aHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD</td>
<td></td>
<td></td>
<td>ACS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.15</td>
<td>0.07-0.31</td>
<td>Overall</td>
<td>0.77</td>
<td>0.62-0.97</td>
</tr>
<tr>
<td>No cirrhosis</td>
<td>0.12</td>
<td>0.05-0.30</td>
<td>No cirrhosis</td>
<td>0.77</td>
<td>0.62-0.99</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>0.26</td>
<td>0.08-0.87</td>
<td>Cirrhosis</td>
<td>0.80</td>
<td>0.62-0.97</td>
</tr>
</tbody>
</table>

Hsu YC, Gut 2015;64:495-503
Improvements in Physical & Mental Function

- N=624 [618 with SVR] and 116 placebo; 81% without cirrhosis

Improvement in patients on DAA therapy versus placebo as early as 4 weeks of treatment and continues after treatment ends.

Improvement of Neurocognitive Function with SVR

- N=168 treated with peg-IFN based therapy; median age 43 yrs, 85% without cirrhosis; N=116 with SVR
- Computer-assisted neuropsychological tests; tested at baseline and 1 yr post-EOT

**TAP=Test Battery of Attentional Performance**

**Vigilance:** measures reaction times to assess sustained attention

**Working memory:** measures reaction times to assess ability to manage a continuous flow of information with short-term memory

HCV Treatment: The Future?

- Pan-genotypic DAA
- Shorter duration with minimal monitoring: 8, 12 & 16 wks
- Aim for Test and treat: Are we ready?
- Better DAA Options in 2016 for:
  - Genotype 3
  - Stage 4 kidney disease/dialysis
  - Decompensated cirrhosis

In 2016: What our new therapeutic options?
GILEAD’S PROGRAMME

• EPCLUSA
  Sofosbuvir (NS5B)/Velpastasvir (NS5A)
  - Pangenotypic FDC
  - ASTRAL1-4 Studies: >90% SVR
    - GT 1-6; Rx naïve and experienced; cirrhosis & decompensated dis
  - FDA approved in June 2016

• Sofosbuvir/Velpatasvir/Voxilaprevir (NS3/4A)
  - Pangenotypic FDC
  - POLARIS 1-4 Studies
POLARIS Program

- Sofosbuvir (NS5B) / Velpatasvir (NS5A) / Voxilaprevir (NS3/4A)

Regimens:

- SOF/VEL/VOX
- SOF/VEL

DAA-Experienced

- POLARIS-1: N = 415
  - NS5A-experienced

- POLARIS-4: N = 333
  - Non-NS5A-experienced

DAA-Naïve

- POLARIS-2: N = 941
- POLARIS-3: N = 219
  - Cirrhosis

Treatment durations:

- 12 weeks
- 8 weeks
- Placebo: 12 weeks
Polaris-1: SVR12 by Genotype

NS5A experienced

6 relapses
GT1a and 3

SOF/VEL/VOX 12 Weeks (n=263)

SVR12, %

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1</td>
<td>146/150</td>
</tr>
<tr>
<td>GT 1a</td>
<td>97/101</td>
</tr>
<tr>
<td>GT 1b</td>
<td>45/45</td>
</tr>
<tr>
<td>GT 2</td>
<td>5/5</td>
</tr>
<tr>
<td>GT 3</td>
<td>74/78</td>
</tr>
<tr>
<td>GT 4</td>
<td>20/22</td>
</tr>
<tr>
<td>GT 5</td>
<td>1/1</td>
</tr>
<tr>
<td>GT 6</td>
<td>6/6</td>
</tr>
</tbody>
</table>

Error bars represent 95% confidence intervals.

Bourlière et al, AASLD 2016
Polaris-2: SVR12 by Genotype (GT 1)

DAA Naive

AEDC, Discontinuation due to AE. Error bars represent 95% confidence intervals.
2 of 2 patients (100%) with GT 1 Other achieved SVR12 (1 each in the SOF/VEL/VOX and SOF/VEL groups).

Jacobson et al AASLD 2016
Polaris-2: SVR12 by Genotype (GT 2–6)

DAA naive

![Graph showing SVR12 by Genotype (GT 2–6)](image)

AEDC, Discontinuation due to AE. Error bars represent 95% confidence intervals.

Jacobson et al AASLD 2016
Polaris-3: SVR12 by Prior Treatment

GT 3 Cirrhosis

**Treatment Naive**
n=152

- SOF/VEL/VOX: 72/75
- SOF/VEL: 76/77

**Treatment Experienced**
n=67

- SOF/VEL/VOX: 34/35
- SOF/VEL: 29/32

Foster et al. AASLD 2016
Polaris-4: SVR12
non-NS5A DAA experienced

Difference driven by GT1a and 3

Zeuzem et al. AASLD 2016

Error bars represent 95% confidence intervals.
MERCK 2016 PROGRAMME

- Grazoprevir (NS3A/4A) + Elbasvir (NS5A) + SOF
- MK-3682/Grazoprevir (NS3A/4A)/Ruzasvir (NS5A)
C-ISLE: EBR/GZR/SOF in GT3 cirrhotics

Grazoprevir (NS3A/4A) + Elbasvir (NS5A) + SOF ± RIBA

**Treatment-naive**
- EBR/GZR + SOF + RBV
- EBR/GZR + SOF

**Treatment-experienced**
- EBR/GZR + SOF
- EBR/GZR + SOF + RBV

Dosing
- RBV (800-1400 mg/d)

*Primary endpoint: HCV RNA <15 IU/mL

Foster et al AASLD 2016
C-Isle: SVR12 (modified Full analysis set)

Genotype 3 Cirrhotics: Grazoprevir (NS3A/4A) + Elbasvir (NS5A) + SOF ± RIBA

Modified full analysis set includes excludes patients who discontinued treatment for reasons unrelated to study medication

Foster et al AASLD 2016
C-CREST (MK3: MK-3682/Grazoprevir/Ruzasvir; N=664)
TN or P/R experienced, with or without cirrhosis (~35%)

GT1 (n = 88)
GT2 (n = 32)
GT3 (n = 53)

GT2 (n = 31)
GT3 (n = 50)

GT1 (n = 88)
GT2 (n = 46)
GT3 (n = 79)

GT2 (n = 16)
GT3 (n = 80)

GT2 (n = 26)
GT3 (n = 50)

GT3 (n = 25)

MK3

MK3 + RBV

MK3

MK3 + RBV

MK3

MK3 + RBV

D1, TW4, TW8, TW12, TW16, FW12

SVR12 1° Endpoint

TW=treatment week; FW=follow-up week; RBV=ribavirin
SVR12 (Per Protocol): 8, 12 or 16 Weeks
MK-3682/Grazoprevir/Ruzasvir

No difference with ribavirin or based on cirrhosis or prior P/R Rx

Lawitz et al AASLD 2016

* One GT2 patient treated with 8 weeks + RBV discontinued at Day 5 due to drug-related AEs of fatigue, malaise
C-Surge: MK3: MK-3682/Grazoprevir/Ruzasvir GT 1 Failed DAA (SOF/LDV or EBR/GZR)

No virologic failure or impact of RAS (Y93 >40%)

Wyles et al AASLD 2016
Abbvie’s DAA 2016 Programme

• Glecaprevir (NS3A/4A) / Pibrentasvir (NS5A)
Glecaprevir (formerly ABT-493) + Pibrentasvir (formerly ABT-530)

**ENDURANCE Trials**
- GT1 non-cirrhotic including HIV co-infection: 8 vs 12 weeks
- GT2 placebo-controlled: 12 weeks
- GT3 active comparator: 12 weeks
- GT4-6: 12 weeks

**MAGELLAN Trials**
- GT1, 4-6 prior DAA failures: 12 vs 16 weeks

**EXPEDITION Trials**
- GT1, 2, 4-6 cirrhotic
- GT1-6 severe renal impairment

**SURVEYOR Trials**
- GT2, 4-6 non-cirrhotic: 8 weeks
- GT3 cirrhotic and/or TE: 12 vs 16 weeks
ENDURANCE-1: G/P for 8 or 12 weeks
GT1 Non-cirrhotics, no NS5-A

Glecapravir/Pribrentasvir

GT1 non-cirrhotic ±HIV-1 TN or TE (IFN / peg-IFN ± RBV / SOF + RBV ± peg-IFN)

G/P 300 mg/120 mg QD (n=351)

G/P 300 mg/120 mg QD (n=352)

Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Patients N=703</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1a</td>
<td>43%</td>
</tr>
<tr>
<td>F2–F3</td>
<td>15%</td>
</tr>
</tbody>
</table>

One virologic failure (8 weeks), No impact of pre-existing RAS (NS5A ~25%)

Zeuzem et al AASLD 2016
ENDURANCE-2: G/P x 12 12 weeks GT2 without Cirrhosis, No NS5A

Glecaprevir/Pibrentasvir

**GT2**
Non-cirrhotic TN or TE
(peg-IFN + RBV / SOF + RBV)

2:1

0 12 24

Time (weeks)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>G/P</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=202</td>
<td>N=100</td>
</tr>
<tr>
<td>Fibrosis Stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0-F1</td>
<td>154 (76)</td>
<td>85 (85)</td>
</tr>
<tr>
<td>F2</td>
<td>18 (9)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>F3</td>
<td>30 (15)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Treatment experienced, n (%)</td>
<td>61 (30)</td>
<td>29 (29)</td>
</tr>
<tr>
<td>PPI use, n (%)</td>
<td>22 (11)</td>
<td>11 (11)</td>
</tr>
</tbody>
</table>

SVR12 (%)

<table>
<thead>
<tr>
<th>ITT</th>
<th>mITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>99</td>
<td>100</td>
</tr>
</tbody>
</table>

**ITT population:** excludes 6 SOF-experienced patients, all of whom achieved SVR12

**mITT population:** ITT population excluding 1 non-virologic failure who achieved SVR4

#73, Kowdley AASLD 2016
SURVEYOR-II, PART 3: G/P for 12-16 weeks
GT3 Infection with Prior Treatment Experience (no NS5A) and/or Cirrhosis

- TN + cirrhosis
- GT3 Non-cirrhotic TE (IFN ± RBV / SOF + RBV ± peg-IFN)
- TE + cirrhosis

G/P 300 mg/120 mg QD

Phase 2/3 Partially randomized Open-label

<table>
<thead>
<tr>
<th>Duration</th>
<th>TE w/o Cirrhosis 12 Weeks N = 22</th>
<th>TE w/o Cirrhosis 16 Weeks N = 22</th>
<th>TN w/ Cirrhosis 12 Weeks N = 40</th>
<th>TE w/ Cirrhosis 16 Weeks N = 47</th>
</tr>
</thead>
</table>

#113, Wyles et al AASLD 2016
SURVEYOR-II, PART 3: G/P for 12-16 weeks
GT3 Infection with Prior Treatment Experience (no NS5A) and/or Cirrhosis

Patients with SVR12 (ITT)

<table>
<thead>
<tr>
<th></th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLE/PIB</td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td>91</td>
</tr>
<tr>
<td>GT3</td>
<td>20/22</td>
</tr>
<tr>
<td>16 weeks</td>
<td>96</td>
</tr>
<tr>
<td>GT3</td>
<td>21/22</td>
</tr>
<tr>
<td>12 weeks</td>
<td>98</td>
</tr>
<tr>
<td>GT3</td>
<td>39/40</td>
</tr>
<tr>
<td>16 weeks</td>
<td>96</td>
</tr>
<tr>
<td>GT3</td>
<td>45/47</td>
</tr>
</tbody>
</table>

| Cirrhosis       | – | – | + | + |
| Treatment-experienced | + | + | – | + |

#113, Wyles et al at AASLD 2016
SURVEYOR-II, Part 4: G/P for 8 weeks
GT2, 4, 5, or 6 without Cirrhosis No NS5A experience

Phase 2, open-label, randomized, multicentre study

GT2, 4, 5, 6
Non-cirrhotic TN or TE
(IFN- or SOF-based regimens)

G/P 300 mg/120 mg QD (N=203)

Time (weeks)

ENDURANCE-4: The safety and efficacy of 12-week G/P treatment were similar to SURVEYOR-II, Part 4

SVR12 (ITT)

#LB-15, Hassanein at al AASLD 2016
EXPEDITION-IV: G/P for 12 weeks in Renal Impairment GT1–6 with or without cirrhosis, P/R +/- SOF (No NS5A)

GT1–6 ± compensated cirrhosis TN or TE (IFN- or SOF-based regimens)
eGFR <30 mL/min/1.73 m²

G/P 300 mg/120 mg QD (N=104)

Demographics

<table>
<thead>
<tr>
<th></th>
<th>Patients N=104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-experienced</td>
<td>42%</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>19%</td>
</tr>
<tr>
<td>GT1/2/3/4/5/6</td>
<td>52%/16%/11%/19%/1%/1%</td>
</tr>
<tr>
<td>CKD stage 4</td>
<td>13%</td>
</tr>
<tr>
<td>CKD stage 5</td>
<td>87%</td>
</tr>
<tr>
<td>Dialysis</td>
<td>82%</td>
</tr>
</tbody>
</table>

SVR4, %

- 99%
- 103/104*

- The patient not achieving SVR4 prematurely discontinued treatment
- Four AEs (4%) led to study drug discontinuation
- One patient died after achieving SVR4 due to a serious AE not related to study drug (intracerebral hemorrhage)

#LB-11, Gane et al AASLD 2016
Impact of PPI on Efficacy of LDV-SOF Therapy

**HCV-Target**
- PPI use at baseline was independent predictor of SVR
- OR=0.41 (95% CI: 0.25-0.67)

**TRIO**

**Propensity-Matched Cohorts**

<table>
<thead>
<tr>
<th>Group</th>
<th>All N=887</th>
<th>Cirrhosis N=337</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PPI</td>
<td>97%</td>
<td>96%</td>
</tr>
<tr>
<td>High dose PPI</td>
<td>98%</td>
<td>96%</td>
</tr>
<tr>
<td>BID PPI</td>
<td>91%</td>
<td>77%*</td>
</tr>
<tr>
<td>Any PPI</td>
<td>98%</td>
<td>96%</td>
</tr>
</tbody>
</table>

*P=0.05

- Only twice daily PPI at baseline associated with lower SVR
- Effect most marked in cirrhotics

Terrault N, Gastroenterology 2016

Tapper E, Hepatology 2016
Multiplicity of Negative Predictors Impacts SVR Rates in Patients with Genotype 1

- LDV-SOF±RBV
- All
- Cirrhotic
- Non-cirrhotic
- HCV < 1 million IU/mL
- HCV ≥ 1 million IU/mL
- GT 1a
- GT 1b
- GT 1a cirrhotic
- GT 1b cirrhotic
- Naïve
- Experienced
- No prior OLT
- Prior OLT
- Decompensated
- Non-decompensated
- No Baseline PPI
- Baseline PPI

SVR12, %

96.5
93.2
98.1
97.5
95.9
96.1
97.3
91.9
95.9
95.9
97.7
96.9
90
87.9
97.6
97.6
93.3

Terrault N, Gastroenterology 2016
Chronic HCV, DAA’s and HCC

Italian Study: 3075 pts with chronic hepatitis C infection: Follow-up for mean of 300.8 days after the start of DAA therapy

- Cumulative incidence rates of HCC not significantly different:
  - F3 advanced fibrosis (0.23% per person per year)
  - Child-Pugh A cirrhotics (1.64% per person per year)
  - Child-Pugh B cirrhotics (2.92% per person per year)

- Incidence rates no different from historic control cohorts with similar patients from the same geographic region (Northern Italy) who did not receive antiviral therapy

- Fibrosis and cirrhosis stage is the driving factor, not oral direct-acting antiviral agents

- Severity of HCC did appear to correlate with antiviral therapy over a 540-day follow-up period
  - 5 (12.2%) pts had portal vein thromboses & 4 (9.7%) had extra-hepatic metastases
Disease Severity in the 41 Patients Who Developed HCC

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 nodule, with typical vascular patterns</td>
<td>20</td>
<td>48.8</td>
</tr>
<tr>
<td>2 or 3 nodules</td>
<td>5</td>
<td>12.2</td>
</tr>
<tr>
<td>&gt;3 nodules or infiltrative hepatocellular carcinoma</td>
<td>16</td>
<td>39.0</td>
</tr>
</tbody>
</table>

- At 12 weeks, HCC more aggressive in pts who did not achieve SVR12 vs pts with SVR vs undetermined response (53.8% vs 33.3% vs 28.6%)
- HCC diagnosed at wk 4 in 3 patients, at wk 8 in 3 patients, at wk 12 in 6 patients, from wk 12 - 23 in 13 patients, and after EOT in 16 pts

Multivariate Analysis: SVR12 significant predictor of HCC: HR 0.20; P = .001

- Changes in immunologic and molecular microenvironment in liver and in tumor suppression mechanisms, which could allow or even promote the growth of previously undiagnosed microscopic hepatocellular carcinoma foci
HCC PATTERNS IN RELATION TO SVR

<table>
<thead>
<tr>
<th></th>
<th>Single HCC Nodule</th>
<th>2-3 HCC Nodules</th>
<th>&gt;3 Nodules/Infiltrative</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR yes</td>
<td>57.2</td>
<td>33.3</td>
<td>9.5</td>
</tr>
<tr>
<td>SVR no</td>
<td>30.8</td>
<td>15.5</td>
<td>14.3</td>
</tr>
<tr>
<td>SVR pending</td>
<td>54.1</td>
<td>28.6</td>
<td>14.3</td>
</tr>
</tbody>
</table>

Romano et al AASLD 2016
PATTERNS OF HCC DEVELOPMENT IN RELATION TO TIMING OF DAA TREATMENT

MONTHS AFTER INITIATION OF DAAs THERAPY

0--3
4--6
7--12
13--18

SINGLE NODULE
2-3 NODULES
> 3 NODULES/INFITRATIVE

Romano et al AASLD 2016
Cumulative incidence of HCC by SVR & cirrhosis

### Cumulative incidence of HCC by SVR

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>No SVR</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray's Test p &lt; .0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative Incidence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Number at risk**
  - SVR: 4663
  - No SVR: 3484

- **Follow-up time (years)**
  - 0.0: 3788, 2778
  - 5.0: 2637, 1939
  - 7.5: 1453, 1152
  - 10.0: 518, 478
  - 12.5: 10, 26

### Cumulative incidence post SVR by cirrhosis

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>No Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray's Test p &lt; .0001</td>
<td></td>
</tr>
<tr>
<td>Cumulative Incidence</td>
<td></td>
</tr>
</tbody>
</table>

- **Number at risk**
  - Cirrhosis: 145, 122, 81, 52, 20, 2
  - No Cirrhosis: 4518, 3666, 2556, 1401, 498, 8

### Incidence rate (95%CI)/ 1000 PY

<table>
<thead>
<tr>
<th>SVR</th>
<th>No SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC</td>
<td>Incidence rate</td>
</tr>
<tr>
<td>SVR</td>
<td>29</td>
</tr>
<tr>
<td>No SVR</td>
<td>145</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>7.0 (3.2, 15.6)</td>
</tr>
<tr>
<td>No Cirrhosis</td>
<td>0.9 (0.6, 1.3)</td>
</tr>
</tbody>
</table>

Median follow-up: 5.6 years

Janjua et al AASLD 2016
HCV: Late Relapse or Reinfection

Systematic review & meta-analysis: 59 studies (>9000 pts)

- Mono-HCV infected "low-risk" patients;
- Mono-HCV infected "high-risk" patients: PWUD or prisoners
- HIV/HCV co-infected patient

Overall 5 year recurrence rates

- Low-risk patients: 0.95%
- High-risk patients: 10.67%
- HCV/HIV co-infected patients: 15.02%

*Increase in reinfection rather than late relapse*

- Prevention campaigns for individuals at high-risk of HCV re-exposure

Simmons et al; Clin Infect Dis 2016, Jan 19
C-EDGE Co-Star

Incidence of reinfection post SVR in 199 patients on OST
~50% illicit drug use

Through FW12

5 reinfections

Through FW24

1 reinfection

Part B FW36

2 reinfections

8 reinfections

2.8 reinfections per 100 person years

8 Total Reinfections From End of Treatment Through All Available Follow-up

- 286.8 person-years of follow-up
- 2.8 reinfections per 100 person years (95% CI: 1.2, 5.5)

Dore et al AASLD 2016
Treatment to Prevent Transmission to Others

- Women of child-bearing age
- PWIDs
- MSM with HIV

- Treatment of persons in these subgroups reduces prevalent and incident infections
- In PWIDs and MSM with HIV, need to treat early disease to achieve elimination

HCV Infection in HIV-infected MSM

- Peg-IFN +RBV

Hepatitis B Reactivation: DAA therapy

US FDA received 24 unique reports of HBV-R associated with DAA Rx

- Boxed warning
- 2 fatal outcomes and 1 liver transplantation
- HBV-R: Pts were heterogeneous: HCV genotype, DAA received, and baseline HBV viral parameters
- At baseline: 7 patients had detectable HBV VL, 4 patients had a positive HBsAg and undetectable HBV VL, & 3 patients had negative HBsAg and undetectable HBV VL
- The remaining cases either did not report these data points, or data were interpretable
- Despite provider knowledge of baseline HBV status, delay in diagnosis and treatment of HBV-R was noted in 5 cases, with possible delay in 3 others
- Limitations: Spontaneous reporting system subject to variable data quality and underreporting
- Unable to estimate incidence of DAA associated HBV-R, and ability to make causal inference is limited
- Patients with history of HBV require clinical monitoring while on DAA’s
  - Need full HBV serology

Bersoff-Matcha et al, LB Abstract 17, AASLD 2016
Hepatitis B Reactivation: DAA therapy

Meta-analysis 35 studies involving 1121 CHC patients

- 30 studies were using interferon
- All studies reported SVR rates, 26 studies reported HBV reactivation, 22 studies reported occurrence of hepatitis due to HBV reactivation

Overall SVR rate was 47% in HBV/HCV co-infected patients

- SVR rate: Interferon (43%) and DAAs (100%); p<0.001

Overall HBV reactivation rate 12.3%: IFN (12.4%) & DAAs (12.2%, p=0.90)

Overall incidence of hepatitis due to HBV reactivation

- 0.3% (0-1.1% in IFN treated) vs. 0.2 -33.2% with DAAs, p=0.02
- Most cases HBV reactivation occurred during follow-up of IFN treatment (3 wks to 72 months post-treatment)
- All cases were observed during DAAs treatment (4 to 11 wks during Rx)

Wang et al; Abstract 918, AASLD 2016
Liver Tx: DAA Therapy and Purgatory MELD: Fact or Fiction?

UNOS database: 20,411 HCV waitlist LT candidates:
• 10,606 candidates 18 months pre-DAA: May 2012 to October 2013
• 9,805 candidates in post-DAA period: January 2014 to June 2015

Compared to pre-DAA period
• HCV waitlist LT candidates during post-DAA: significantly lower rate
  o Removal due to death (7.4 % to 11.5%, p < 0.01)
  o Too sick to transplant (7.9% to 11.3%, p < 0.01)
• Post-DAA HCV waitlist LT candidates had a significantly lower rate of liver transplantation (29.9% to 38.7%, p < 0.01)

This should be taken into account in setting of poor donor access

Cholankeril et al, Abstract 859, AASLD 2016
Alcoholic Liver Disease

Acute alcoholic hepatitis

Cirrhosis

HCC

Alcoholic

Cirrhosis

Fibrosis

Steatohepatitis

Fatty liver

ALD

Acute alcoholic hepatitis

Years

10
20
30

HCC

Years
STOPAH Trial: Prednisolone or Pentoxifylline for AH

Multicenter, double-blind, randomized trial: 1103 pts

- Prednisolone reduction: 28-day mortality
  14% (Pred) vs 19% (PTX) vs 17% (placebo)
- No outcome improvement: 90 days or 1 yr
- Prednisone: serious infections 13% vs 7%
- 37% completely abstinent at 1 yr
## Abstinence and 1-Year Mortality

<table>
<thead>
<tr>
<th>Alcohol consumption at Day 90</th>
<th>Odds Ratio for 1-year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Abstinent</td>
<td>321</td>
</tr>
<tr>
<td>Not reduced</td>
<td>50</td>
</tr>
<tr>
<td>Reduced but above safety limits</td>
<td>48</td>
</tr>
<tr>
<td>Reduced to below safety limits</td>
<td>59</td>
</tr>
</tbody>
</table>
Granulocyte-Colony Stimulating Factor (G-CSF) plus N-Acetyl Cysteine (NAC) in Severe Alcoholic Hepatitis

- **Rationale:** G-CSF +/- NAC is superior to placebo
- **Underpowered** *(NEED DEFINITIVE TRIAL)*

Abstract # LB4, Sharma et al, PGI Chandigarh
Highly selected patients: 8.3% patients with AH, 1st episode
- 2.9% of LTx performed

Criteria for acceptance for LTx: Needed to be approved by
- Patient and patient’s family
- 4 groups of physicians caring for patient
  - Residents/fellows
  - Addiction specialist
  - Hepatologist
  - Liver Tx anaesthetist and surgeon
- Recidivism: 3 pts (720, 740 and 1140 days post LTx)
17 patients with AH vs. 26 abstinent cirrhosis
100% survival at 1-year in AH
Recidivism: AH: 23.5% vs. Cirrhosis: 29.2%
Harmful drinking: AH: 23.5% vs. Cirrhosis: 11.5%

Lee Ann Surgery 2016

9 patients with AH vs. matched AH (no OLTX)
89% 6-month survival (and 1-year survival)
Recidivism: 2 slips (minor alcohol use)
1 harmful drinking (12

Im. Am J Transplant 2016
Alcoholic Cirrhosis and Statins

Propensity score matched cohort: 2275 pts compensated cirrhosis and 1435 pts with decompensated cirrhosis

- 25% patients on statins in each group
- **Primary end point:** Incidence of death at 15 years
- **Mortality Rates Halved**

<table>
<thead>
<tr>
<th>Cirrhosis Group</th>
<th>Statin Users</th>
<th>Nonusers</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compensated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of death at 15 years</td>
<td>31%</td>
<td>50%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Median survival</td>
<td>7.8 years</td>
<td>3.5 years</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Decompensated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of death at 15 years</td>
<td>38%</td>
<td>54%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Median survival</td>
<td>3.9 years</td>
<td>2.2 years</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

- Improved survival in patients with Child-Pugh class A or B cirrhosis, but not in patients with class C

Gastroenterology, 2016;150:1160-1170.e3)
Alcoholic Cirrhosis and Statins

Mortality rates lower in statin users

- Compensated cirrhosis (86 vs 199 per 1000 person-years)
  - Adjusted HR 0.45; \( P < .0001 \)

- Decompensated cirrhosis (132 vs 290 per 1000 person-years);
  - Adjusted HR, 0.55; \( P < .0001 \)

Risk for decompensation: Secondary end point

- Lower in statin users (10% vs 25%; adjusted HR 0.31; \( P < .0001 \))

- Statins are thought to have an anti-inflammatory effect on the liver

- Reduces portal hypertension, a prognostic marker for death

Propensity score matching was used to rule out as many confounders

Gastroenterology. 2016;150:1160-1170.e3
CHOLESTATIC LIVER DISEASE
PBC

• **Chronic immune-mediated lymphocytic cholangitis**
  
  • Early diagnosis and initiation of UDCA (13-15 mg/kg/day)
    
    o 66% patients have expected survival equivalent to general population
    
    o Only a minority will develop cirrhosis

**Proposed Name change: Primary Biliary Cholangitis**

• Proposed by Dame Sheila Sherlock in 1959!
• Accepted in 2015 by AASLD, EASL and AGA

**Can we stratify risk of progression to cirrhosis?**

*On treatment (UDCA) biochemical response at 1 year—most robust endpoint to stratify risk of progression and potential need for 2nd line Rx*

• **GLOBE score**: [http://globalpbc.com/globe](http://globalpbc.com/globe)

• **UK-PBC risk score**: [http://www.uk-pbc.com/resources/tools/riskcalculator/](http://www.uk-pbc.com/resources/tools/riskcalculator/)
GLOBE score: 

\[
(0.044378 \times \text{age at start of UDCA therapy} + 0.93982 \times \text{NL}(\text{Bili x ULN at 1 year}) + (0.335648 \times \text{NL}(\text{ALP x ULN at 1 year})) - 2.266708 \times \text{Alb x LLN at 1 year} - 0.002581 \times \text{PLT at 1 year}) + 1.216865
\]
Predictive Significance of ALP and Bilirubin Values

Survival (%) at 15 Years

<table>
<thead>
<tr>
<th>ALP ≤2 x ULN</th>
<th>Normal Bilirubin</th>
<th>Abnormal Bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td>79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALP &gt;2 x ULN</th>
<th>Normal Bilirubin</th>
<th>Abnormal Bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>

Abbreviations: ALP, alkaline phosphatase; ULN, upper limit of normal.

OCA International Trials—Subjects Achieving Composite Endpoint

Primary Endpoint: Composite endpoint of ALP <1.67 x ULN, ≥15% ALP reduction, normal bilirubin

Phase II
- OCA
- OCA + UDCA

Phase III
- OCA ± UDCA

Placebo (n = 134)
- OCA Titrated (n = 70)
- OCA 10 mg (n = 131)

Subjects (%)

3 months | 3 months
--- | ---
Placebo | 4%
OCA Titrated | 5%
OCA 10 mg | 7%

3 months | 6 months | 12 months
--- | --- | ---
Placebo | 1% | 2%
OCA Titrated | 5% | 7%
OCA 10 mg | 6% | 8%

**P < .05
***P < .0001

Abbreviations: ALP, alkaline phosphatase; OCA, obeticholic acid; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
Graphic courtesy of Kris V. Kowdley, MD.
Long-Term Effect of Obeticholic Acid on Transient Elastography and AST to Platelet Ratio Index in Patients with PBC

![Graph showing the comparison of APRI and Transient Elastography between Placebo ± UDCA, OCA 5-10 mg ± UDCA, and OCA 10 mg ± UDCA.](image)

- **APRI**
  - DB Month 12
  - OLE Month 12
  - Mean (SD) Change from Baseline in APRI Score
  - n= 68, 60, 59, 58, 59, 55

- **Transient Elastography**
  - DB Month 12
  - OLE Month 12
  - Mean (SD) Change from Baseline in Liver Stiffness (kPa)
  - n= 34, 32, 26, 27, 29, 26

Abstract # 209: Hirschfield et al
A phase 2 proof of concept study of MBX-8025 in patients with Primary Biliary Cholangitis (PBC) who are inadequate responders to ursodeoxycholic acid (UDCA)

- Phase 2A, PPAR-delta for PBC with non-response to UDCA
- Dose-dependent transaminase elevation

![Graph showing the effect of MBX-8025 on ALP levels over time.]

Placebo (N = 12)
MBX-8025 50 mg (N = 13)
MBX-8025 200 mg (N = 10)

ABSTRACT # LB9  Jones et al
NRS Itch Intensity: % change from baseline

Numerical rating scale

% change from baseline (LS mean)

Abstract # 205, Hegade et al
PSC

- **MRCP** preferred diagnostic imaging
- **Liver biopsy**: Small duct PSC or AIH overlap
- Test IgG4 at least once
- **UDCA doses ≥28 mg/kg/day should not be used**
- **Better Px**: Normalisation of liver biochemistry spontaneously or UDCA
  - 20 mg/kg/day frequently used in clinical practice
- Routine stenting after dilatation of dominant stricture not recommended
- Dominant strictures should be evaluated: Biopsies, brushings & FISH
- **Refer for Liver Transplant when MELD>14**
  - Increased risk of ischaemic cholangiopathy with DCD organs
- Annual colonoscopy, preferably chromoendoscopy: PSC + colitis
- PSC without IBD: colonoscopy every 3-5 years
- Screening for CCA with cross-sectional imaging and serial CA19-9 every 6-12 months

Am J Gastro 2015;110:646
24-norUDCA is side chain shortened UDCA

Significant dose-dependent reduction of s-ALP values during 12 weeks of norUDCA compared to placebo with the highest effect at 1500mg/day

Biochemical response to norUDCA was independent of UDCA pre-Rx & response

- European study
- 12 week study
- Alk Phos Endpoint

Trauner et al, Abstract # 210

\[ \text{norUDCA (NU) reduces ALP in a dose-dependent fashion} \]
CIRRHOSIS
A randomized controlled trial comparing lactulose + albumin vs lactulose alone for hepatic encephalopathy

- Prospective, randomized controlled trial
- N= 120 (60 in each arm)
- Main difference was related to sepsis-related death

Abstract # 247. Sharma et al, ILBS and GB Pant Hospital, New Delhi
Efficacy and Safety of Rifaximin Monotherapy Versus Lactulose Combination Therapy for the Prevention of Overt Hepatic Encephalopathy (HE) Recurrence

**Graph:**
- **HR, 1.96; 95% CI, 1.0–3.7; P = 0.04**

- **Rifaximin 500 mg BID**
- **Rifaximin 500 mg BID + lactulose**

**Key Points:**
- Phase 4 open label 24 wk study
- Multi-center
- N= 222
- Hospitalization less in combo (ns)
- Safety profile similar

**Additional Note:**
During 6 months breakthrough HE was reported in fewer patients treated with rifaximin + lactulose (13.9%) vs rifaximin alone (24.8%)

Abstract # 248: Sanyal et al, Salix Pharmaceuticals
Rifaximin IR 40 mg improved all cause mortality + hospitalization composite clinically meaningful benefit endpoint

Benefits mainly in those with alcohol cirrhosis and low MELD. Abstract # 86, Sanyal et al

Abstracts 2064: Bajaj et al, Salix Pharmaceuticals
*Patients with more frequent surveillance were diagnosed with earlier staged HCC*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Surveillance &lt; q 12 months (N = 287)</th>
<th>Surveillance &gt; q 12 months (N= 148)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal vein thrombosis</td>
<td>6.7%</td>
<td>21.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tumor size &gt;5 cm</td>
<td>23.3%</td>
<td>22.9%</td>
<td>0.952</td>
</tr>
<tr>
<td>BCLC Stage 0 or A</td>
<td>56.8%</td>
<td>63.6%</td>
<td>0.504</td>
</tr>
<tr>
<td>Received OLT or surgical resection</td>
<td>27.5%</td>
<td>16.7%</td>
<td>0.270</td>
</tr>
<tr>
<td>Milan criteria for liver transplants</td>
<td>66.0%</td>
<td>50.0%</td>
<td>&lt;0.037</td>
</tr>
<tr>
<td>UCSF criteria for liver transplants</td>
<td>81.9%</td>
<td>67.9%</td>
<td>&lt;0.031</td>
</tr>
</tbody>
</table>

*On multivariate analysis:*

- Age and sex were not significant predictors for adherence, while
- **Significant independent predictors for adherence:** Asian ethnicity (HR 2.4, 1.8-3.3), presence of hepatic decompensation (HR 2.3, 1.8-3.1), and more frequent clinical visits (HR 1.4 [per visit], 1.1-1.8)
Health Disparities: sub-Saharan Africa

Burden of liver disease in sub-Saharan Africa is substantial

Challenges

• Lack of data to accurately establish disease prevalence
• Lack of access to health facilities - diagnostic and interventional
• Access and cost of medications

Apply similar programmes to HIV/AIDS to combat liver disease in SSA

- PEPFAR
- Global Fund to Fight AIDS, TB and Malaria

→ brought medication at affordable prices to SSA