Hepatitis C and Liver Cancer: Success of New Therapies and Treatments

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Division of Clinical Care and Research
Hepatocellular carcinoma is rising in incidence globally and tripled in the US over the last 3 decades.

Hepatocellular carcinoma is the 5th most common cancer and 2nd most common cause of cancer mortality worldwide.

Viral hepatitis is a significant risk for developing HCC.

Hepatitis viruses may have direct and indirect effects of hepatic carcinogenesis.
LIVER CANCER

- MD Mortality Trend: Rising 4.1%/year since 2004*
- MD Comparable to US Incidence Rate 7.9 versus 7.8/100,000 (2010-2014)*
- MD Comparable to US Mortality Rate 6.5 versus 6.3/100,000 (2014)*

- Stage distribution and 5 Year Survival
  - 43%, 31% local
  - 27%, 11% regional
  - 18%, 3% distant

- Risk factors:
  - Chronic Hepatitis B and C,
  - Cirrhosis, EtOH, Obesity, Diabetes
  - Aflatoxin, Toxins, Anabolic steroids,
  - Tobacco use, parasites ***

- Populations at risk:
  - 45+ years, males
  - Asian Americans, Pacific Islanders, Hispanics

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*Cancer Control P.L.A.N.E.T. ** SEER *** ACS
MORTALITY OF LIVER CANCER

Mortality ASR
Both sexes

Source: GLOBOCAN 2012 (IARC)

Accessed from the WHO International Agency on Research on Cancer on 11/2/2017
Available from http://globocan.iarc.fr/Pages/Map.aspx
RISK FACTORS FOR HCC

- HBV: 5-100 fold ↑ risk
- 4.3% of US HCC
- HCV: 15-20 fold ↑ risk
- 20.5% of US HCC
- Aflatoxin: 1.5-2 fold ↑ risk
- 13.4% of US HCC
- Alcohol: 1.5-2 fold ↑ risk
- 32% of US HCC

Adapted from Herceg Z and Paliwal A Mutation Research 2011; White Clin Gastroenterol Hepatol 2012; Makarova-Rusher Cancer 2016; Ramadori Cancers 2017
# Alcohol, Hepatitis and HCC

<table>
<thead>
<tr>
<th>Author/Country</th>
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<th>Hepatitis C</th>
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<tr>
<td></td>
<td>Cases/control (number)</td>
<td>Odds ratio (95% CI)</td>
<td>Cases/control (number)</td>
<td>Odds ratio (95% CI)</td>
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<td>Tagger et al, Italy</td>
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<tr>
<td>Daily alcohol (g/d)</td>
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<tr>
<td>&lt;40</td>
<td>31/219</td>
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<td>40–80</td>
<td>27/157</td>
<td>1.5 (0.7–2.9)</td>
<td>32/7</td>
<td>62.6 (23.3–168)</td>
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<tr>
<td>&gt;80</td>
<td>102/203</td>
<td>7.3 (4.0–13.1)</td>
<td>42/5</td>
<td>126 (42.8–373)</td>
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</tr>
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<td>Hassan et al, United States</td>
<td></td>
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</tr>
<tr>
<td>Daily alcohol</td>
<td></td>
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<tr>
<td>No</td>
<td>40/136</td>
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<tr>
<td>Yes</td>
<td>75/94</td>
<td>2.4 (1.3–4.4)</td>
<td></td>
<td></td>
<td>53.9 (7.0–415.7)</td>
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<tr>
<td>&lt;80 g/day</td>
<td>33/63</td>
<td>1.7 (0.9–3.7)</td>
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<td></td>
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</tr>
<tr>
<td>&gt;80 g/day</td>
<td>42/31</td>
<td>4.5 (1.4–14.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yu et al, Taiwan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>53/81</td>
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<tr>
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<td>60/44</td>
<td>2.1 (1.2–3.7)</td>
<td>6/0</td>
<td>Unable to calculate</td>
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</tr>
</tbody>
</table>
ESTIMATED 71 MILLION PEOPLE WITH HCV

Abstract  Twenty-two patients who had an episode of transfusion-associated hepatitis not positive for hepatitis B antigen were examined for development of antibody to hepatitis A and B antigens, cytomegalovirus and Epstein-Barr virus. Antibody response to the 27-nm virus-like hepatitis A antigen was measured by immune electron microscopy. In none of the 22 patients studied did serologic evidence of infection with hepatitis A virus develop during the study period. Nine of the 22 patients had antibody responses to cytomegalovirus, but it was difficult to relate these seroconversions to their hepatitis. In addition, all 22 patients had pre-existing antibody to the Epstein-Barr virus. It seems likely that at least a proportion of such antigen-negative transfusion-associated hepatitis is caused by other infectious agents, not yet identified. (N Engl J Med 292:767-770, 1975)
VIRAL FEATURES

- **RNA virus**
  - Positive single stranded
  - Family Flaviviridae
  - Genus Hepacivirus
    - Related genus Flavivirus - Dengue, Yellow Fever
  - In vivo replication: hepatocytes
  - Highly error prone, trillions of virions/day

Electron microscopic image of hepatitis C virus (HCV) virions...
UNLIKE HBV AND HIV, HCV CAN BE CURED

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>HIV</th>
<th>Hepatitis C</th>
<th>Hepatitis B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>1 million</td>
<td>5 million</td>
<td>2 million</td>
</tr>
<tr>
<td>Genome</td>
<td>RNA</td>
<td>RNA</td>
<td>DNA</td>
</tr>
<tr>
<td>Mutation Rates</td>
<td>Very high</td>
<td>Very high</td>
<td>High</td>
</tr>
<tr>
<td>Virions produced daily</td>
<td>$10^{10}$</td>
<td>$10^{12}$</td>
<td>$10^{13}$</td>
</tr>
<tr>
<td>Drug Targets</td>
<td>Multiple</td>
<td>Multiple</td>
<td>One</td>
</tr>
<tr>
<td>Genetic archive</td>
<td>Yes</td>
<td>NO</td>
<td>Yes</td>
</tr>
<tr>
<td>Ability to Cure</td>
<td>No</td>
<td>YES (No DNA integration)</td>
<td>No (cccDNA)</td>
</tr>
<tr>
<td>Current therapeutic goal</td>
<td>Lifelong suppression</td>
<td>Cure: Clearance from plasma and liver</td>
<td>Lifelong suppression</td>
</tr>
</tbody>
</table>

Adapted from Soriano V, JAC 2008; 62
NATURAL HISTORY OF HEPATITIS C

Adapted from hepatitisc.uw.edu
THE CHANGING FACE OF HCV IN US

Adapted from Davis GL et al Gastroenterol 2010;138:513-521
BIOLOGICAL DRIVERS OF HCC

NATURAL HISTORY OF HEPATITIS C

Adapted from hepatitisc.uw.edu
First description of non A non B hepatitis

1975

1989

1990

1992

1997

1998

2001

2002

2011

2012

Interferon alfa + ribavirin used to cure hepatitis C

Isolation and cloning of hepatitis C virus

Interferon alfa 2b used to cure hepatitis C

Consensus Interferon used to cure hepatitis C

Pegylated interferon alfa 2b with ribavirin used to cure hepatitis C

Interferon alfa 2a used to cure hepatitis C

Interferon alfa + ribavirin used to cure hepatitis C

Pegylated interferon alfa 2a with ribavirin used to cure hepatitis C

Kohli A. ...Kotttilil S. JAMA 2014
HCV CURE IMPROVES OUTCOME

Sustained Viral Response (SVR)

– Durable
  - 99% stay HCV negative for > 10 years
– Leads to improved histology
– Leads to clinical benefits
  - Decreased decompensation
  - Prevents de novo esophageal varices
  - Decreased hepatocellular carcinoma
  - Decreased mortality

SVR REDUCES ALL-CAUSE MORTALITY

21,839 treated patients in VA Clinical Case registry; 16,864 with follow up
High rates of co-morbidities (DM, HTN, ETOH, CAD)
SVR: GT1: 35%, GT2: 72%, GT3 62%

HCV TREATMENT IMPROVES FIBROSIS

74% of Patients with Cirrhosis at Baseline Were No Longer Cirrhotic at Year 5

Marcellin, P et al. Lancet 2013; 381(9865):468-75
ADVANCES IN HEPATITIS C TREATMENTS

EVOLUTION OF HEPATITIS C TREATMENT

- First description of non A non B hepatitis
- Interferon alfa 2b used to cure hepatitis C
- Consensus Interferon used to cure hepatitis C
- Pegylated interferon alfa 2b with ribavirin used to cure hepatitis C
- Addition of protease inhibitors to peg-IFN alfa and ribavirin

- Isolation and cloning of hepatitis C virus
- Interferon alfa 2a used to cure hepatitis C
- Interferon alfa + ribavirin used to cure hepatitis C
- Pegylated interferon alfa 2a with ribavirin used to cure hepatitis C

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1992

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1997

Interferon alfa + ribavirin used to cure hepatitis C

1998

Pegylated interferon alfa 2b with ribavirin used to cure hepatitis C

2001

Pegylated interferon alfa 2a with ribavirin used to cure hepatitis C

2002

Addition of protease inhibitors to peg-IFN alfa and ribavirin

2011

Proof of principle that therapy with directly acting antivirals only can cure hepatitis C

2012

Kohli A. ...Kottiliil S. JAMA 2014
ADVANCES IN HEPATITIS C TREATMENTS

DIRECTLY ACTING ANTIVIRAL THERAPY FOR HEPATITIS C

ION Phase 3 Program (ION-1, ION-2, ION-3)

Results: Efficacy Summary (ITT)

- 97% (1887/1951) overall SVR rate
- 3% (64/1951) did not achieve SVR
  - 1.8% (36) relapsed
  - 1.3% (26) were either lost to follow up or withdrew consent
  - 0.1% (2) virologic breakthrough (both due to non-adherence)

*excluding one subject with genotype 4 infection

Error bars represent 95% confidence intervals.
DIRECTLY ACTING ANTIVIRAL THERAPY FOR HEPATITIS C

C-EDGE TN Study: grazoprevir/elbasvir in genotype 1, 4 or 6

$SVR_{12}$ (HCV RNA < 15 IU/ml) by subgroup, % (95% CI)

<table>
<thead>
<tr>
<th>Group</th>
<th>Male</th>
<th>Female</th>
<th>CC</th>
<th>Non-CC</th>
<th>Cirrhosis</th>
<th>HCV RNA &gt; 800 000 IU/ml</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>171</td>
<td>145</td>
<td>106</td>
<td>208</td>
<td>246</td>
<td>94</td>
</tr>
<tr>
<td></td>
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<td>222</td>
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</table>
DIRECTLY ACTING ANTIVIRAL THERAPY FOR HEPATITIS C

ENDURANCE-1 Study: glecaprevir/pibrentasvir in genotype 1 without cirrhosis

Secondary efficacy endpoints (SVR\textsubscript{12}): ITT population

<table>
<thead>
<tr>
<th></th>
<th>8 Weeks</th>
<th>12 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>99</td>
<td>99,7</td>
</tr>
<tr>
<td>Mono-infected</td>
<td>99</td>
<td>99,7</td>
</tr>
<tr>
<td>HIV co-infected</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>SOF-experienced</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

ITT population: all patients receiving study drug; none excluded

* 1 patient experienced on-treatment virologic failure, 1 patient discontinued on D2 due to non-compliance, 1 patient missing SVR\textsubscript{12} data

** 1 patient missing SVR\textsubscript{12} data
# Approved HCV Regimens in the US

<table>
<thead>
<tr>
<th></th>
<th>Harvoni</th>
<th>Viekira Pak</th>
<th>Zepatier</th>
<th>Epclusa</th>
<th>Mavyret</th>
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<tbody>
<tr>
<td>Contains</td>
<td>LDV/SOF</td>
<td>PrOD</td>
<td>EBR/GBR</td>
<td>SOF/VEL</td>
<td>GLE/PIB</td>
</tr>
<tr>
<td>Duration</td>
<td>8-24 weeks</td>
<td>12-24 weeks</td>
<td>12-16 weeks</td>
<td>12-24 weeks</td>
<td>8-16 weeks</td>
</tr>
<tr>
<td>Efficacy</td>
<td>~93-98%</td>
<td>~93-98%</td>
<td>~93-98%</td>
<td>~93-98%</td>
<td>~93-98%</td>
</tr>
</tbody>
</table>

- **Harvoni**: Contains LDV/SOF, approved in October 2014, duration 8-24 weeks, efficacy ~93-98%, cost (12wk) $94,500 ± RBV $5,000, total $94,500 ± RBV $5,000.
- **Viekira Pak**: Contains PrOD, approved in January 2015, duration 12-24 weeks, efficacy ~93-98%, cost (12wk) $83,319 ± RBV $5,000, total $83,319 ± RBV $5,000.
- **Zepatier**: Contains EBR/GBR, approved in January 2016, duration 12-16 weeks, efficacy ~93-98%, cost (12wk) $74,760 ± RBV $6,700, total $74,760 ± RBV $6,700.
- **Epclusa**: Contains SOF/VEL, approved in June 2016, duration 12-24 weeks, efficacy ~93-98%, cost (12wk) $39,600.
- **Mavyret**: Contains GLE/PIB, approved in August 2017, duration 8-16 weeks, efficacy ~93-98%.
HCV TREATMENT RESTRICTED BY COST

For Sovaldi patients, expensive hepatitis C cure is priceless

Maker of $1,000 hepatitis C pill was focused on profits, not patients, report finds
# HCV Treatment is Restricted by Cost

<table>
<thead>
<tr>
<th>Medication</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>WAC for 1 Day</th>
</tr>
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<tbody>
<tr>
<td>Daclatasvir</td>
<td>Daklinza</td>
<td>Bristol-Myers Squibb</td>
<td>$750</td>
</tr>
<tr>
<td>Elbasvir-Grazoprevir</td>
<td>Zepatier</td>
<td>Merck &amp; Co., Inc.</td>
<td>$650</td>
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<tr>
<td>Ledipasvir-sofosbuvir</td>
<td>Harvoni</td>
<td>Gilead Sciences</td>
<td>$1125</td>
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<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir</td>
<td>Technivie</td>
<td>AbbVie</td>
<td>$912</td>
</tr>
<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir</td>
<td>Viekira Pak</td>
<td>AbbVie</td>
<td>$992</td>
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<tr>
<td>Simeprevir</td>
<td>Olysio</td>
<td>Janssen</td>
<td>$790</td>
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<tr>
<td>Sofosbuvir</td>
<td>Sovaldi</td>
<td>Gilead Sciences</td>
<td>$1000</td>
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</table>

Adapted from hepatitisc.uw.edu
HCV TREATMENT IS RESTRICTED BY COST

<table>
<thead>
<tr>
<th>Regimen</th>
<th>SVR rates</th>
<th>WAC Price</th>
<th>Cost per SVR</th>
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</thead>
<tbody>
<tr>
<td>Pegasys + Ribavirin x 48 weeks(^1)</td>
<td>41%</td>
<td>$41,758</td>
<td>$101,849</td>
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<tr>
<td>Telaprevir + PegIFN + Ribavirin x 24 weeks(^2)</td>
<td>75%</td>
<td>$86,843</td>
<td>$115,791</td>
</tr>
<tr>
<td>Sofosbuvir + PegIFN + Ribavirin x 12 weeks</td>
<td>90%</td>
<td>$94,421</td>
<td>$104,912</td>
</tr>
<tr>
<td>Sofosbuvir + Ledipasvir x 8 weeks</td>
<td>94%</td>
<td>$63,000</td>
<td>$67,021 ($36,191(^?))*</td>
</tr>
<tr>
<td>Sofosbuvir + Ledipasvir x 12 weeks</td>
<td>99%</td>
<td>$94,500</td>
<td>$95,454 ($51,545(^?))*</td>
</tr>
</tbody>
</table>

HEALTHCARE COSTS OF UNTREATED HCV, BY SEQUELAE

HCV TREATMENT WITH DAAS IS COST EFFECTIVE, BUT NOT AFFORDABLE

- Prevalent Disease
- High Cost
- Media Coverage
- High Demand

Payer Restrictions and Rationing of Care
POTENTIAL COST OF STATE-FUNDED HEPATITIS C TREATMENT

Adapted from Express Scripts, 2014
Maryland: C

- Liver damage restrictions
  - ≥ F2 – Medicaid and FFS, 1 MCO ≥ F3
- Sobriety restrictions
  - Screening for active alcohol/substance use
- Provider restrictions
  - Prescription written by/in consultation with a specialist
- Restrictions differ for FFS and MCOs

https://stateofhepc.org
US ESTIMATES OF HCV CASCADE OF CARE

Major gap is in screening: most pts unaware of diagnosis

60% of pts seeing HCV provider are not treated

CHANGING EPIDEMIOLOGY OF HCV IN THE US

LACK OF SPECIALIST AVAILABILITY LIMITS ACCESS TO HCV TREATMENT

Patients with Chronic HCV: 2,700,000
Specialist Providers: 20,000
ASCEND STUDY DESIGN

Two urban health systems

16 providers

5 Nurse Practitioners
5 Primary Care Providers
6 Specialists (ID/Hepatology)

Uniform 3-hour training

600 patients

LDV/SOF 8-24 weeks

SVR$_{12}$

Visit Adherence
Prescription Adherence

Kattakuzhy, S et al Ann Int Med 2017
ASCEND Study Flow

681 patients consented

36 exclusion criteria or treated

45 LTF

600 patients started on LDV/SOF

150 NP Treatment

11 discontinued early

9 LTF

0 deaths

156 PCP Treatment

18 discontinued early

12 LTF

1 death

141 with SVR data

294 Specialist Treatment

38 discontinued early

27 LTF

3 deaths

264 with SVR data

143 with SVR data

Kattakuzhy, S et al Ann Int Med 2017
SVR (INTENTION TO TREAT)

Kattakuzhy, S et al Ann Int Med 2017
Higher Rates of Visit Adherence with Non-Specialist Providers

Kattakuzhy, S et al Ann Int Med 2017
HIGH PRESCRIPTION ADHERENCE

- 100% Adherence: 87%
- <100% Adherence: 13%

Kattakuzhy, S et al Ann Int Med 2017
SVR (ITT) BY PRESCRIPTION ADHERENCE

Kattakuzhy, S et al Ann Int Med 2017
ASCEND SUMMARY

- Non-specialist providers have high rates of success with HCV treatment, comparable to specialists with appropriate training.

- In the absence of insurance-based provider restrictions and prior authorization, rapid treatment uptake can be accomplished.

- There is data to support elimination of provider restrictions around provision of HCV care.

Kattakuzhy, S et al Ann Int Med 2017
…regulatory agencies should ensure that drugs have been evaluated by long term follow up of clinical outcomes (not just surrogate markers) in several thousands of patients…

“This evidence for our main outcomes of interest come from short-term trials, and we are unable to determine the effect of long-term treatment with DAAs…DAAs may reduce the number of people with detectable virus in their blood, but we do not have sufficient evidence from randomized trials that enables us to understand how SVR affects long-term clinical outcomes. SVR is still an outcome that needs proper validation in randomized clinical trials.”


Jakobson, et al *Cochrane Database Syst Rev* 2017
HCC RISK PERSISTS AFTER DAA THERAPY IN PTS WITH HCV-RELATED CIRRHOSIS

- Retrospective analysis of 344 HCV-infected pts with CPT A or B cirrhosis treated with DAAs (SVR: 89%)
  - Pts followed for 12-24 wks after treatment completion
  - No HCC at baseline, but previous HCC permitted

- Overall HCC incidence after DAA therapy: 7.6%
  - In pts without previous HCC: 3.2%
  - In pts with previous HCC: 29.0%

- More advanced liver disease and previous HCC significant risk factors for HCC after DAAs

<table>
<thead>
<tr>
<th>Factor</th>
<th>No HCC (n = 318)</th>
<th>HCC (n = 26)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP class B, %</td>
<td>10.1</td>
<td>26.9</td>
<td>.02</td>
</tr>
<tr>
<td>Mean liver stiffness, kPa</td>
<td>23.2</td>
<td>28.1</td>
<td>.01</td>
</tr>
<tr>
<td>Liver stiffness, kPa &lt; 21.3</td>
<td>134</td>
<td>5</td>
<td>.005</td>
</tr>
<tr>
<td>Liver stiffness, kPa &gt; 21.3</td>
<td>101</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Mean platelets, x 1000/mm³</td>
<td>124.4</td>
<td>102.3</td>
<td>.02</td>
</tr>
<tr>
<td>Previous HCC, n</td>
<td>42</td>
<td>17</td>
<td>.0001</td>
</tr>
<tr>
<td></td>
<td>276</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

HCC RECURRENCE FOLLOWING HCV DAA THERAPY

- Retrospective study of pts with history of HCC before starting HCV DAAs (N = 105)

- 10 pts had HCC recurrence or progression

- Among pts starting DAAs ≤ 4 mos after CR, 4 pts (20%) died
  - Deaths occurred in Months 9, 10, 15, 16 after starting DAA

- Death, n (%) 5 (20.8)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Pts With Recurrence (n = 24)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time from DAA start to first recurrence, mos (IQR)</td>
<td>3.5 (2-7.6)</td>
</tr>
<tr>
<td>Median time from first to second recurrence/progression, mos (IQR)</td>
<td>6 (3.2-8.2)</td>
</tr>
</tbody>
</table>

- *Pts from cohort with confirmed radiologic assessment, no confounding factors.
HCC RECURRENCE EQUIVALENT WITH DAAS AND IFN

- Meta-analysis and meta-regression analysis comparing risk of HCC after SVR with DAA- vs IFN-based therapy in 41 studies (N = 13,875)

**Pts With First HCC Occurrence After SVR**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DAA</th>
<th>IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>60</td>
<td>52</td>
</tr>
<tr>
<td>Cirrhosis, %</td>
<td>90</td>
<td>87</td>
</tr>
<tr>
<td>Child-Pugh score B/C, %</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Follow-up, yrs</td>
<td>1.0</td>
<td>5.5</td>
</tr>
</tbody>
</table>

**Pts With HCC Recurrence After SVR**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DAA</th>
<th>IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with previous curative HCC treatment, %</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>Follow-up, yrs</td>
<td>1.3</td>
<td>5.0</td>
</tr>
</tbody>
</table>

- After adjusting for these factors, **no difference in risk of HCC occurrence (aRR: 0.75) or recurrence (aRR: 0.62) between DAAs and IFN**

- “The more advanced cirrhosis population who can be treated by DAA compared to IFN-based therapy and the higher DAA cure rates among patients with cirrhosis mean that the impact on population-level HCC incidence should be markedly higher in the DAA-era.”

HCV CURE WITH DAAS REDUCES MORTALITY

DAA-induced SVR is associated with a 43% reduction in mortality.

Survival in ERCHIVES Veterans (N = 13,940*†)[1]

Proportion Surviving

0.5 1 5 10 15 20 Mos

DAA-induced SVR is associated with a 43% reduction in mortality

*For 18 mos of follow-up.
†BL cirrhosis: PrOD, 24.9%; LDV/SOF, 29.4%; untreated, 19.4%.
HCV CURE REDUCES HCC

DAA-induced SVR is associated with a 71% reduction in HCC risk


‡For 38,204 pt-yrs of follow-up.
 DOES EARLY SCREENING HELP?

<table>
<thead>
<tr>
<th></th>
<th>Combined</th>
<th>Center 1</th>
<th>Center 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>mean ± SD (years)</td>
<td>59.06 ± 9.9</td>
<td>58.64 ± 10.8</td>
<td>59.18 ± 9.74</td>
</tr>
<tr>
<td></td>
<td>mean ±SD (ng/mL)</td>
<td>5487.9 ± 3147.11</td>
<td>3188.01 ± 1697.32</td>
<td>6134.69 ± 4006.08</td>
</tr>
<tr>
<td>Size of Lesions</td>
<td>mean ± SD (cm)</td>
<td>5.27 ± 1.29</td>
<td>5.16 ± 3.26</td>
<td>5.31 ± 2.92</td>
</tr>
<tr>
<td>Gender</td>
<td>Male n (%)</td>
<td>137 (83.5%)</td>
<td>31 (86.11%)</td>
<td>106 (82.81%)</td>
</tr>
<tr>
<td>Surveillance</td>
<td>Yes</td>
<td>87 (60.98%)</td>
<td>26 (72.22%)</td>
<td>74 (54.81%)</td>
</tr>
<tr>
<td>Child-Pugh Class</td>
<td>A</td>
<td>32 (19.51%)</td>
<td>22 (61.11%)</td>
<td>10 (7.81%)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>72 (43.90%)</td>
<td>8 (22.22%)</td>
<td>64 (50%)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>60 (36.59%)</td>
<td>6 (16.67%)</td>
<td>54 (42.19%)</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td></td>
<td>11 (7%)</td>
<td>1 (3%)</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>HBV only</td>
<td></td>
<td>10 (6%)</td>
<td>1 (3%)</td>
<td>9 (7%)</td>
</tr>
<tr>
<td>HBV &amp; ETOH</td>
<td></td>
<td>1 (1%)</td>
<td>--</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>HCV</td>
<td></td>
<td>73 (46%)</td>
<td>11 (31%)</td>
<td>62 (48%)</td>
</tr>
<tr>
<td>HCV only</td>
<td></td>
<td>42 (26%)</td>
<td>9 (25%)</td>
<td>33 (26%)</td>
</tr>
<tr>
<td>HCV &amp; ETOH</td>
<td></td>
<td>31 (20%)</td>
<td>2 (6%)</td>
<td>29 (23%)</td>
</tr>
<tr>
<td>HBV &amp; HCV &amp; ETOH</td>
<td></td>
<td>40 (25%)</td>
<td>13 (36%)</td>
<td>27 (21%)</td>
</tr>
<tr>
<td>ETOH only</td>
<td></td>
<td>35 (22%)</td>
<td>9 (25%)</td>
<td>26 (20%)</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td>5 (3%)</td>
<td>2 (6%)</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>

Kohli A……Kotttilil S. *SpringerPlus* 2014; 3: 610
SCREENING DETECTS EARLY HCC

Kohli A……Kottilil S. *SpringerPlus* 2014; 3: 610
SURVEILLANCE WAS NOT ASSOCIATED WITH IMPROVED SURVIVAL

Kohli A……Kottilil S. SpringerPlus 2014; 3: 610
# EVIDENCE FAVORING SURVEILLANCE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N of participants (studies)</th>
<th>Overall quality of evidence</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early tumor detection rate</td>
<td>10,904 (38 observational studies)</td>
<td>⬤️⬤️⬤️◯◯ LOW</td>
<td>OR 2.11 (1.88 to 2.33)</td>
</tr>
<tr>
<td>Early tumor detection rate (using BCLC to define early stage)</td>
<td>6,573 (6 observational studies)</td>
<td>⬤️⬤️⬤️◯◯ LOW</td>
<td>OR 1.96 (1.41 to 2.73)</td>
</tr>
<tr>
<td>Curative treatment rate</td>
<td>24,374 (34 observational studies)</td>
<td>⬤️⬤️⬤️⬤️* MODERATE</td>
<td>OR 2.24 (1.99 to 2.52)</td>
</tr>
<tr>
<td>3-year survival rate*</td>
<td>10,850 (23 observational studies)</td>
<td>⬤️⬤️⬤️⬤️* MODERATE</td>
<td>OR 1.90 (1.67 to 2.17)</td>
</tr>
<tr>
<td>Early detection (ultrasound only)</td>
<td>(5 observational studies)</td>
<td>⬤️⬤️⬤️◯◯ LOW</td>
<td>OR 2.04 (1.55 to 2.68)</td>
</tr>
<tr>
<td>Early detection (ultrasound +/- AFP)</td>
<td>(14 observational studies)</td>
<td>⬤️⬤️⬤️◯◯ LOW</td>
<td>OR 2.16 (1.80 to 2.60)</td>
</tr>
<tr>
<td>Receipt of curative treatment (ultrasound +/- AFP)</td>
<td>(24 observational studies)</td>
<td>⬤️⬤️⬤️◯◯ LOW</td>
<td>OR 2.19 (1.89 to 2.53)</td>
</tr>
</tbody>
</table>

*Upgraded because of large effect size

Adapted from Heimbach *Hepatology* 2017
EFFECTIVE SURVEILLANCE PROGRAMS PROLONG SURVIVAL

<table>
<thead>
<tr>
<th></th>
<th>Japan: N=1174</th>
<th>Hong Kong: N=1675</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surveillance rate:</strong></td>
<td>75%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td><strong>Median survival:</strong></td>
<td>52 months</td>
<td>17.8 months</td>
</tr>
<tr>
<td><strong>Early stage at dx:</strong></td>
<td>62%</td>
<td>31.7%</td>
</tr>
<tr>
<td><strong>Curative therapy:</strong></td>
<td>63%</td>
<td>44.1%</td>
</tr>
</tbody>
</table>

Pros: Adjusted for lead time bias
Cons: Mixed etiologies

Johnson Br J Cancer 2017
CONCLUSIONS

- Hepatitis C is an important preventable cause of HCC worldwide
- Prevention of HCC is possible with curative treatment for HCV, but we need to expand access
- Improving surveillance for and treatments for HCC remains a challenge
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