Hashem B El-Serag, MD, MPH
Chief, Gastroenterology and Hepatology
Baylor College of Medicine, Houston

Chemoprevention Using Antiviral Treatments:
The Case of Hepatocellular Carcinoma
Antiviral Therapy and HCC

- Antiviral therapies for hepatitis B and hepatitis C can prevent (a lot) but not completely eliminate HCC
- To impact national and global incidence of HCC:
  - Improvement in identification of infected persons, accessibility of care and affordability of antiviral therapy
  - Time not on our side
- Good example of population health converging on precision medicine
The Incidence and 5-Year Survival of HCC in United States (1973-2007)

Disparities
- Race
- Gender
- Geography
### Viral Hepatitis and the Attributable Risk of HCC

<table>
<thead>
<tr>
<th>Primary liver cancer cases</th>
<th>HBV Attributable fraction (%)</th>
<th>HCV Attributable fraction (%)</th>
<th>Cases attributable to HBV or HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Developed countries</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>110,800</td>
<td>23.3</td>
<td>19.9</td>
<td>48,000</td>
</tr>
<tr>
<td><strong>Developing countries</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>515,300</td>
<td>58.8</td>
<td>33.4</td>
<td>475,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>54.4</strong></td>
<td><strong>31.1</strong></td>
<td><strong>535,000</strong></td>
</tr>
</tbody>
</table>

Adapted from Parkin, 2006.
HCV Cirrhosis and HCC
(3-5% per year)

Multiple small foci of HCC
HBV and HCC

- HBV DNA integrated into tumor cell DNA in 90% of HCC patients
- HCC occurs in those with and without cirrhosis
  - BUT cirrhosis is the major risk
- HBV DNA levels correlate with HCC risk

Baseline HBV DNA Level, copies/mL, at study entry
- ≥1 Million
- 100,00-999,999
- 10,000-99,999
- 300-9,999
- <300

Entire Cohort (N=3653)

Chen C-J et al, JAMA 2006;295:65-73
HBV Vaccination and HCC: Taiwan Experience

- HCC prevention extended from childhood to early adulthood
- Failures: incomplete vaccination, maternal HBsAg or HBeAg

Decreased Incidence of Hepatocellular Carcinoma in Hepatitis B Vaccinees: A 20-Year Follow-up Study


# Approved Therapies for HBV

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Approval Date</th>
<th>Antiviral Potency</th>
<th>Risk of Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-IFN</td>
<td>(2005)</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Lamivudine (LMV)</td>
<td>1995</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Adefovir (ADV)</td>
<td>2002</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Entecavir (ETV)</td>
<td>2005</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Telbivudine (TBV)</td>
<td>2006</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>2008</td>
<td>+++</td>
<td>-</td>
</tr>
</tbody>
</table>

Preferred first-line agents

AASLD Guidelines 2009
Nucleoside Analogue Therapy in the Prevention of HCC: Meta-analysis

Overall: 2.7% NA vs. 11% controls

N=2289, 5 studies

Cirrhosis: 3.9% NA vs. 22.4% controls
Non-cirrhotics: 1.8% NA vs. 8% controls

Sung APT 2008;28:1067
HCV and HCC

- Prevention of HCC = prevention of cirrhosis
  - HCC occurs only in setting of advanced fibrosis
  - Unlike HBV, no integration in host DNA
- Viral eradication is achievable
  - SVR12 correlates with long-lasting viral clearance and improved outcomes
Risk Difference in HCC in HCV Patients with and without SVR

Messori A, Clin Drug Investig, 2015

<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimate (95% C.I.)</th>
<th>Ev/Trt</th>
<th>Ev/Ctrl</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Stages</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asahina et al. 2010</td>
<td>-0.078 (-0.099, -0.057)</td>
<td>22/686</td>
<td>149/1356</td>
</tr>
<tr>
<td>Diepenik et al. 2014</td>
<td>-0.052 (-0.093, -0.011)</td>
<td>9/222</td>
<td>29/314</td>
</tr>
<tr>
<td>Dohmen et al. 2013</td>
<td>-0.175 (-0.276, -0.074)</td>
<td>6/279</td>
<td>12/61</td>
</tr>
<tr>
<td>Harada et al. 2014</td>
<td>-0.015 (-0.029, -0.001)</td>
<td>1/447</td>
<td>6/250</td>
</tr>
<tr>
<td>Hung et al. 2011</td>
<td>-0.090 (-0.122, -0.057)</td>
<td>35/1027</td>
<td>54/443</td>
</tr>
<tr>
<td>Kawamura et al. 2010</td>
<td>-0.051 (-0.068, -0.035)</td>
<td>12/1081</td>
<td>61/577</td>
</tr>
<tr>
<td>Kramer et al. 2011</td>
<td>-0.030 (-0.035, -0.025)</td>
<td>52/4252</td>
<td>432/10276</td>
</tr>
<tr>
<td>Kurokawa et al. 2009</td>
<td>-0.051 (-0.094, -0.008)</td>
<td>4/139</td>
<td>21/264</td>
</tr>
<tr>
<td>Okancue et al. 2002</td>
<td>-0.100 (-0.122, -0.078)</td>
<td>4/375</td>
<td>110/595</td>
</tr>
<tr>
<td>Otaki et al. 2012</td>
<td>-0.106 (-0.152, -0.061)</td>
<td>1/185</td>
<td>22/197</td>
</tr>
<tr>
<td>Prada et al. 2007</td>
<td>-0.060 (-0.093, -0.027)</td>
<td>0/91</td>
<td>17/266</td>
</tr>
<tr>
<td>Rutter et al. 2015</td>
<td>-0.098 (-0.149, -0.048)</td>
<td>10/551</td>
<td>19/163</td>
</tr>
<tr>
<td>Sinn et al. 2008</td>
<td>-0.038 (-0.072, -0.004)</td>
<td>4/296</td>
<td>10/194</td>
</tr>
<tr>
<td>Takahashi et al. 2011</td>
<td>-0.094 (-0.154, -0.034)</td>
<td>1/89</td>
<td>12/114</td>
</tr>
<tr>
<td>Tateyama et al. 2011</td>
<td>-0.166 (-0.222, -0.111)</td>
<td>3/139</td>
<td>44/234</td>
</tr>
<tr>
<td>Yoshida et al. 1999</td>
<td>-0.036 (-0.049, -0.023)</td>
<td>10/789</td>
<td>79/1611</td>
</tr>
<tr>
<td><strong>Subgroup a (P=0.85, P=0.000)</strong></td>
<td>-0.067 (-0.083, -0.051)</td>
<td>172/16688</td>
<td>1077/17815</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimate (95% C.I.)</th>
<th>Ev/Trt</th>
<th>Ev/Ctrl</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advanced Fibrosis/Cirrhosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breck et al. 2007</td>
<td>-0.289 (-0.406, -0.172)</td>
<td>1/37</td>
<td>21/176</td>
</tr>
<tr>
<td>Bruno et al. 2007</td>
<td>-0.141 (-0.153, -0.066)</td>
<td>7/124</td>
<td>122/759</td>
</tr>
<tr>
<td>Cardoso et al. 2010</td>
<td>-0.139 (-0.209, -0.067)</td>
<td>6/103</td>
<td>40/204</td>
</tr>
<tr>
<td>Hasegawa et al. 2007</td>
<td>-0.219 (-0.353, -0.083)</td>
<td>3/48</td>
<td>16/57</td>
</tr>
<tr>
<td>Hung et al. 2006</td>
<td>-0.113 (-0.233, -0.003)</td>
<td>5/73</td>
<td>11/59</td>
</tr>
<tr>
<td>Lee et al. 2015</td>
<td>-0.157 (-0.092, -0.226)</td>
<td>2/46</td>
<td>30/37</td>
</tr>
<tr>
<td>Morgan et al. 2010</td>
<td>-0.071 (-0.116, -0.037)</td>
<td>2/140</td>
<td>33/386</td>
</tr>
<tr>
<td>Van der Meer et al. 2012</td>
<td>-0.183 (-0.219, -0.137)</td>
<td>7/192</td>
<td>76/338</td>
</tr>
<tr>
<td>Velosa et al. 2011</td>
<td>-0.194 (-0.239, -0.056)</td>
<td>1/39</td>
<td>20/51</td>
</tr>
<tr>
<td><strong>Subgroup b (P=0.63, P=0.000)</strong></td>
<td>-0.222 (-0.306, -0.135)</td>
<td>34/402</td>
<td>372/2007</td>
</tr>
<tr>
<td><strong>Overall (P=0.52, P=0.000)</strong></td>
<td>-0.100 (-0.129, -0.060)</td>
<td>206/11490</td>
<td>1449/19822</td>
</tr>
</tbody>
</table>

NNT = 15
NNT = 4.5
Figure 1. Timeline of the introduction of antiviral therapy for HCV infection


Overall SVR rates (%)

Abbreviations: BOC, boceprevir; IFN, interferon; PegIFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response; TPR, telaprevir
**DAAs and Prevention of HCC**

---

### Advantages of DAAs

- SVR rates ≥90% across genotypes
- Safe and well-tolerated, even in cirrhotics
- Short duration therapy
- High provider and patient acceptability

---

<table>
<thead>
<tr>
<th>NS3/4A inhibitors (-previr)</th>
<th>NS5A inhibitors (-asvir)</th>
<th>NS5B inhibitors (-buvir)</th>
</tr>
</thead>
<tbody>
<tr>
<td>telaprevir*</td>
<td>ledipasvir*</td>
<td>sofosbuvir*</td>
</tr>
<tr>
<td>boceprevir*</td>
<td>ombitasvir*</td>
<td>dasabuvir*</td>
</tr>
<tr>
<td>simeprevir*</td>
<td>daclatasvir*</td>
<td>beclabuvir*</td>
</tr>
<tr>
<td>paritaprevir*</td>
<td>GS-5816*</td>
<td>GS-9669*</td>
</tr>
<tr>
<td>ABT-493§</td>
<td>ABT-530§</td>
<td>TMC-055§</td>
</tr>
<tr>
<td>asunaprevir§</td>
<td>elbasvir§</td>
<td>MK-8408§</td>
</tr>
<tr>
<td>grazoprevir§</td>
<td>MK-8408§</td>
<td>JNJ-845§</td>
</tr>
<tr>
<td>vedroprevir§</td>
<td>MK-8408§</td>
<td>JNJ-845§</td>
</tr>
<tr>
<td>GS-9857§</td>
<td>MK-8408§</td>
<td>JNJ-845§</td>
</tr>
</tbody>
</table>

*FDA-approved, §in clinical trials

---

Lam BP, Therap Adv Gastroenterol, 2015
The HCV Care Cascade

3,500,000 in U.S.

- 100% Chronic HCV-Infected
- 50% Diagnosed and Aware
- 43% Access/Linkage to Care
- 27% HCV RNA Confirmed
- 16% Prescribed HCV Treatment
- 9% Achieved SVR

Highly Efficacious Viral Treatments Are Not Enough

- PEG-IFN/RBV: 100% All HCV patients
- 95% SVR: 100%
- 95% SVR and higher rates of diagnosis/treatment: 100%

- Diagnosis and treatment: 20% for PEG-IFN/RBV and 20% for 95% SVR, 90% for higher rates of diagnosis/treatment

- Cure: 10% for PEG-IFN/RBV and 19% for 95% SVR, 85% for higher rates of diagnosis/treatment

Slide courtesy of Prof. Michael Manns
The Quality in the Continuum of Cancer Care (QCCC) Conceptual Framework

Population Health

Precision Medicine

2013
Hepatitis C Virus Testing of Persons Born During 1945 to 1965: Recommendations From the Centers for Disease Control and Prevention


HCC Incidence Following HCV SVR (Cure)
Risk Factors: Age, Cirrhosis, Diabetes

Cumulative Incidence of HCC

Years after SVR

Cirrhosis

No cirrhosis

El-Serag HB, et al AASLD 2015
Obesity and HCC

Distal vs. Proximal Associations

- **Proximal** associations
  - Help in prevention, diagnosis and treatment
  - Understand cancer pathogenesis

Abdominal Fat
Humoral Mechanisms
NAFLD / NASH

Obesity
Diabetes

HCC
Non Alcoholic Fatty Liver Disease (NAFLD)
Spectrum of Hepatic Pathology

- Steatosis
- Steatohepatitis
- Cirrhosis
- Hepatocellular carcinoma
### Prevalence, Relative Risk Estimates, and Population Attributable Fraction

<table>
<thead>
<tr>
<th></th>
<th>Prevalence in general population</th>
<th>Risk estimate of HCC</th>
<th>Population attributable fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBV</strong></td>
<td>0.5-1%</td>
<td>20-25</td>
<td>5-10%</td>
</tr>
<tr>
<td><strong>HCV</strong></td>
<td>1-2%</td>
<td>20-25</td>
<td>20-25%</td>
</tr>
<tr>
<td><strong>Alcoholic liver disease</strong></td>
<td>10-15%</td>
<td>2-3</td>
<td>20-30%</td>
</tr>
<tr>
<td><strong>Metabolic syndrome</strong></td>
<td>30-40%</td>
<td>1.5-2.5</td>
<td>30-40%</td>
</tr>
</tbody>
</table>
Obesity and HCC

Summary

- Relative risk of HCC is modestly elevated in obese and diabetic persons but the absolute risk is low.
  - Weak/modest causal association
- Factors influencing HCC risk among obese person are unclear.
  - Abdominal obesity
  - Early onset/long duration
- Factors that influence HCC risk among diabetics are unclear
  - Type 2 diabetes
  - Long duration
  - Not treated with metformin
- Proximal associations include inflammatory mechanisms, NAFLD/NASH, others
  - The possibility of obesity related HCC developing in non-cirrhotic liver
- Obesity/diabetes related HCC has not translated (yet) into a large burden
Cancer Prevention and Research Institute of Texas (CPRIT)

The Texas Hepatocellular Carcinoma Consortium (THCCC)

PROJECT 1. Risk Factors of Hepatocellular Carcinoma in Non-alcoholic Fatty Liver Disease

PROJECT 2. Metabolic Syndrome and Risk Prediction of HCC

PROJECT 3. Circadian Disruption and Bile Acids as HCC Risk Factors

PROJECT 4. Novel Biomarkers for Hepatocellular Carcinoma

PROJECT 5. A comparative effectiveness randomized controlled trial of strategies to increase HCC surveillance

CORE 1. The Cohorts and Samples Core (CSC)

CORE 2. The Statistical Coordinating Core (SCC)

Administrative Core

Prospective cohort
Multi city
5000 patients with cirrhosis
Antiviral Therapy and HCC

- Antiviral therapies for hepatitis B and hepatitis C can prevent (a lot) but not completely eliminate HCC
- To impact national and global incidence of HCC:
  - Improvement in identification of infected persons, accessibility of care and affordability of antiviral therapy
  - Time not on our side
- Good example of population health converging on precision medicine