European HIV Hepatitis Co-infection (EHHC) Conference
10-11 December 2015, London

Plenary Session 4: Hepatitis B

Liver Cancer
Pathogenesis, Screening & Treatment

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No conflicts of interest to disclose.
Overview of the Talk

- Pathogenesis of HCC.
  - Molecular and Clinical differences in HBV vs HCV
  - Contribution of HIV

- Epidemiology
  - The magnitude of the problem.
  - Relevance of HCC as a source of morbidity/mortality in people living with HIV.

- Screening and Diagnosis

- Management of HCC
Top 5 reasons to be interested in HCC.

1. Rising incidence in the Western World.
3. Well established risk factors (population at risk)
4. Highly multidisciplinary management.
5. Leading cause of morbidity/mortality in co-infected patients.
Hepatocellular Carcinoma

- Commonest primary liver cancer (90%)
- 5th most common solid tumor
- 3rd most fatal
- M/F ratio 2.4
- Last and most adverse consequence of Chronic Liver Disease.

- Multiphasic carcinogenesis
  inflammation → fibrosis → carcinoma

>80% HCC arise in CLD (any cause)
2-4% annual incidence
HCC: a Complex Pathogenesis

HBV 10-15%*
- Growth factor activation

HCV 60-70%*
- Chronic injury
- Inflammation
- Cirrhosis
- Regeneration
- Genetic and/or epigenetic alterations

Alcohol
- NAFLD/NASH
- Metabolic Disorders
- Environmental factors (AFB1)

HBV and HCV infections lead to chronic injury and inflammation, which can progress to cirrhosis and regeneration. Genetic and/or epigenetic alterations contribute to the development of HCC. Environmental factors such as alcohol and NAFLD/NASH also play a role.

Direct genotoxic effect (integration)
Epigenetic effects (cccDNA)

* Europe Incidence

HCC: the magnitude of the problem

Surveillance, Epidemiology, and End Results (SEER) registries.

Annual age-adjusted incidence rates per 100,000 and trends, all hepatocellular carcinoma cases and by sex (1975-2005)

- Viral (HCV diffusion in the West)
- Non viral aetiology ("cryptogenetic" cirrhosis)

Increase in incidence in 30 years

Alterkuse, J Clin Oncol. 2009
Hepatitis B and HCC

- Worldwide: $>50\%$ of all HCC cases and $>95\%$ childhood cases.

- Global Annual Mortality
  328,000 HBV HCC
  155,000 HCV HCC

HBV 2nd most harmful carcinogen after tobacco.

Hepatocellular Carcinoma: HBV induced carcinogenesis
Hepatitis B Virus (HBV)

- **Risk of HCC with chronic HBV increased if:**
  - Elevated HBV-DNA
  - Male
  - Advanced Age
  - Long duration of infection
  - Family history of HCC
  - Aflatoxin, alcohol, tobacco
  - Co-infection with HCV, Delta virus, HIV

**REVEAL:**
- prospective, multicenter, observational cohort study
- 7 Taiwanese townships; individuals aged 30-65 years eligible
- (N = 89,293) recruited 1991-1992
- HBsAg(+) with adequate baseline HBV DNA sample
- (N = 3851)

Hepatitis C Virus (HCV)

- Responsible for 1/3 of HCCs worldwide.
- HCC invariably “late complication”
- 20-30% Chronic HCV → Cirrhosis in 2-3 decades.
- 1-4%/yr Cirrhosis → HCC (up to 8% in Japan).
Hepatocellular Carcinoma: HCV induced carcinogenesis

Jeong SW, Clin Mol Hepatol, 2012

Genotoxicity
Inflammation
Immunity
Avoidance of Apoptosis

Limitless proliferative potential
promoting

promoting

promoting

promoting

promoting

HCV core, NS3, NS5A
HCV Core
HCV Core, NS5A
PPARα
Steatosis

ROS
Cell growth signal
Genomic instability
HCC
TGF-β
Wnt/β-catenin

Apoptosis

PI3K/Akt
HCV Core, NS3, NS5A
HCV polyprotein

Immune response
Chronic Hepatitis
Cirrhosis
Telomere dysfunction
Immune surveillance

HCV Core, E2

HCC

HCV core, NS3, NS5A

Jeong SW, Clin Mol Hepatol, 2012
REVEAL-HCV STUDY: Cumulative Lifetime HCC Incidence

- 101 HCV cases
- Cumulative lifetime HCC incidence 18.5%
- After adjusting for smoking, alcohol, obesity, diabetes, HCC risk increased if
  - Male
  - HCV RNA level
  - Raised ALT
  - G1

Figure 1 Cumulative lifetime risk (30-80 years old) of hepatocellular carcinoma.

Lee et al. WJG 2014
The Natural History of Compensated Cirrhosis due to HCV

HCC was the first to develop complication and the major cause of death.
HCV: A mission far from being accomplished.

Despite the optimism from DAA, long term complications of HCV are on the rise

Screening & Diagnosis of HCC
HCC in ESLD: a recognized challenge.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>23%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>32%</td>
</tr>
<tr>
<td>Ascites</td>
<td>8%</td>
</tr>
<tr>
<td>Jaundice</td>
<td>8%</td>
</tr>
<tr>
<td>Anorexia/weight loss</td>
<td>10%</td>
</tr>
<tr>
<td>Malaise</td>
<td>6%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4%</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>2%</td>
</tr>
</tbody>
</table>

- Actively look for HCC in any case of decompensated liver disease
- Ideal scenario for screening in “high risk populations”
  - How to define “high risk”
  - What diagnostic methods should be used?

Gastroenterology 2002
A study of hepatitis B carriers in China

18,816 randomized to: surveillance with AFP + US biannual vs. no surveillance

Endpoints: pick up rate of HCC, survival benefit.

Adherence to surveillance was 58%

HCC related mortality was reduced by 37% in surveillance arm.

Liver US: 6-monthly
- Sensitivity near 94% (63% in early stage HCC)
- More intense schedules (3 mo.) not beneficial (Trinchet 2011)
- However: shortened recall for high risk patients (ie. suspicious unifocal nodules <1cm): 2-3 monthly.

AFP: not indicated (Qidong Study – no benefit from AFP based screening, Chen 2003)
- Diagnostic test ≠ screening test
- Fluctuating levels, cut-off considerations, 50-80% non-expressors

No specific recommendations for HIV+

EASL/EORTC Practice Guidelines 2012
Dual Supply and Diagnostic Criteria

Mass/Nodule on US

- <1 cm
  - Repeat US at 4 mo
  - Growing/Changing character: Investigate according to size
  - Stable

- 1-2 cm
  - 4-phase CT or dynamic contrast enhanced MRI
    - 1 or 2 positive techniques**: HCC radiological hallmarks**
    - Yes: HCC
    - No: Biopsy

- >2 cm
  - 4-phase CT or dynamic contrast enhanced MRI
    - 1 positive technique: HCC radiological hallmarks**
    - Yes: HCC
    - No: Biopsy

Inconclusive

Pre contrast

Arterial Phase

Delayed Phase
Linking staging, prognosis and treatment.

**Prognostic Domains:**
- At least 7 staging systems
- Limited role for TNM

- **Radiologic Staging**
  - Max tumor diameter
  - N nodules
  - PVT / N+ M+

- **Liver function**
  - Child Pugh Class
  - MELD
  - Portal HTN

- **Performance Status**

- **Tumour Markers:**
  - AFP >400

**Woman Holding a Balance, Johannes Vermeer (1664)**
The Barcelona Clinic Liver Cancer Staging System

BCLC

Prognosis
Treatment Allocation

HCC

Stage 0
PST 0, Child-Pugh A

Stage A-C
PST 0-2, Child-Pugh A-B

Stage D
PST >2, Child-Pugh C*

Very early stage (0)
Single <2 cm, Carcinoma in situ

Early stage (A)
Single or 3 nodules ≤3 cm, PS 0

Intermediate stage (B)
Multinodular, PS 0

Advanced stage (C)
Portal invasion, N1, M1, PS 1-2

Terminal stage (D)

Portal pressure/bilirubin

Increased

Associated diseases

No

Yes

Normal

Liver transplantation (CLT/LDLT)

RF/PEI

TACE

Sorafenib

Best supportive care

Resection

Curative treatment (30-40%)
Median OS >60 mo; 5-yr survival: 40-70%

Target: 20%
OS: 20 mo (45-14)

Target: 40%
OS: 11 mo (6-14)

Target: 10%
OS: <3 mo

Llovet 1999
When to hope for a cure?

Liver Resection

- Normal portal pressure, Bili <17
- Portal pressure, Bili <17
- Portal pressure, Bili ≥ 17

Log Rank 0.00001

0 12 24 36 48 60 72 84

Patients with a single tumor ≤ 5 cm
Child A cirrhosis
N=77

Liver Transplantation

- Milan Criteria

N=48 from 268 consecutive referrals 1991-1994
No vascular invasion/distant metastasis

Mazzaferro et al, NEJM 1996

Llovet et al, Hepatology 1999
Intermediate Stage HCC - TACE

- **TACE**: LR therapy, dual ischaemic/cytotoxic effect.
- **Operator-dependent** technique delivered into a largely heterogeneous patient population

A delicate balance:

**Survival Benefit**

BCLC B, PS 0, Child <B7 Compensated cirrhosis

**Adverse Events**

Liver failure

Pre TACE

Post 3x TACE

Level I evidence
2 RCTs, 1 MA
Advanced Stage HCC – Systemic Therapies

- **Indication**: Extrahepatic spread/PVT (BCLC-C) PS 0/1 Expected OS = 6-12 months

- **Paucity** of systemic treatments
  - Chemorefractory disease
  - Early experience with Adriamycin (ORR 10%)

- **Sorafenib**
  - Oral, multi-targeted TKI licensed in 2008
  - Sole approved agent
  - Systematic failure of phase III trials thereafter

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Phase</th>
<th>Sample size</th>
<th>Response rate (%)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxic chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeo et al.50</td>
<td>PIAF vs. adriamycin</td>
<td>3</td>
<td>94/94</td>
<td>20.9 vs. 10.5</td>
<td>8.6 vs. 6.83</td>
</tr>
<tr>
<td>Mok et al.60</td>
<td>Nolatrexed vs. doxorubicin</td>
<td>2</td>
<td>37/17</td>
<td>0</td>
<td>4.9 vs. 3.7</td>
</tr>
<tr>
<td>Posey et al.61</td>
<td>TI38067 vs. adriamycin</td>
<td>2/3</td>
<td>169/170</td>
<td>NA</td>
<td>5.7 vs. 5.6</td>
</tr>
<tr>
<td>Gish et al.62</td>
<td>Nolatrexed vs. doxorubicin</td>
<td>3</td>
<td>444</td>
<td>1.4 vs. 4.0</td>
<td>5.5 vs. 8 (P = 0.0068)</td>
</tr>
<tr>
<td>Patt et al.50</td>
<td>Thalidomide</td>
<td>2</td>
<td>37</td>
<td>6%</td>
<td>6.8</td>
</tr>
<tr>
<td>Pastorelli et al.53</td>
<td>Pegylated doxorubicin + gemcitabine</td>
<td>2</td>
<td>35</td>
<td>23%</td>
<td>8.8</td>
</tr>
</tbody>
</table>
Sorafenib

- Originally developed as Raf-1
- Off-target effects
Sorafenib

Child A, PS 0-2
Discontinuation of Rx upon progression.

OS Median

Europe/USA
(n=602)
10.7 vs 7.9 m

Asia
(n=226)
6.5 vs 4.2 m

TTP Median

Europe/USA
5.5 vs 2.8 m
74%

Asia
2.8 vs 1.4 m
74%

Objective Responses

Europe/USA
< 3% (70% SD)

Asia
< 3%

Llovet, J. M. et al. NEJM 2007 (Europe/USA)
What is the relevance of HCC in people living with HIV?
The contribution of HIV to Hepatocarcinogenesis

Mechanistic Effects
The contribution of HIV to Hepatocarcinogenesis

Evidence from Epidemiological Studies

Table 2. Hepatocellular Carcinoma Standardized IRRs Comparing HIV-Infected Patients With HIV-Negative Controls From Two Multivariate Poisson Regression Models (n = 42,037)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1.68</td>
<td>1.02 to 2.77</td>
</tr>
<tr>
<td>HCV</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Alcohol abuse/dependence</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age</td>
<td>1.05</td>
<td>1.03 to 1.07</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>2.06</td>
<td>1.05 to 4.06</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4.88</td>
<td>2.20 to 10.81</td>
</tr>
<tr>
<td>Unknown/other</td>
<td>1.33</td>
<td>0.58 to 3.00</td>
</tr>
</tbody>
</table>

NOTE: Boldfacing indicates significance at the P < .05 level. White race is baseline. Abbreviations: IRR, incidence rate ratio; HCV, hepatitis C virus.

Cirrhosis and Hepatocellular Carcinoma in HIV-Infected Veterans With and Without the Hepatitis C Virus: a Cohort Study, 1992-2001


Incidence rate ratios (IRR)

HIV+/HIV-

- HIV+ male veterans (n=14,018)
- HIV controls (n=28,036)
- age-, race-, sex-, and location-matched

Incresed incidence of Cirrhosis/HCC in HCV coinfected ++ post-HAART

HIV not sufficient as causative factor (despite experimental evidence)

Longer survival

? Direct effect of HAART
Evolving Trends in the prevalence of Cirrhosis and HCC

Veteran Affairs Healthcare DB
24,000 patients/year receiving HIV care
1996-2009

**Prevalence (1996-2009)**

- **HCV co-infected**
  - Cirrhosis: 3.5% to 13.2%
  - 3.7x

- **HCV infection**
  - 5.82 (5.0-6.7)

- **HBV infection**
  - 2.40 (2.0-2.9)

- **Age**
  - 1.03 (1.02-1.04)

- **Hispanic ethnicity**
  - 1.76 (1.4-2.2)

- **Diabetes**
  - 1.79 (1.6-2.1)

- **Alcohol abuse**
  - 1.78 (1.5-2.1)

- **Black ethnicity**
  - 0.56 (0.48-0.64)

- **HCV eradication**
  - 0.61 (0.4-0.9)

---

**Adjusted OR 95% CI**

- **HCV infection**
  - 10.0 (6.1-16.4)

- **HBV infection**
  - 2.82 (1.7-4.7)

- **Age**
  - 1.05 (1.03-1.08)

- **Low CD4 count**
  - 2.36 (1.3-4.2)
The burden of HCC in HIV+ patients mortality

Rosenthal E., HIV Medicine 2015

- **Mortavic Study**: multicenter, prospective, cross-sectional study.
- Prospectively recorded deaths, survey every 5 years 1995-2010.
- 24 centres (France), 26,000 patients, 230 deaths, 30 liver-related.

Steady increase in LRM
Liver related mortality

<table>
<thead>
<tr>
<th>Year of the survey</th>
<th>1995</th>
<th>1997</th>
<th>2001</th>
<th>2003</th>
<th>2005</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of deaths from liver disease</td>
<td>21</td>
<td>36</td>
<td>38</td>
<td>27</td>
<td>48</td>
<td>30</td>
</tr>
<tr>
<td>Total number of HIV-infected patients in the survey</td>
<td>17,000</td>
<td>26,000</td>
<td>25,000</td>
<td>21,000</td>
<td>24,000</td>
<td>26,000</td>
</tr>
<tr>
<td>Male gender [n (%)]</td>
<td>15 (71)</td>
<td>30 (83)</td>
<td>30 (79)</td>
<td>22 (81)</td>
<td>41 (85)</td>
<td>23 (77)</td>
</tr>
<tr>
<td>Age (years) [median (IQR)]</td>
<td>40 (38–46)</td>
<td>39 (36–45)</td>
<td>42 (37–46)</td>
<td>42 (40–43)</td>
<td>45 (43–50)</td>
<td>48 (43–54)</td>
</tr>
<tr>
<td>Injecting drug use transmission group [n (%)]</td>
<td>6 (29)</td>
<td>14 (39)</td>
<td>29 (76)</td>
<td>26 (100)*</td>
<td>25 (53)*</td>
<td>20 (67)</td>
</tr>
<tr>
<td>Alcohol consumption &gt; 30 g/day [n (%)]</td>
<td>6 (29)</td>
<td>16 (44)</td>
<td>19 (50)</td>
<td>16 (59)</td>
<td>21 (48)*</td>
<td>11 (41)</td>
</tr>
<tr>
<td>HBsAg positive [n (%)]</td>
<td>8 (38)</td>
<td>15 (42)</td>
<td>8 (21)</td>
<td>2 (7)</td>
<td>13 (27)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>HCC [n (%)]</td>
<td>1 (5)</td>
<td>4 (11)</td>
<td>9 (24)</td>
<td>4 (15)</td>
<td>12 (25)</td>
<td>12 (41)*</td>
</tr>
<tr>
<td>Previous HCV treatment [n (%)]</td>
<td>4 (19)</td>
<td>3 (8)</td>
<td>10 (26)</td>
<td>12 (44)</td>
<td>17 (38)*</td>
<td>13 (43)</td>
</tr>
<tr>
<td>Latest CD4 cell count (cells/μL) [median (IQR)]</td>
<td>113 (30–250)</td>
<td>131 (53–306)</td>
<td>158 (80–297)</td>
<td>132 (78–255)</td>
<td>237 (116–327)</td>
<td>349 (182–500)</td>
</tr>
<tr>
<td>cART [n (%)]</td>
<td>0</td>
<td>15 (42)</td>
<td>28 (74)</td>
<td>23 (85)</td>
<td>43 (90)</td>
<td>30 (100)</td>
</tr>
</tbody>
</table>

- **HCC** – leading and increasing cause of LRM in HIV+
  Despite
    - cART (100% in 2010)
    - HIV control
    - HCV therapy

Rosenthal E., HIV Medicine 2015
Does HIV+ influence the natural history of HCC?
The natural history of HIV+ HCC

Prognostic factors of survival of hepatocellular carcinoma in HIV/hepatitis C virus-coinfected patients.

- Mostly cross-sectional, case-control retrospective studies
- HIV/HCV coinfection
- Single-center experience

Do the epidemiology, physiological mechanisms and characteristics of hepatocellular carcinoma in HIV-infected patients justify specific screening policies? Gelu-Simeon, AIDS. 2014.
Diagnosis and Outcome of HIV+ HCC

- Large retrospective, multi-centre case control study
- HIV+ HCC (n=62), HIV- HCC (n=226), North America

Features of HIV+ HCC:
- Coinfection almost universal feature (HCV>HBV)
- Younger Age at diagnosis
- Median OS 7 months despite balanced staging
- Active HIV replication – worse OS only in untreated HCC

<table>
<thead>
<tr>
<th>Feature</th>
<th>HIV-positive n = 63</th>
<th>HIV-negative n = 226</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCLC stage (n, %)</td>
<td>n = 62</td>
<td>n = 214</td>
<td>0.47</td>
</tr>
<tr>
<td>A</td>
<td>16 (25.8%)</td>
<td>44 (20.6%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>15 (24.2%)</td>
<td>45 (21.0%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>24 (38.7%)</td>
<td>86 (40.2%)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>7 (11.3%)</td>
<td>39 (18.2%)</td>
<td></td>
</tr>
<tr>
<td>UNOS TNM stage, n (%)</td>
<td>n = 48</td>
<td>n = 169</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (2.1%)</td>
<td>2 (1.2%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12 (25.0%)</td>
<td>47 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8 (16.7%)</td>
<td>28 (16.6%)</td>
<td>0.98</td>
</tr>
<tr>
<td>4a</td>
<td>9 (18.8%)</td>
<td>34 (20.1%)</td>
<td></td>
</tr>
<tr>
<td>4b</td>
<td>18 (37.5%)</td>
<td>58 (34.3%)</td>
<td></td>
</tr>
<tr>
<td>Okuda stage, n (%)</td>
<td>n = 63</td>
<td>n = 226</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>17 (27.0%)</td>
<td>53 (23.5%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>41 (65.1%)</td>
<td>143 (63.3%)</td>
<td>0.49</td>
</tr>
<tr>
<td>III</td>
<td>5 (7.9%)</td>
<td>30 (13.3%)</td>
<td></td>
</tr>
<tr>
<td>JIS score, mean ± SD</td>
<td>2.59 (±1.3), n = 37</td>
<td>2.36 (±1.3), n = 133</td>
<td>0.90</td>
</tr>
<tr>
<td>CLIP score, mean ± SD</td>
<td>2.10 (±1.3), n = 63</td>
<td>2.14 (±1.5), n = 226</td>
<td>0.84</td>
</tr>
<tr>
<td>BCLC advanced stages (C and D)</td>
<td>31 (50.0%)</td>
<td>125 (58.4%)</td>
<td>0.24</td>
</tr>
<tr>
<td>UNOS TNM advanced stages (4a and 4b)</td>
<td>27 (56.3%)</td>
<td>92 (54.4%)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; UNOS TNM, United Network of Organ Sharing-modified Tumor Node Metastasis; JIS, Japan Integrated Staging; CLIP, Cancer of the Liver Italian Program; SD, standard deviation.
HCC is a highly lethal malignancy with multiple areas of unmet medical needs.

HCC is a **leading** and **increasing** cause of morbidity and mortality in HIV+, especially in the context of co-infection.

Prevention is key to optimize outcomes and reduce LRM.

No specific recommendation for enhanced screening for HCC in HIV+.

BCLC algorithm is key for prognosis/treatment allocation.

HIV status should not be a barrier in curative & palliative interventions.

Conclusions
THANK YOU!

Dr. David J Pinato
david.pinato@imperial.ac.uk