HIV and Liver Transplantation: challenges and opportunities

HIVPA Brighton June 2009

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Key messages

- Identifying patients early
- Causes of liver disease in HIV
- Hepato-cellular carcinoma
- Liver transplantation in HIV
- Multi-disciplinary approach
HBV, HCV, HDV, HAV, Ethanol, Opportunistic infections, Steatosis, Drugs i.e. NRTI, NNRTI, PI.
Viral hepatitis and HIV

- ESLD now leading cause of mortality and morbidity in HIV+ patients\(^1\)

- HBV co-infection: 4-17\%\(^2\)
  - HCV co-infection: 5-95\%\(^2\)

- 1 in 6 ESLD secondary to HIV+/HCV will require assessment for LT\(^3\)

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\(^1\) Kemmer et al 2008, Nat Clin Prac Gastro; 5(8); 426-7
\(^2\) Samuel et al 2008, Hepatology; 48; 697-707
\(^3\) Gonzalez-Garcia et al, 2005, Enferm Infecc Microbiol Clin;23(6):340-8
HIV/HBV Coinfection

Liver-related Mortality Rate (per 1000 person-years)

- HIV-/HBsAg-
- HIV+
- HBsAg
- HIV+/HBsAg+

Increase in new cases of acute HCV infections

- Test for trend p-value using Poisson regression p<0.001
- Error bars = 95% CI

Browne RE, et al. 2nd IAS 2003; Abstract 972
HIV/HCV co-infection

Outcome of cirrhosis after 1st decompensation
HCV mono-infected vs HIV(+)/HCV(+)

HAART induced hepatotoxicity

- Abnormal LFTs on HAART not uncommon
- HAART induced hepatotoxicity 8.5-23% \(^1\)
- Predictors of hepatotoxicity:
  - abnormal LFTs + Didanosine
  - ↑ Cr (> 1.5 ULN) and ↓ platetlet (<75)

\(^1\) Servoss JC et al, J Acq Imm Def Synd, 2006
ESLD and HIV

• More rapid progression of fibrosis 1, 2, 3
• Complications appear clinically similar
• More rapid decompensation 4, 5, 6, 7
• Survival reduced after 1st decompensation 4, 5
• Limits of MELD and Child-Pugh in predicting survival compared with non-HIV ESLD 5

3. Puoti, M, Bonacini, M et al. Liver fibrosis progression is related to CD4 cell depletion in patients coinfected with Hepatitis C Virus and human immunodeficiency virus Journal of Infectious Diseases 2001; 183:134-7
Liver fibrosis

  - ↑BMI
  - HCV RNA
  - ↑BMIs
  - Didanosine

- Pineda et al, CROI 2009.
  - Older age
  - Etoh > 50g/d
  - CD4 <200
  - ↑ length HCV Infx
NUMBER OF CADAVERIC DONORS AND TRANSPLANTS IN THE UK, 1993 - 2002 AND PATIENTS ON THE ACTIVE AND SUSPENDED WAITING LISTS AT 31 DECEMBER
MELD: Model for End Stage Liver Disease

Based on logistic regression multivariate analysis of predictors of 90 day mortality in cirrhotic patients undergoing TIPS. Best fit given by:

\[ 9.6 \ln (Cr) + 11.2 \ln (INR) + 3.8 \ln (Bili) + 6.4 \]

Range:
- 6 – 10 = mild, well compensated
- 11 - 18 = moderate
- 19 – 24 = advanced
- 25 – 29 = critical
- 29+ = terminal

MELD calculator: www.unos.org/resources
UKELD

$$[(5.39 \times \ln(\text{INR})) + (1.485 \times \ln(\text{creatinine})) + (3.13 \times \ln(\text{Bil})) - (81.565 \times \ln(\text{Na}))] + 435$$

- [www.uktransplant.nhs.uk](http://www.uktransplant.nhs.uk)
- UKELD > 49 – minimal listing
- Superior predictor of mortality than MELD on waiting list\(^1\)

Barber et al, AASLD, Abstract 611, Boston 2007
Key pre-OLT selection and evaluation issues

Pre-OLT evaluation
HIV+ : Survivors vs Non-Survivors

Model for End Stage Liver Disease score predicts risk of mortality before liver transplantation in HIV-infected individuals

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretransplantation</td>
<td>MELD ≥ 25</td>
</tr>
<tr>
<td></td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>P Value</td>
</tr>
<tr>
<td>MELD ≥ 25</td>
<td>15</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Detectable HIV-1 RNA</td>
<td>3.2</td>
<td>.02</td>
</tr>
<tr>
<td>CD4+ cell count &lt; 200</td>
<td>1.5</td>
<td>.37</td>
</tr>
<tr>
<td>cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV coinfection</td>
<td>1.0</td>
<td>.97</td>
</tr>
</tbody>
</table>

Liver Transplantation in HIV in UK

• Standard listing criteria for HIV- patients

• CD4+ ≥ 200 or CD4+ ≥ 100 with PHT
  Undetectable HIV VL
  Absence of an ‘AIDS’ defining illness
Any Cirrhotic should be “considered” for liver transplantation when they develop:

- Evidence of Liver Dysfunction as:
  (Child >7 / MELD > 10)

- First episode of decompensation
  (Ascites, SBP, HRS, GIB, Encephalopathy, HCC)

Refractory or Intractable Ascites
Multiple Variceal Bleeding episodes
Severe Jaundice
Refractory Encephalopathy
Severe Synthetic liver dysfunction
HCC

- 5th most common cancer world wide
- 30,000 cases/year in Europe
- Associated with cirrhosis in 80% cases
- Main risk factors are HBV and HCV
High HBV viral load is associated with increased incidence of HCC

All participants (n=3,653)

Cumulative incidence of HCC

Baseline HBV DNA Level (copies/mL)
- ≥10^6
- 10^5–<10^6
- 10^4–<10^5
- 300–<10^4
- <300 (reference)

p<0.001
p=0.06

Deaths from HCC:

15/110 cases (15%) in 2000

35/138 cases (25%) in 2005

Why increase in HCC cases?

- Success of HAART?
- Increased awareness
- Is HIV virus oncogenic?

- Increase in HIV/HCV?
  - Rx w PEGIFN/RIB modest success
HIV and HCC

- Younger (median age 42)\(^1\)
- Lower CPS\(^2\)
- Multiple and invasive tumours\(^2\)
- HCV co-infection\(^2\)
- Falling CD4 counts\(^2\)

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Liver Transplantation for Hepatocellular Carcinoma

**MILAN CRITERIA 1996**

- Single tumour < 5 cm diameter
- Up to 3 nodules < 3 cm diameter
- No vascular invasion
- No extra hepatic disease

48 patients:
1yr survival 84%
4yr survival 74%

Liver Transplantation for Hepatocellular Carcinoma

**UCSF Criteria 2001**

70 patients

- 1 yr survival: 91.3%
- 5 Year Survival: 72.4%
- Recurrence: 11.4%

50% 1 yr survival outside this criteria

Single tumour < 6.5 cm diameter
No more than 3 nodules largest < 4.5 cm with Total diameter < 8 cm

Yao et al. Hepatology 2001
“Up to Seven”: size of largest tumour (cm) + no. tumours

Mazzaferro et al, Predicting survival after liver transplantation in patients with HCC beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncology, Jan 2009; 10
Size of largest tumour (mm) + no. of lesions

Provides 3 and 5 year survival
Rx for HCC(1)

- LT
- RFA
- TACE
- Surgical resection

Screening for HCC
6/12 USS and AFP
Outcomes of all HIV positive Liver Transplant recipients.

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>n</th>
<th>Patient survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neff, 2003, USA</td>
<td>16</td>
<td>100 80</td>
</tr>
<tr>
<td>Ragni, 2003, USA</td>
<td>23</td>
<td>86.6 80</td>
</tr>
<tr>
<td>Norris, 2004, UK</td>
<td>14</td>
<td>78.6 69.8</td>
</tr>
<tr>
<td>Rafecas, 2004, Spain</td>
<td>4</td>
<td>100 -</td>
</tr>
<tr>
<td>Moreno, 2005, Spain</td>
<td>4</td>
<td>100 -</td>
</tr>
<tr>
<td>Radecke, 2005, Germany</td>
<td>5</td>
<td>60 -</td>
</tr>
<tr>
<td>Schreibman, 2007, USA</td>
<td>15</td>
<td>73.3 -</td>
</tr>
<tr>
<td>Vennarecci, 2007, Italy</td>
<td>12</td>
<td>83.3 58.3</td>
</tr>
<tr>
<td>Mindikogulu, 2008, USA</td>
<td>138</td>
<td>80 70</td>
</tr>
</tbody>
</table>
Liver Transplantation for HIV: Analysis of outcomes suggest HIV+/HCV co-infected patients have prohibitively poor survival at 5 years


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AASLD 2008 Abstract 6, Hepatology; Abstract 6; Vol 48, No. 4 (suppl).
Aims/Methods

- Retrospective analysis of all adult patients undergoing LT at King’s College Hospital between Jan 1995 to May 2008

- Primary aim: survival post LT in HIV+
  Compare outcomes between HIV+/HCV vs HCV
  - Donor age
  - Recipient age
  - MELD score
Results (1)

- **2430** HIV- transplanted Jan 95 – May 08
- **34** HIV+ patients assessed for LT
- **24** HIV+ underwent LT
  (1% total LT activity)
- **302** (13%) transplanted for HCV mono-infection
Results (2)

24 HIV+: 21♂ 3♀

[HIV+/HCV]  
\[n = 11\]

[HIV+/Other]  
\[n = 13\]
Results (3)

[HIV+/HCV]  
- n = 11  
  - 3 x pre-ART  
  - 1 x intolerant ART post LT

[HIV+/Other]  
- n = 13  
  - 2 x cHBV  
  - 3 x HCC/cHBV  
  - 1 x HPS/ALD  
    - 1 x ALD  
    - 2 x SALF  
    - 2 x aHBV  
    - 2 x HAT  
  - HBV DNA (-)  
  - Super Urgent
Results (4)

[HIV+/HCV]
median CD4+ = 265 cells/µL (IQR 314)
6 x detectable HIV VL (3 pre-ART)

[HIV+/Other]
median CD4+ = 259 cells/µL (IQR 148)
4 x detectable HIV VL (fulminant presentation)
Immunosuppression

- **Dual IS:**
  - 23 patients - Steroids and Tacrolimus
  - 1 patient – Azathioprine and Cyclosporine
    (Tacrolimus 5-10 ng/ml, cyclosporine 100-250 ng/ml)

- Steroid withdrawal: median 4 months
### Characteristics of HIV- and HIV+ patients
**Jan 1995 – May 2008**

<table>
<thead>
<tr>
<th></th>
<th>HIV-</th>
<th>HIV+</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2430</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>Men</td>
<td>1363 (56%)</td>
<td>21 (88%)</td>
<td>-</td>
</tr>
<tr>
<td>Recipient age</td>
<td>37.8 +/- 21.7</td>
<td>41.5 +/- 9.4</td>
<td>NS</td>
</tr>
<tr>
<td>Donor age</td>
<td>39.2 +/- 18.2</td>
<td>40.7 +/- 16.7</td>
<td>NS</td>
</tr>
<tr>
<td><strong>MELD</strong></td>
<td><strong>19.1 +/- 9.7</strong></td>
<td><strong>14.3 +/- 8.2</strong></td>
<td>0.02</td>
</tr>
<tr>
<td>Mean Follow up (months)</td>
<td><strong>47.2 +/- 42.9</strong></td>
<td><strong>37.1 +/- 35.4</strong></td>
<td>NS</td>
</tr>
</tbody>
</table>
### Characteristics of HIV+/HCV co-infection and HIV/Other patients

<table>
<thead>
<tr>
<th></th>
<th>HIV+/HCV</th>
<th>HIV+/Other</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>11</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>Men</td>
<td>9 (82%)</td>
<td>12 (92%)</td>
<td>-</td>
</tr>
<tr>
<td>Recipient age</td>
<td>40 +/- 7.4</td>
<td>42.1 +/- 11.2</td>
<td>NS</td>
</tr>
<tr>
<td>Donor age</td>
<td>36.8 +/- 17.48</td>
<td>44 +/- 15.94</td>
<td>NS</td>
</tr>
<tr>
<td>MELD</td>
<td>17 +/- 9.2</td>
<td>10.14 +/- 4.74</td>
<td>0.028</td>
</tr>
<tr>
<td>Mean Follow up (months)</td>
<td>20.7 +/- 21.2</td>
<td>60.5 +/- 32.9</td>
<td>0.002</td>
</tr>
</tbody>
</table>
### Characteristics of HIV+/HCV co-infection and HCV mono-infection patients

<table>
<thead>
<tr>
<th></th>
<th>HIV+/HCV</th>
<th>HCV</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>11</td>
<td>302</td>
<td>-</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>9 (82%)</td>
<td>199 (60%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Recipient age</strong></td>
<td>40 +/- 7.4</td>
<td>52.6 +/- 8.5</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Donor age</strong></td>
<td>36.8 +/- 17.4</td>
<td>45.83 +/- 15.29</td>
<td>NS</td>
</tr>
<tr>
<td><strong>MELD</strong></td>
<td>17 +/- 9.2</td>
<td>14.5 +/- 7.5</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Mean Follow up</strong></td>
<td>20.7 +/- 21.2</td>
<td>38.4 +/- 29</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Comparison of survival probabilities in HIV+/Other, HCV and HIV+/HCV.

Survival Functions

Survival rates at 1 and 5 years:
- HIV+/Other group (100% and 100%)
- HCV group (82% and 64%)
- HIV+/HCV group (64% and 40%)

Logrank P=0.003

Univariate analysis demonstrated that MELD score was significantly associated with survival after LT (p=0.016)
Mortality

HIV+/HCV

- 3 x HCV recurrence/sepsis: pre-ART
  1 cholestatic recurrence of HCV

- 2 x sepsis alone
Key post-OLT management issues

Progression to a fibrosis score ≥F2
HIV(+)/HCV(+) vs HIV(-)/HCV(+)

Future prospects

- Non-invasive markers:
  15% patients unwilling to have liver biopsy.
- Identifying Prognostic factors
- Post LT Rx of HCV
- Role of IS
Conclusion

- Multi-factorial causes of liver disease
- Increased rates of HCC
- MDT approach: LT is a real option for HIV+ patients
Question 1

Accelerated fibrosis is associated with (T/F):

A) Raised BMI
B) Alcohol use
C) HCV co-infection
D) Younger age
Question 2

Which statement is correct?

A) HIV/HCV co-infected patients have similar survival rates as HCV mono-infected patients

B) The number of new cases of acute HCV infections is static in HIV patients

C) Likelihood of vertical transmission of HCV in HIV+ patients is increased

D) CVS disease is the leading cause of mortality and morbidity after AIDS
Question 3

Which statement is correct?

A) MELD score incorporates Cr, INR and Albumin

B) UKELD score incorporates Na, Cr, Bili, INR

C) All HIV positive patients need to have an undetectable HIV VL when undergoing LT

D) HBV VL does not directly correlate with the risk of HCC
Question 4

Best answer:

A) A multi-disciplinary approach is essential in managing HIV positive patients with ESLD

B) HIV positive patients with ESLD should be identified early

C) HIV positive patients not co-infected with HCV have excellent survival outcomes post LT

D) More aggressive recurrence of HCV post LT is observed in HIV positive patients

E) ALL OF THE ABOVE
Thank you
HCV RNA

STOP

HCV RNA <2 log₁₀ drop

HCV RNA >2 log₁₀ drop

RVR

YES

Detectable HCV RNA?

24 weeks of treatment

48 weeks of treatment

TW 0

TW 4

TW 12

TW 24

TW 48

Geno 2,3
HCV RNA

STOP

HCV RNA <2 log_{10} drop

HCV RNA >2 log_{10} drop

RVR

YES

Detectable HCV RNA?

48 weeks of treatment

72 weeks of treatment

Geno 1,4

TW 0

TW 4

TW 12

TW 24

TW 48

TW 72