Reopening the Liver Transplant and HIV Debate:
The Pro’s

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Liver Transplantation in HIV-HCV Co-Infected Patients
Can we do better?

- US Trial demonstrates comparable patient and graft survival following kidney tx in HIV infected recipients
- US Trial demonstrates comparable patient and graft survival following liver tx in HIV HBV coinfectected recipients
- US Trial demonstrates poorer patient and graft outcomes HIV HCV coinfectected liver recipients
US Multicenter NIH Trial HIV TR

- 275 transplant recipients
  - 125 LT
  - 150 RT
- Enrolled 2000–03
- Median follow-up >4 yrs

Selection Criteria
- Standard transplant criteria
- CD4 ≥200 for KT, ≥100 for LT candidates
- Undetectable HIV RNA or expected control post-transplant for candidates unable to tolerate ARVs
- Treated OIs except visceral KS, PML, chronic cryptosporidiosis
## Kidney Transplant Outcomes

### Patient Survival

<table>
<thead>
<tr>
<th></th>
<th>1 Year</th>
<th>3 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIVTR</td>
<td>95.3</td>
<td>90.6</td>
</tr>
<tr>
<td></td>
<td>(90.4,97.7)</td>
<td>(83.8,94.7)</td>
</tr>
<tr>
<td>SRTR ≥65 yr</td>
<td>91.8</td>
<td>79.5</td>
</tr>
<tr>
<td></td>
<td>(91.1,92.4)</td>
<td>(78.0,80.9)</td>
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</table>

### Graft Survival

<table>
<thead>
<tr>
<th></th>
<th>1 Year</th>
<th>3 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIVTR</td>
<td>90.7</td>
<td>75.5</td>
</tr>
<tr>
<td></td>
<td>(84.7,94.4)</td>
<td>(66.8,82.2)</td>
</tr>
<tr>
<td>SRTR ≥65 yr</td>
<td>88.3</td>
<td>74.4</td>
</tr>
<tr>
<td></td>
<td>(87.5,89.1)</td>
<td>(72.9,75.9)</td>
</tr>
</tbody>
</table>
Time to First Rejection

![Graph showing time to first rejection for Kidney (HTR) and Kidney (UNOS) with data points and annotations]

- Kidney (HTR)
- Kidney (UNOS)

N=53  N=31  N=13
Patient Survival in HBV-HIV Transplant Recipients

*No deaths due to recurrent HBV or HIV-related complications

P=0.09

HBV 100%
HBV-HIV 86%

Median follow-up 3.5 years

Coffin C, et al. AJT; 10:1268 - 1275; 2010
HBV Recurrence & Viremia

• No recurrent HBsAg
• No histologic recurrence
• 53% detectable HBV DNA post-transplant
  – Mean HBV DNA 108 IU/ml (range 20-790 IU/ml)
  – More frequent in patients with detectable HBV DNA pre-transplant and those with prior treated acute rejection
• No *persistently* detectable HBV DNA
HBV Conclusions
NO DEBATE !
IT WORKS

- Short-term patient and graft survival in HBV/HIV co-infected recipients similar to HBV mono-infected
- Recurrent HBV prevented with HBIG and antivirals
  - Low level viremia in ~ half supports the long-term use of combined HBIG plus antivirals
  - HBIG may be particularly important to prevent virologic breakthrough due to antiviral drug resistance
Concerns in HCV-HIV Coinfected LT Recipients

- Prior studies in HCV-HIV coinfected transplant recipients indicate:
  - Higher rates of wait-list mortality
  - Worse post-LT survival
  - More severe recurrent HCV disease
  - Poor response to HCV treatment

*Castells L, Transplantation 2007;83:354–358.*
Patient Survival
HCV-HIV (n=89) vs HCV Transplant (n=235) Recipients

HCV Monoinfected:  N=183  N=116  N=70
HCV-HIV Coinfected:  N=60  N=43  N=26

p<0.001
Graft Survival
HCV-HIV vs HCV Transplant Recipients

HCV Monoinfected: N=174
HCV-HIV Coinfected: N=57

HCV Monoinfected: N=109
HCV-HIV Coinfected: N=39

HCV Monoinfected: N=67
HCV-HIV Coinfected: N=24

p<0.001
Causes of Graft Loss

HCV-HIV Coinfected*

- Multi-Organ Failure/ Sepsis/ Septicemia: 38%
- Other/ Unknown: 10%
- Rejection: 14%
- Post-surgical Complications: 17%
- Recurrent HCV: 21%

HCV Monoinfected

- Multi-Organ Failure/ Sepsis/ Septicemia: 15%
- Other/ Unknown: 21%
- Malignancy: 13%
- Rejection: 6%
- Post-surgical Complications: 19%
- Recurrent HCV: 26%

* No deaths/graft losses due to HIV-associated OIs or ONs

Terrault N, Liver Transplant 2012
## Predictors of Graft Survival in HCV-HIV Coinfected Multivariate Analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI at Enrollment &lt; 21</td>
<td>3.1 (1.3, 7.7)</td>
<td>0.01</td>
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<tr>
<td>SLKT</td>
<td>3.8 (1.6, 9.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Anti-HCV Positive Donor</td>
<td>2.5 (1.1, 5.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Donor Age (by decade)</td>
<td>1.3 (1.0, 1.6)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* As time-varying covariate
Graft Survival
HCV-HIV vs HCV vs SRTR ≥65 Yrs

P=0.79
Cumulative Rate of Severe Recurrent HCV

Median follow-up (IQR):
0.6 yr (0.1, 1.5) HIV-HCV, 62% ≥ 2 Bx
1.0 yrs (0.2, 2.2) HCV, 64% ≥ 2 Bx

No difference in graft loss due to recurrent HCV between groups
## Predictors of Severe HCV Disease

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>1.7 (0.9, 3.1)</td>
<td>0.11</td>
<td>1.4 (0.7, 2.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Recipient age</td>
<td>0.9 (0.9, 1.0)</td>
<td>0.02</td>
<td>0.9 (0.8, 1.0)</td>
<td>0.046</td>
</tr>
<tr>
<td>Recipient female sex</td>
<td>2.3 (1.0, 5.0)</td>
<td>0.04</td>
<td>3.5 (1.4, 8.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Treated AR**</td>
<td>3.5 (1.5, 8.4)</td>
<td>0.005</td>
<td>3.3 (1.3, 8.7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

HIV coinfection is not independent predictor of severe HCV disease

*Adjusted for clustering
**As time-varying covariate
Time to First Treated Acute Rejection

50% of AR episodes occurred ≤21 days of LT
Acute Rejection

- Rates of acute rejection are 2-fold higher in HCV-HIV LT recipients than in HCV LT recipients (35% vs 18%)
- Treated acute rejection is independent predictor of:
  - Graft loss overall
  - Graft loss in HCV-HIV coinfected patients
  - Severe HCV recurrence
Possible Reasons for High Rates of Acute Rejection in Coinfected Patients

- Overly cautious use of IMS in early post-LT period
- Difficulties in achieving adequate immunosuppression due to drug interactions
- A higher rate of misdiagnosis of acute rejection
- Reflects dysregulated immune responses in coinfected patients
Support for Protease Inhibitor Free Regimens for the HIV infected transplant recipient

- Tricot et al. Safety and efficacy of Raltegravir in HIV-infected transplant recipients cotreated with immunosuppressive drugs. AJT 2009
- Moreno et al. Raltegravir-based highly active antiretroviral therapy has beneficial effects on the renal function of HIV-infected patients after solid organ transplantation. Liver Transplantation 2010
Efficacy (mITT) of Peg-IFN/RBV in Coinfected LT Recipients

* Excludes 2 patients still on treatment
Clearance of HCV
UCSF Experience – 19/30 doing well

3 spontaneous clearers

9 treated with interferon/ribavirin

7 have not required treatment

4 have cleared virus and have sustained response

2 have cleared virus and still on treatment

3 non-responders
SPONTANEOUS HCV CLEARER: 52001

LT 11/03 for HCV-related ESLD, hepatocellular cancer

- Cholestasis, recurrent HCV on liver bx, total bilirubin 13 at 3 months.
- Persistent HCV, elevated LFTs at 6 months.
- Spontaneous resolution of HCV infection thereafter.
- (PCR negative at 52 weeks, and 10 years).
Increasing breadth of responses to defined HCV specific CTL epitopes associated with viral clearance

3 MO

6 MO

12 MO

SFC/10^6 input PBMC
Summary – How can we improve results in HIV HCV coinfection recipients?

- **PATIENT SELECTION** –
  - no combined liver – kidney transplants
  - no HCV positive donors
  - BMI >20

- **BETTER IMMUNOSUPPRESSION**
  - better drug exposure
  - avoid PI based regimens to minimize DDI
Summary – How can we improve results in HIV HCV coinfected recipients?

- TREATMENT FOR HCV –
  - Necessity for more tolerable regimens
  - Interferon free regimens imperative secondary to immunostimulatory impact of interferon
  - Challenging group of transplant recipients not included in rapidly evolving protocols and clinical trials
HIV and Liver Transplantation
What Have We Learned?

• Transplantation is an option for HIV-infected patients with end-stage liver disease
• There has been no significant HIV clinical, virologic nor immunologic disease progression in the immunosuppressed patients.
• There has been no evidence of impaired graft function due to HIV
• Rejection rates unexpectedly high
• Can improve results in HIV HCV coinfected recipients with improved donor/patient selection, better immunosuppression, and tolerable HCV treatment regimens
“Keep calm......Carry on”

Winston Churchill