Management of Chronic HCV Cirrhosis: Pre and Post-Liver Transplantation

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Director of Hepatology
Director, Viral Hepatitis Center
Transplantation
University of Pennsylvania
Hepatitis C-Related Cirrhosis Is Projected to Peak Over the Next 10 Years

- 25% of patients with HCV currently have cirrhosis
- 37% of patients with HCV are projected to develop cirrhosis by 2020, peaking at 1 million

Davis GL, et al. *Gastroenterology* 2010

1 million deaths related to cirrhosis or liver cancer
Indications for Liver Transplantation 2007 (UNOS Registry)

- HCV (+/-HCC) 40%
- ETOH 13%
- cryptogenic 10%
- NASH 6%
- other 3%
- fulminant metab 3%
- malign 3%
- PBC 5%
- PSC 5%
- CAAIH 5%
- HBV 4%

Source: SRTR ustransplant.org
Kaplan-Meier Estimates of Patient Survival According to Hepatitis C Status

Log-rank $X^2 = 19.7$

$P < 0.0001$

Forman LM et al Gastroenterology 2002;122:889-896
Kaplan-Meier Estimates of Allograft Survival According to Hepatitis C Status

Log-rank $X^2 = 52.85$

$P < 0.0001$

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>HCV+</th>
<th>HCV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (years)</td>
<td>4805</td>
<td>6986</td>
</tr>
<tr>
<td>1</td>
<td>3040</td>
<td>4755</td>
</tr>
<tr>
<td>2</td>
<td>1922</td>
<td>3300</td>
</tr>
<tr>
<td>3</td>
<td>1111</td>
<td>2080</td>
</tr>
<tr>
<td>4</td>
<td>502</td>
<td>984</td>
</tr>
<tr>
<td>5</td>
<td>97</td>
<td>211</td>
</tr>
</tbody>
</table>

Forman LM et al Gastroenterology 2002;122:889-896
Milestones in Therapy of CHC
Average SVR Rates from Clinical Trials

1991
Standard Interferon

1998
Ribavirin

2001
Peginterferon

2011
Direct Acting Antivirals

SVR (%)

6%
IFN 6m

16%
IFN 12m

34%
IFN/RBV 6m

42%
IFN/RBV 12m

39%
Peg-IFN 12m

55%
Peg-IFN/RBV 12m

70+% Pega-IFN/RBV/DAA

Adapted from US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring MD.
Issues with Current Therapy

• Response rate – reasonable
• Tolerability of Peg-IFN + RBV, and now a Protease Inhibitor
• Challenging populations
  – Cirrhosis
  – Co-infections
  – Transplanted populations
Compensated Cirrhosis
Classification of Chronic Liver Disease

Histological

F1-F3

Clinical

Non-cirrhotic

Compensated

Compensated

Decompensated

Symptoms

None

None (no varices)

None (varices present)

Ascites, VH, encephalopathy

Sub-stage

- Stage 1

Stage 2

Stages 3 and 4

Hemodynamic

(HVPG, mmHg)

>6 Stage 1

>10

>12

Biological

Fibrogenesis and Angiogenesis

Scar and X-linking

Thick (acellular) scar and nodules

Insoluble scar

Garcia Tsao G et al Hepatology 51:145-9;2010
Sustained Virologic Response (SVR) following Pegylated Interferon alfa-2a and RBV in Bridging Fibrosis/Cirrhosis

- No bridging fibrosis or cirrhosis
- Bridging fibrosis (excluding cirrhosis)
- Cirrhosis

SVR %

<table>
<thead>
<tr>
<th>Condition</th>
<th>Genotype 1 or 4 (48 weeks treatment)</th>
<th>Genotype 2 or 3 (24 weeks treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No bridging fibrosis or cirrhosis</td>
<td>60 % (N=242)</td>
<td>76 % (N=629)</td>
</tr>
<tr>
<td>Bridging fibrosis (excluding cirrhosis)</td>
<td>51 % (N=63)</td>
<td>61 % (N=119)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>33 % (N=36)</td>
<td>57 % (N=70)</td>
</tr>
</tbody>
</table>

Bruno S et al Hepatology 2010;51:388-97
Telaprevir (Treatment Naïve study; ADVANCE): Rates of Sustained Virologic Response (SVR) by Fibrosis Stage

PR(48) = PEG-IFN with ribavirin (for 48 weeks).

Boceprevir (Treatment Naïve): SVR and Relapse Rate by Fibrosis Score

Bruno S, et al. 46th EASL; Berlin, Germany; March 30-April 3, 2011; Abst. 7.
Clinical Trials vs. Real World

Clinical trials (including cirrhotics)

- **ADVANCE**: Telaprevir 9%, Boceprevir 12%, PegIFN + RBV 7%
- **SPRINT-2**: Telaprevir 12%, Boceprevir 9%, PegIFN + RBV 12%
- **REALIZE**: Telaprevir 12%, Boceprevir 5%, PegIFN + RBV 5%
- **RESPOND-2**: Telaprevir 12%, Boceprevir 5%, PegIFN + RBV 5%

Real world (cirrhotics only)

- **FRENCH REAL WORLD**
  - Telaprevir 49%
  - Boceprevir 38%

Patients with Serious AEs (%)

- ADVANCE: Telaprevir 9%, Boceprevir 7%, PegIFN + RBV 12%
- SPRINT-2: Telaprevir 12%, Boceprevir 9%, PegIFN + RBV 12%
- REALIZE: Telaprevir 12%, Boceprevir 5%, PegIFN + RBV 5%
- RESPOND-2: Telaprevir 12%, Boceprevir 5%, PegIFN + RBV 5%

- FRENCH REAL WORLD: Telaprevir 49%, Boceprevir 38%

**Note**: Telaprevir and Boceprevir are DDI and FIXA inhibitors, respectively.
HCV Therapy with Protease Inhibitors: University of Pennsylvania Experience

Bahirwani R et al 2012
HCV Therapy with Protease Inhibitors: Treatment Response

Telaprevir

- RVR: 55%
- eRVR: 47%

Boceprevir

- < 1 log drop HCV RNA by Week 4: 57%
- Undetectable HCV RNA by Week 8: 28%

Bahirwani R et al 2012
### HCV Therapy with Protease Inhibitors: Anemia

<table>
<thead>
<tr>
<th>Anemia</th>
<th>Ribavirin Dose Reduction, ESA, &amp; Blood Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb &lt; 10 g/dL</td>
<td>100%</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>72%</td>
</tr>
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<td></td>
<td>30%</td>
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*ESA (Erythropoiesis-stimulating agents)*

Bahirwani R et al 2012
Decompensated Cirrhosis
<table>
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<th>Classification of Chronic Liver Disease</th>
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<td><strong>Histological</strong></td>
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<td>F1-F3 (Non-cirrhotic)</td>
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<td>F4 (Cirrhosis)</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>Non-cirrhotic</td>
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<tr>
<td>Compensated</td>
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<tr>
<td>Decompensated</td>
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<tr>
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Garcia Tsao G et al Hepatology 51:145-9;2010
LADR: Effect of Genotype

Virologic Response

Everson GT et al Hepatology 42:255-62;2005
Results With Liver Transplantation (Out of 47 Transplanted Patients)

<table>
<thead>
<tr>
<th>HCV RNA</th>
<th>Posttransplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretransplant</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

Of the three who relapsed -- one was genotype 4, completed a full course, and was transplanted 6 weeks later. Analysis of blood at day of transplant revealed + RNA. Another completed only 6 weeks of Rx prior to urgent LTx for hepatoma. The third patient’s treatment course was interrupted by TACE Rx.

Everson GT et al Hepatology 42:255-62;2005
Prevention of Post-Transplant Recurrence of HCV Infection

<table>
<thead>
<tr>
<th>Study</th>
<th>Total</th>
<th>HCV RNA negative</th>
<th>Post-LTx Negative HCV RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>EOT</td>
<td>SVR</td>
</tr>
<tr>
<td>Everson</td>
<td>124</td>
<td>46%</td>
<td>24%</td>
</tr>
<tr>
<td>Forns</td>
<td>30</td>
<td>30%</td>
<td>NA</td>
</tr>
<tr>
<td>Thomas¹</td>
<td>20</td>
<td>60%</td>
<td>NA</td>
</tr>
<tr>
<td>Crippin</td>
<td>15</td>
<td>33%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Abbreviations: EOT: end of treatment; SVR: sustained virologic response; LTx: liver transplantation. A total of 99 patients underwent liver transplantation, either deceased or living donor, and 22 remained free of HCV infection post-transplant (22%).

¹ Although there were 27 patients reported, only the 20 who received antiviral therapy are shown in this table. Seven were excluded from treatment due to platelet count ≤ 50,000/µl.
Hepatic Decompensation During Antiviral Therapy in HCV Advanced Liver Cirrhosis

- Retrospective cohort study
- 68 cirrhotic treatment-naive pts
- Mean age: 51 years
- MELD: 9.2 ± 2.7
- Child-Pugh: 5.4 ± 0.8
- Genotype 1: 65% SVR 23%
- Genotype non 1: 35%, SVR 34%

Risk of hepatic decompensation (37% on 72 weeks FU)

![Graph showing the risk of hepatic decompensation according to baseline MELD score and platelet count]

- According to baseline MELD score:
  - MELD <10: 22%
  - 10-13: 59%
  - >13: 83%

- According to baseline platelet count:
  - >120,000/µl: 23%
  - <120,000/µl: 51%

Baseline MELD score and platelet count should be considered before HCV antiviral therapy in advanced cirrhosis in order to reduce hepatic decompensation.

Dultz G, AASLD 2011, Abs. 1048.
Triple Therapy in a Patient with HCC and HCV-Prior to Transplant and Post-Transplant Course

TPV: Telaprevir. PegIFN: Peginterferon. RBV: Ribavirin

HCV RNA (log)

ALT (U/L)

Liver Transplantation / HCV Therapy Discontinued

HCV RNA Not Quantifiable or Negative

Week of HCV Therapy

Week After Liver Transplantation
HCV after Liver Transplantation
Pegylated Interferon and RBV in HCV infection after Liver Transplantation: Systematic Review

19 Studies, 611 patients

PEG-IFN alfa 2a and RBV therapy

2 prospective randomized trials

SVR
Untreated controls 0/27 - 0%
Peg-IFN alfa + RBV 25/75 - 33%

9 prospective studies

SVR
Peg-IFN alfa + RBV 101/315 - 32%

17 nonrandomized trials

SVR
Peg-IFN alfa + RBV 64/221 - 29%

8 retrospective studies

Berenguer M. J Hepatol 2008;49:274-87
IL28B Genotype and Response to Antiviral Therapy

P = 0.0095

Donor/Recipient IL28B genotype

Charlton M et al
Efficacy of HCV Therapy: Sustained Virologic Response

Non-transplant

Transplant

IFN 6 months

IFN 12 months

IFN plus RBV

Peg-IFN

Peg-IFN plus RBV

6 %

0 %

0 %

38 %

39 %

19 %

60 %

25 %

35 %*

*Sustained Virologic Response %

* Castells L et al
Adherence and Safety Profile of HCV Therapy in Liver Transplant Recipients

- **Dose reduction (Suboptimal doses):**
  - IFN: 16%
  - IFN plus RBV: 35%
  - Peg-IFN: 45%
  - Peg-IFN plus RBV: 45%

- **Withdrawal:**
  - IFN: 10%
  - IFN plus RBV: 15%
  - Peg-IFN: 15%
  - Peg-IFN plus RBV: 45%

**Timeline:**
- 6 months: IFN, Peg-IFN
- 12 months: IFN plus RBV
Protease Inhibitors in Liver Transplantation
## Clinical Pharmacology and Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP 450</th>
<th>P-glycoprotein</th>
<th>Non-CYP metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Telaprevir</strong></td>
<td>CYP 3A4:</td>
<td>Substrate</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>• Substrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Boceprevir</strong></td>
<td>CYP 3A4/5:</td>
<td>Substrate</td>
<td>AKR</td>
</tr>
<tr>
<td></td>
<td>• Substrate</td>
<td></td>
<td>Substrate</td>
</tr>
<tr>
<td></td>
<td>• Inhibitor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CYP = cytochrome P  
AKR= aldo-ketoreductase  

Protease Inhibitors for Recurrent Hepatitis C Post OLT

<table>
<thead>
<tr>
<th></th>
<th>Boceprevir</th>
<th>Telaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>1.3 fold</td>
<td>4 fold</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>5 fold</td>
<td>35 fold</td>
</tr>
</tbody>
</table>

Fluctuation in CNI levels

- Risk
- Toxicity
- Graft Rejection
Major Caveat

TPV and BOC block CYP 3A4 and P-glycoprotein - CSA, TAC, Sirolimus levels increase
Drug-Drug Interaction in HCV Liver Transplant Recipient

Adverse Events (Treatment)

Anemia (RBV Dose Reduced to 600 mg ESA)

Anemia (ESA)

Hospital Admission/Anemia (Blood Transfusion, RBV Dose Reduced to 200 mg)

Week of Treatment

HCV RNA

Tacrolimus

HCV RNA Undetectable/Negative

PEG/RBV

BOC/PEG/RBV

PEG/RBV

Follow Up

Tacrolimus Dosage

- 2 mg QD
- 0.5 mg QD Every 5 Days
- Suspended
- 0.5 mg QD Every Other Day
- 0.5 mg QD
- Held 1 Day, Altered 0.5 mg OD with 0.5 mg BID
- Held 1 Day, Altered 0.5 mg OD with 0.5 mg BID
- 2 mg BID

*HCV RNA at Week 8 was Detectable but not Quantifiable
**BR**

**Triple Therapy in a Liver Transplant Recipient-Failure and now on Daclatasvir Regimen**

**Graph Description:**
- **HCV RNA (log)**
- **Tac Level (mcg/L)**

**Months of HCV Therapy**

**Legend:**
- HCV RNA Not Quantifiable or Negative
- * HCV RNA at that time period was Detectable but not Quantifiable

**Table:**

<table>
<thead>
<tr>
<th>PEG/RBV</th>
<th>Boceprevir/PEG/RBV</th>
<th>Daclatasvir/PEG/RBV</th>
</tr>
</thead>
</table>

* HCV RNA at that time period was Detectable but not Quantifiable
PI for Severe HCV Recurrence after Liver Transplantation

- 28 G1 patients, 5 transplant centers, severe HCV recurrence
- SOC treatment-failure post LT: 24 G1 patients
- HCV recurrence: Chronic hepatitis ≥F2 (n=20) or cholestatic hepatitis (n=8)
- 16 patients under cyclosporine, 12 patients under tacrolimus

Coilly A, EASL 2012, Abs. 47.
PI for Severe HCV Recurrence after Liver Transplantation: Virological Response

**Week 4**

- TPV (n = 11)
  - RVR+: 56%
  - cRVR+: 36%

- BOC (n = 17)
  - RVR+: 88%
  - cRVR+: 35%

**Week 8**

- TPV (n = 10)
  - VR+: 70%
  - cVR+: 75%

- BOC (n = 16)
  - VR+: 75%
  - cVR+: 56%

RVR: >2 log UI HCV RNA reduction

cRVR: Undetectable HCV RNA

VR: >2 log UI/ml HCV RNA reduction

cVR: undetectable HCV RNA

Coilly A, EASL 2012, Abs. 47.
# PI for Severe HCV Recurrence after Liver Transplantation: French Experience Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Boceprevir (n=17)</th>
<th>Telaprevir (n=11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>1</td>
<td>ns</td>
</tr>
<tr>
<td>Infections</td>
<td>12%</td>
<td>18%</td>
<td>ns</td>
</tr>
<tr>
<td>Myelotoxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia &lt;10 g/dL</td>
<td>71%</td>
<td>55%</td>
<td>ns</td>
</tr>
<tr>
<td>Anemia &lt;8 g/dL</td>
<td>18%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Neutropenia (&lt;1 G/L)</td>
<td>24%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;50 G/L)</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dermatological AE</td>
<td>1</td>
<td>1</td>
<td>ns</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>1</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
<td>0</td>
<td>ns</td>
</tr>
</tbody>
</table>

93% EPO, 14% Blood Transfusion, Mean RBV reduction: 25% (-33-90)

Coilly A, EASL 2012, Abs. 47.
Protease inhibitor Based Therapy in Liver Transplant Recipients-Issues

- **Population at baseline is challenging for HCV therapy**
  - Subset qualify for treatment; renal insufficiency limits dose of ribavirin
  - Tolerability a problem-primarily anemia and neutropenia
  - High viral loads-relative to non-transplant population
  - Cholestatic hepatitis C a unique challenge

- **Protease inhibitor related issues**
  - another layer of adverse events-anemia, skin rash
  - drug-drug interactions-major concerns
Evolving Treatment Landscape of Direct Acting Anti-Viral Agents

**DAA combinations**

**NS5A inhibitor**

**Protease inhibitors**

**Others**

**Nuc-Polymerase inhibitors**

**Preclinical**
- Phase I
  - Phase II
  - Phase III

**Approved**
- Boceprevir (MSD)
- Telaprevir (J&J/Vertex)
- Daclatasvir (BMS)
- Sofosbuvir (Gilead)
- BMS 791325 (nuc/non-nuc BMS)
- R0622 (Roche)
- Medivir (Tibotec)
- GL59393 (GSK)
- ABT333, ABT7072 (ABT)
- VX222 (Vertex)
- IDX375 (Idenix/NVS)
- BI201127 (BI)

**Alisporivir cyclophilins**

**Boceprevir (MSD)**

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**IFN lamda (BMS)**

**Daclatasvir (BMS)**

**GS 5885**

**Non Nuc-Polymerase inhibitors**

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**BI201127 (BI)**

**IFN lamda (BMS)**

**Daclatasvir (BMS)**

**GS 5885**

**Non Nuc-Polymerase inhibitors**

**DAA combinations**

**Protease inhibitors**

**NS5A inhibitor**

**Others**

**Nuc-Polymerase inhibitors**
Treatment Options in the Future for HCV

- NS5B Nucleotide Polymerase Inhibitor ± RBV
- NS5A Inhibitor ± RBV
- Pangenotypic Protease Inhibitor ± RBV
- Interferon ± RBV
- NS5B Non-nucleoside Polymerase Inhibitor ± RBV
- Other

**Issues that dictate treatment**

1. Treatment duration: 12, 24, or 48 weeks
2. Genotype 1b vs 1a
3. Non-genotype 1
4. Cirrhosis
5. Race and ethnicity
6. IL28B status
7. Viral resistance
8. Cost
Treatment Options in the Future for HCV

- NS5A Inhibitor ± RBV
- Pangentotypic Protease Inhibitor ± RBV
- NS5B Non-nucleoside Polymerase Inhibitor ± RBV
- Interferon ± RBV
- Other

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4. Cirrhosis
5. Race and ethnicity
6. IL28B status
7. Viral resistance
8. Cost
Treatment Options in the Future for HCV

Issues that dictate treatment

1. Treatment duration: 12, 24, or 48 weeks
2. Genotype 1b vs 1a
3. Non-genotype 1
4. Cirrhosis
5. Race and ethnicity
6. IL28B status
7. Viral resistance
8. Cost

Platform

NS5B Non-nucleoside Polymerase Inhibitor ± RBV
NS5A Inhibitor ± RBV
Pangenotypic Protease Inhibitor ± RBV
Interferon ± RBV
Other
Upcoming Clinical Trials studying treatment in patients with chronic HCV and cirrhosis

- ClinicalTrials.gov Identifier: NCT1704755
  - Population: Chronic HCV genotype 1 with compensated cirrhosis
    - Regimen: ABT-450/ritonavir/ABT-267, ABT-333 and ribavirin

- ClinicalTrials.gov Identifier: NCT01756079
  - Population: Chronic HCV genotype 1 with compensated cirrhosis and previous non-response to peginterferon/ribavirin treatment
    - Regimen: Boceprevir, PegIFN-2b and ribavirin

- ClinicalTrials.gov Identifier: NCT01500616
  - Population: Chronic HCV genotype 1 and HIV coinfection with severe fibrosis or compensated cirrhosis
    - Regimen: Telaprevir, Peg-IFN-alfa and ribavirin

- ClinicalTrials.gov Identifier: NCT01687257
  - Population: Chronic HCV and portal hypertension and cirrhosis with or without decompensation
    - Regimen: Sofosbuvir and ribavirin

www.clinicaltrials.gov
Upcoming Clinical Trials studying treatment in patients with chronic HCV and cirrhosis

- ClinicalTrials.gov Identifier: NCT01463956
  - Population: Chronic HCV genotype 1 and cirrhosis while awaiting liver transplantation with MELD < 18
  - Regimen: Boceprevir, peginterferon and ribavirin

- ClinicalTrials.gov Identifier: NCT01260350
  - Population: Chronic HCV genotype 1 prior null responders with cirrhosis
  - Regimen: Sofosbuvir, GS-5885 with and without ribavirin

- ClinicalTrials.gov Identifier: NCT01640808
  - Population: Prior HCV-positive HCC completely cured and positive HCV-RNA
  - Regimen: NIK-333 (peretinoin) VS placebo
Upcoming Clinical Trials studying treatment in post liver transplant patients with chronic HCV

- ClinicalTrials.gov Identifier: NCT01687270
  - Population: HCV-related liver transplantation with reinfection
    - Regimen: Sofosbuvir and ribavirin

- ClinicalTrials.gov Identifier: NCT01779518
  - Population: HCV-related liver transplantation with aggressive, recurrent infection (life expectancy < 18 months if HCV left untreated)
    - Regimen: Sofosbuvir and ribavirin with and without peginterferon

- ClinicalTrials.gov Identifier: NCT01782495
  - Population: Genotype 1 HCV-related liver transplantation
    - Regimen: ABT-450/ritonavir/ABT-267, ABT-333 and ribavirin

- ClinicalTrials.gov Identifier: NCT01560468
  - Population: Waitlisted for HCV-related liver disease and receiving a deceased donor liver allograft (Intervention given at time of transplantation)
    - Regimen: HCV entry inhibitor (ITX 5061)

- ClinicalTrials.gov Identifier: NCT01560468
  - Population: Waitlisted for genotype 1 HCV-related liver disease and receiving antiviral therapy up to 16 weeks prior to OLT
    - Regimen: HCV immune globulin (Civacir)
Thank You!