Hepatitis B and Hepatitis C Virus in non-Liver Transplant Recipients

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Financial Disclosures

• **Research Grants**
  Merck, Gilead, Abbvie, Intercept, Bristol Myers Squibb

• **Advisory Boards**
  Merck, Gilead and Bristol Myers Squibb

• **Consultancy Agreements**
  Merck, Gilead Sciences, Intercept and Bristol Myers Squibb
Introduction

Discuss management and role of Antiviral therapy against Hepatitis B and C in non-liver transplant recipients
It is a DNA virus
It belongs to the
Family: **Hepadnaviridae**
Genera: **Orthohepadnaviridae**

**Other members of**
**Orthohepadnaviridae are**
- Woodchuck hepatitis virus
- Ground squirrel hepatitis virus

**GENOTYPE A-H**
A1 & D in INDIA
HBV and Solid Organ Transplant

- HBV can cause liver-related morbidity and mortality in non-liver transplant recipients

- Active HBV occurs
  - Pre-Transplant HBsAg+
  - Transmitted by donor organ
  - Reactivation (post transplant) induced by immunosuppression
### HBV and Solid Organ Transplant

#### Hepatitis B Serology (Donor/Recipient)

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>HBsAb</th>
<th>HBcAb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active HBV</strong></td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Immunity</strong></td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>low level</strong></td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
HBV and Solid Organ Transplant

Donor : HBsAg +

- Organs from HBsAg + donors universally transmits HBV, and has been associated with HBV liver-related morbidity and mortality

- Use of these donor organs remains a relative contraindication

- Occasional HBsAg+ donors have been transplanted into naïve heart and kidney recipients and also into HBsAg+ liver recipients with minimal morbidity

- These organs can be used with the utilization of HBV prophylaxis (Nucleos(t)ide Analogues, Lam/TDF/ENT : +/- HBIG)
**QUESTION:** A donors kidneys, heart, lungs, and liver are offered. The donor is found to have HBsAg(-), HBsAb(+), and HBcAb(+). At your center we would?

a) Transplant the kidneys, heart and lungs into any suitable recipient because the risk of transmission of HBV is very low but if possible select a HBsAb+ recipient

b) Not use any organs from this donor as I never did understand any of that HBV serology

c) Transplant the liver only into HBV immune recipients, a high status HBsAg+ or a HBV non-immune recipient, with NA and HBIG coverage

d) Use all organs from this donor since the risk of HBV transmission in this setting has not been described
HBV and Solid Organ Transplant

Donor : HBcAb +

- Donors with HBcAb(+) status are not uncommon
  - Canada (79/1656) 4.7%
  - US Population 5.4%
  - UNOS 3.8%

- Low HBV endemic areas (US, Canada) : 1-5%
HBV and Solid Organ Transplant

Donor: HBcAb+

- Isolated HBcAb(+) donors:
  - Potentially infectious (low level active infection)
  - Immunity (low Ab titer)

- Is there an organ specific risk?
- Is the recipient HBV status important?
- Is recipient therapy/prophylaxis required?
# HBV and Solid Organ Transplant

## Donor: HBcAb +

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Organ</th>
<th>HBV Infections</th>
<th>Nos. Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krieger</td>
<td>2001</td>
<td>Renal</td>
<td>0</td>
<td>1/26 (3.8%)</td>
</tr>
<tr>
<td>Madayag</td>
<td>1997</td>
<td>Renal</td>
<td>0</td>
<td>0/45</td>
</tr>
<tr>
<td>Satterthwaite</td>
<td>1997</td>
<td>Renal</td>
<td>0</td>
<td>0/38</td>
</tr>
<tr>
<td>Paletta</td>
<td>1996</td>
<td>Heart</td>
<td>0</td>
<td>0/8</td>
</tr>
<tr>
<td>Wachs</td>
<td>1995</td>
<td>Heart</td>
<td>0</td>
<td>0/7</td>
</tr>
<tr>
<td>Radomski</td>
<td>1995</td>
<td>Renal</td>
<td>0</td>
<td>1/42 (2.4%)</td>
</tr>
<tr>
<td>Cirocco</td>
<td>1994</td>
<td>Renal</td>
<td>0</td>
<td>0/10</td>
</tr>
<tr>
<td>Kadian</td>
<td>1994</td>
<td>Renal</td>
<td>0</td>
<td>0/16</td>
</tr>
<tr>
<td>Miller</td>
<td>1993</td>
<td>Heart</td>
<td>0</td>
<td>0/13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heart</td>
<td>0</td>
<td>0/12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal</td>
<td>0</td>
<td>0/19</td>
</tr>
</tbody>
</table>
HBV and Solid Organ Transplant

Donor: HBcAb +

(HBcAb+ donors to Liver Allograft Recipients)

Dodson (Transplantation, 1997): 118 donors

<table>
<thead>
<tr>
<th>Recip. status</th>
<th>%HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>cAb-, sAb+</td>
<td>0%</td>
</tr>
<tr>
<td>cAb+/-, sAb+/-</td>
<td></td>
</tr>
<tr>
<td>cAb-, sAb-</td>
<td>72%</td>
</tr>
<tr>
<td>cAb-, sAb+</td>
<td>0%</td>
</tr>
<tr>
<td>cAb+, sAb-</td>
<td>13%</td>
</tr>
</tbody>
</table>

- No restriction on sAb+ donors
- No need to test donor sAb
**QUESTION:** A donor’s kidneys, heart, lungs, and liver are offered. The donor is found to have HBsAg(-), HBsAb(+), and HBcAb(+). At your center we would?

a) **Transplant the kidneys, heart and lungs into any suitable recipient because the risk of transmission of HBV is very low but if possible select a HBsAb+ recipient**

b) Not use any organs from this donor as I never did understand any of that HBV serology

c) **Transplant the liver only into HBV immune recipients, a high status HBsAg+ or a HBV non-immune recipient, with NA and HBig coverage**

d) Use all organs from this donor since the risk of HBV transmission in this setting has not been described
HBV and Solid Organ Transplant

Recipient: HBsAg +

High risk of HBV reactivation if aviremic +/- rapid progressive liver disease

- Prior to effective HBV therapy --- Death

- Currently nucleos(t)ide analogues are used
  - Lamivudine, Entecavir, Tenofovir (TDF / TAF)

- Regardless of HBV DNA at baseline
HBV and Solid Organ Transplant

Recipient: HBcAb +

- Isolated HBcAb +
  - Reactivation can occur
  - Monitor at regular intervals (serology, DNA)

- HBcAb +, HBsAb +
  - Reactivation (serologically or clinically) can occur secondary to low level viral replication in the liver, even years after loss of HBsAg
  - Prophylactic vs Preemptive therapy with NA
HBV and Solid Organ Transplant

Recipient: Summary

• HBsAg(+) recipient:
  – Initiate LAM/Tenofovir

• HBcAb(+) and HBsAb(-) recipient:
  – Potential for reactivated HBV disease
  – Monitor serology (HBsAg/HBV DNA), treatment with NA

• HBcAb(+) and HBsAb (+) recipients:
  – Low risk of reactivation
## HBV and Solid Organ Transplant

### Summary

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<td>HBsAg</td>
<td>HBCaAb</td>
<td>HBSAb</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+/-</td>
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**Legend:**
- Transplant (A) – consider for transplant – no concerns
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<tbody>
<tr>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+/−</td>
<td>Transplant (C)</td>
</tr>
<tr>
<td>HBsAg</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Transplant (C)</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td></td>
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<td>+/−</td>
</tr>
<tr>
<td>HBcAb</td>
<td>+</td>
<td>+/−</td>
</tr>
<tr>
<td>HBsAb</td>
<td>+</td>
<td>−</td>
</tr>
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</tr>
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<td>+</td>
</tr>
<tr>
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<td>−/−</td>
<td>+</td>
</tr>
<tr>
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<td>+/−</td>
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[Schulich Medicine & Dentistry] [Western]
## HBV and Solid Organ Transplant

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<td>HBsAg+</td>
</tr>
<tr>
<td></td>
<td>HBCAb</td>
<td>HBCAb+</td>
</tr>
<tr>
<td></td>
<td>HBsAb</td>
<td>HBsAb+</td>
</tr>
<tr>
<td>HBsAg+</td>
<td></td>
<td>Transplant (C)</td>
</tr>
<tr>
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<td></td>
<td>Transplant (C)</td>
</tr>
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<td></td>
<td>Transplant (C)</td>
</tr>
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Introduction
HCV and Solid Organ Transplant

- Patients with ESRD/HD
  - Several outcome studies of HCV infected patients on HD

- Cardiac and Lung Transplant Candidates
  - Natural history data is scanty
HCV and Solid Organ Transplant

Pre – Kidney Transplant

Risk of Death on HD with HCV+

Survival (%)

Anti-HCV -

Anti-HCV +

p=0.03

52%

32%

0 1 2 3 4 5 6 7 8

Espinosa M. Nephrol Dial Transplant, 2001
HCV and Solid Organ Transplant

Pre – Kidney Transplant

Risk of Death in HD with HCV

<table>
<thead>
<tr>
<th></th>
<th>HCV +</th>
<th>HCV -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>33%</td>
<td>23%</td>
</tr>
<tr>
<td>(91/276)</td>
<td>(p&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>Deaths with HCC</td>
<td>5.5%</td>
<td>0%</td>
</tr>
<tr>
<td>(p&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from Cirrhosis</td>
<td>8.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>(p&lt;0.01)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HCV positivity **Independent risk factor** for death: \( RR \ 1.57 \ (1.23-2.0, \ p<0.001) \)

**Consistent globally**

HCV and Solid Organ Transplant

Post – Kidney Transplant

- 834 Renal Tx recipients (128 HCV, 216 HBV, 490 matched controls)
- 10 years follow up

<table>
<thead>
<tr>
<th></th>
<th>HCV + (%)</th>
<th>HCV - (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5 yr</strong></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Pt and Graft</td>
<td></td>
<td></td>
</tr>
<tr>
<td>survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>10 yr</strong></td>
<td>65% (p&lt;0.001)</td>
<td>85%</td>
</tr>
<tr>
<td>Pt and Graft</td>
<td>49% (p&lt;0.01)</td>
<td>69%</td>
</tr>
<tr>
<td>survival</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Cirrhosis and Presence of HCV : independent predictors of survival

Mathurin et al, 1999
HCV and Solid Organ Transplant

Post – Kidney Transplant

Mathurin et al, 1999
HCV and Solid Organ Transplant

Heart and Lung

SRTR data 1993-2007: 443 HCV+/20,244 HCV-, F/U 5.6 yrs

<table>
<thead>
<tr>
<th>Adult Heart Recipients</th>
<th>HCV +</th>
<th>HCV -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>40%</td>
<td>31.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p&lt;0.001)</td>
</tr>
</tbody>
</table>
HCV and Solid Organ Transplant

Heart and Lung

Survival of Cardiac Recipients Based on HCV Status

SRTR : Gasink LB et al. JAMA 2006:1843-50
HCV Treatment Evolution

1989

2017

IFN 6m
IFN 12m
IFN/RBV 12m
PEG 12m
PEG/RBV 12m
PEG/RBV/PI 6-12m
DAA 3m
# HCV and Solid Organ Transplant

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mild-moderate CKD (eGFR 30-80 ml/min)</th>
<th>Severe CKD (eGFR &lt;30 ml/min)</th>
<th>ESRD/Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvoni</td>
<td>Standard dosing</td>
<td>Data not available</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Epclusa</td>
<td>Standard dosing</td>
<td>Data not available</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Holkira</td>
<td>Standard dosing</td>
<td>Use with caution</td>
<td>Data not available</td>
</tr>
<tr>
<td>Zepateir</td>
<td>Standard dosing</td>
<td>Standard dosing</td>
<td>Standard Dosing</td>
</tr>
</tbody>
</table>
# HCV and Solid Organ Transplant 2012

<table>
<thead>
<tr>
<th>Candidate</th>
<th>HCV Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>Treat while awaiting Renal transplant (HD)</td>
<td>Rarely Not 2013/14, wait IFN free</td>
</tr>
<tr>
<td>Treat after Renal transplant</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
</tr>
<tr>
<td>Treat while awaiting Heart transplant</td>
<td>NO Not Ideal</td>
</tr>
<tr>
<td>Treat after Heart transplant</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
</tr>
<tr>
<td>Treat will awaiting Lung transplant</td>
<td>Rarely Unknown</td>
</tr>
<tr>
<td>Treat after Lung transplant</td>
<td></td>
</tr>
</tbody>
</table>
## HCV and Solid Organ Transplant 2017

<table>
<thead>
<tr>
<th>Candidate</th>
<th>HCV Therapy</th>
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<tbody>
<tr>
<td><strong>Renal</strong></td>
<td>YES</td>
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<tr>
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<td>YES</td>
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HCV and Solid Organ Transplant 2017

Current Therapies

• Can be used PRE or POST
• Very effective (>95% cure)
• Trivial side effects
• Transplant DDI can be avoided
• Transplant candidates/recipients are NOT special populations for HCV any longer
Trial of Transplantation of HCV-Infected Kidneys into Uninfected Recipients

Serum HCV RNA (log_{10} IU/ml) vs. Days after Transplantation
eradication

treatment

elimination

health

protection

international

intervention

medical
Thank You!
**POLARIS Trials**

<table>
<thead>
<tr>
<th>DAA-Experienced</th>
<th>DAA-Naïve</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POLARIS-1</strong></td>
<td></td>
</tr>
<tr>
<td>N = 415</td>
<td></td>
</tr>
<tr>
<td>NS5A-experienced</td>
<td></td>
</tr>
<tr>
<td>± cirrhosis</td>
<td></td>
</tr>
<tr>
<td>GT</td>
<td></td>
</tr>
<tr>
<td>1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>SOF/VEL/VOX</td>
<td></td>
</tr>
<tr>
<td>12 weeks (n=263)</td>
<td></td>
</tr>
<tr>
<td>Placebo (n=152)</td>
<td></td>
</tr>
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Grazoprevir
Voxilaprevir
Paritaprevir
Velpatasvir
Elbasvir
Ombitasvir

POLARIS-1: SOF/VEL/VOX for 12 Weeks in NS5A Inhibitor-Experienced HCV GT 1–6

*Other included SOF/VEL experienced, EBR/GZR experienced, and other investigational combinations and/or medications from discontinued programs.

3 patients received both LDV and DCV; DCV, daclatasvir; LDV, ledipasivir; OMB, ombitasvir.

Bourliere M, AASLD 2016, Oral 194
POLARIS-1: SOF/VEL/VOX for 12 Weeks in NS5A Inhibitor-Experienced HCV GT 1–6

SVR12 Results Overall and by Cirrhosis Status

Overall*
- 96% SVR12
- 253/263 patients
- 6 relapses
- 1 breakthrough**
- 2 withdrew consent
- 1 LTFU

No Cirrhosis
- 99% SVR12
- 140/142 patients
- 1 withdrew consent
- 1 LTFU
- 6 relapses
- 1 breakthrough**

Cirrhosis
- 93% SVR12
- 113/121 patients
- 1 withdrew consent

* p <0.001 for superiority compared with prespecified 85% performance goal for SOF/VEL/VOX

** Exposure was consistent with non-adherence

Bourliere M, AASLD 2016, Oral 194
POLARIS-1: SOF/VEL/VOX for 12 Weeks in NS5A Inhibitor-Experienced HCV GT 1–6

SVR12 Results by Genotype

GT 1
- 1 relapse
- 1 breakthrough
- 1 withdrew consent
- 1 LTFU

GT 1a
- 4 relapses

GT 1b
- 1 relapse
- 1 withdrew consent

GT 2
- 5

GT 3
- 4 relapses

GT 4
- 1 relapse
- 1 withdrew consent

GT 5
- 1

GT 6
- 6

Bourliere M, AASLD 2016, Oral 194
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</tr>
<tr>
<td>SOF/VEL</td>
<td></td>
</tr>
<tr>
<td>12 weeks (n=182)</td>
<td></td>
</tr>
<tr>
<td>SOF/VEL/VOX</td>
<td></td>
</tr>
<tr>
<td>12 weeks (n=182)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
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<tr>
<td>(n=151)</td>
<td></td>
</tr>
</tbody>
</table>

POLARIS-4: SOF/VEL/VOX or SOF/VEL for 12 Weeks in Non-NS5A Inhibitor DAA-Experienced HCV GT 1–4

Other NS5B included mericitabine (n=7); other NS5B+NS3 included deleobuvir+faldaprevir (n=14), mericitabine+danoprevir (n=8), and SOF+telaprevir (n=6); one patient without prior DAA exposure is excluded; SMV, simeprevir; SOF, sofosbuvir.
POLARIS-4: SOF/VEL/VOX or SOF/VEL for 12 Weeks in Non-NS5A Inhibitor DAA-Experienced HCV GT 1–4

SVR12 Results by Cirrhosis Status

SVR12, %

**SOF/VEL/VOX**

- **12 weeks**
  - No Cirrhosis: 96/98
  - Cirrhosis: 81/84

**SOF/VEL**

- **12 weeks**
  - No Cirrhosis: 94
  - Cirrhosis: 77/82

Zeuzem S, AASLD 2016, Oral 109
The SVR12 rate was 97% (431/445) in DAA-experienced patients treated with SOF/VEL/VOX for 12 weeks; Rates were similar regardless of genotype.

Roberts, EASL 2017, SAT-280
# POLARIS Trials

<table>
<thead>
<tr>
<th>DAA-Experienced</th>
<th>DAA-Naïve</th>
</tr>
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<tbody>
<tr>
<td><strong>POLARIS-1</strong></td>
<td><strong>POLARIS-2</strong></td>
</tr>
<tr>
<td>N = 415</td>
<td>N = 941 ± cirrhosis</td>
</tr>
<tr>
<td>NS5A-experienced</td>
<td>Non-NS5A-experienced</td>
</tr>
<tr>
<td>± cirrhosis</td>
<td>± cirrhosis</td>
</tr>
<tr>
<td>GT 1 2 3 4 5 6</td>
<td>GT 1 2 3 4 5 6</td>
</tr>
<tr>
<td><strong>SOF/VEL/VOX</strong></td>
<td><strong>SOF/VEL/VOX</strong></td>
</tr>
<tr>
<td>12 weeks (n=263)</td>
<td>8 weeks (n=501)</td>
</tr>
<tr>
<td>Placebo (n=152)</td>
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</tr>
<tr>
<td><strong>SOF/VEL</strong></td>
<td><strong>SOF/VEL</strong></td>
</tr>
<tr>
<td>12 weeks (n=151)</td>
<td>12 weeks (n=440)</td>
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</table>

POLARIS Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
<th>GT Distribution</th>
<th>Treatment Options</th>
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<tr>
<td><strong>POLARIS-1</strong></td>
<td>N = 415 NS5A-experienced ± cirrhosis</td>
<td>1 2 3 4 5 6</td>
<td>Placebo (n=152) SOF/VEL/VOX 12 weeks (n=263)</td>
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<tr>
<td><strong>POLARIS-4</strong></td>
<td>N = 333 Non-NS5A-experienced ± cirrhosis</td>
<td>1 2 3 4</td>
<td>SOF/VEL/VOX 12 weeks (n=182)</td>
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<tr>
<td><strong>POLARIS-2</strong></td>
<td>N = 941 ± cirrhosis</td>
<td>1 2 3 4 5 6</td>
<td>SOF/VEL/VOX 8 weeks (n=501)</td>
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<tr>
<td><strong>POLARIS-3</strong></td>
<td>N = 219 Cirrhosis</td>
<td>1 2 3 4 5 6</td>
<td>SOF/VEL/VOX 8 weeks (n=110)</td>
</tr>
</tbody>
</table>

**Notes:**
- Bourliere M, AASLD 2016, Oral 194.
- Foster GR, AASLD 2016, Oral 258
Integrated Efficacy Analysis of POLARIS-2 and 3

Efficacy of SOF/VEL/VOX for 8 Weeks in DAA-Naïve Patients

<table>
<thead>
<tr>
<th></th>
<th>SVR12, (%)</th>
<th>Total</th>
<th>GT 1</th>
<th>GT 1a</th>
<th>GT 1b</th>
<th>GT 2</th>
<th>GT 3</th>
<th>GT 4</th>
<th>GT 5</th>
<th>GT 6</th>
<th>Other</th>
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<tr>
<td></td>
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<td>95</td>
<td>93</td>
<td>92</td>
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<td>0</td>
<td>3</td>
<td>2</td>
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</tbody>
</table>

97% SVR (427/441) in DAA-naïve GT 1b, 2–6 patients treated with SOF/VEL/VOX for 8 weeks. Lower SVR in patients with HCV GT 1a infection.

Roberts, EASL 2017, SAT-280
Thank You!