DOT of Sofosbuvir/Ribavirin +/- Peginterferon with Minimal Monitoring for the Treatment of Hepatitis C in PWUD in Chennai, India (C-DOT)

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HCV in India

• Estimated 6.3 million HCV viremic persons
• Primary modes of transmission:
  – Contaminated medical injections
  – Blood and blood products
  – Injection drug use
Injection Drug Use & India

HCV in India

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  - Injection drug use
- Distribution of HCV genotypes
HCV Genotypes in India

Source: Solomon SS, CROI 2013

HCV in India

Generic SOF ushers in a new era for HCV treatment!
HCV in India

• Estimated 6.3 million HCV viremic persons
• Primary modes of transmission:
  – Contaminated medical injections
  – Blood and blood products
  – Injection drug use
• Distribution of HCV genotypes
• Optimal strategy to deliver HCV therapy to PWID unclear
• DOT is the cornerstone of TB treatment in India

Hypothesis

“Directly observed therapy will be associated with high rates of treatment completion and SVR among people who use drugs in Chennai, India”
Eligibility Criteria

• Inclusion Criteria:
  1. ≥18 years of age
  2. Written informed consent
  3. History of drug use or active drug use
  4. HCV RNA+
  5. HCV treatment naïve
  6. ALT ≤10 ULN
  7. AST ≤10 ULN
  8. Hgb >12 (males) and >11 (females)

• Exclusion criteria:
  1. Active HBV infection (HBsAg positive)
  2. Evidence of decompensated cirrhosis
  3. Pregnant OR partner pregnant

Methods

• Stratified blocked randomization with varying block sizes was used
Methods

• Study started September 2015
• SOF+PR and SOF+R only two generic pangenotypic regimens available at the time
  – SOF (Spegra, Emcure Pharmaceuticals Ltd)
  – RBV (Univirin, Unison Pharmaceuticals)
  – PEG alfa 2a (Taspiance, Emcure Pharmaceuticals Ltd)

Generic SOF, PEG and RBV
Methods

• Study started September 2015
• SOF+PR and SOF+R only two generic pangenotypic regimens available at the time
• Medication delivery by DOT
  – Weekly clinic visit for PEG injections in SOF+PR arm (INR 100 compensation)
  – SOF+RBV delivered in the field by outreach workers after confirmation of identity (biometric)

Laboratory testing/monitoring

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X*</td>
<td>X**</td>
<td></td>
<td></td>
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<tr>
<td>HCV genotyping</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CBC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X**</td>
<td>X**</td>
<td>X**,**</td>
<td></td>
</tr>
<tr>
<td>LFT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X**,**</td>
<td>X**,**</td>
<td>X**</td>
<td></td>
</tr>
</tbody>
</table>

*only in the SOF+PR arm; ** only in the SOF+RBV arm
Statistical Methods

- Primary analyses were Intention to Treat (ITT), missing=failure
- Fishers exact test and Mann Whitney U test were used to compare categorical and continuous variables, respectively
- As treated (AT) analyses conducted among those who completed treatment (n=44) to identify factors associated with SVR

Demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>SOF+PR (n=25)</th>
<th>SOF+RBV (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years, (IQR)</td>
<td>46 (41 – 50)</td>
<td>46 (44 – 47)</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>25 (100)</td>
<td>25 (100)</td>
</tr>
<tr>
<td>Median monthly income, in USD (IQR)</td>
<td>90 (68 – 1290)</td>
<td>90 (72 – 150)</td>
</tr>
<tr>
<td>History of substance use in the prior month, n(%)</td>
<td>13 (52)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Liver stiffness category, n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• &lt;8 kPa</td>
<td>15 (60)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>• 8-12.3 kPa</td>
<td>5 (20)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>• &gt;12.3 kPa</td>
<td>5 (20)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>FIB-4 Index, n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Class 1, ≤1.45</td>
<td>6 (24)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>• Class 2, 1.46 - 3.25</td>
<td>16 (64)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>• Class 3, &gt;3.25</td>
<td>3 (12)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Median HCV RNA in log10 copies/ml, (IQR)</td>
<td>6.5 (6.1 – 6.6)</td>
<td>6.1 (5.5 – 6.7)</td>
</tr>
<tr>
<td>HCV Genotype, n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 1a</td>
<td>2 (8)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>• 3a</td>
<td>22 (88)</td>
<td>20 (80)</td>
</tr>
<tr>
<td>• 6n</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>HIV co-infected, n(%)</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Median HOMA-IR</td>
<td>1.3 (0.7 – 3.4)</td>
<td>2.4 (1.1 – 5.6)</td>
</tr>
</tbody>
</table>
## Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Arm 1 (N=25) 12 weeks SOF+PR</th>
<th>Arm 2 (N=25) 24 weeks SOF+R</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Treatment completion, n(%)</td>
<td>22 (88.0)</td>
<td>22 (88.0)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained virologic response*, n(%)</td>
<td>22 (88.0)</td>
<td>15 (60.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Median number of serious adverse events, IQR</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Median change in insulin resistance (HOMA-IR), IQR</td>
<td>1.2 (-0.1, 9.1)</td>
<td>0.1 (-1.3, 6.1)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Other outcomes</strong></td>
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<tr>
<td>Percentage completed doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 0–30%</td>
<td>3 (12)</td>
<td>3 (12)</td>
<td></td>
</tr>
<tr>
<td>• 75–90%</td>
<td>3 (12)</td>
<td>2 (8)</td>
<td>0.93</td>
</tr>
<tr>
<td>• &gt;90–95%</td>
<td>2 (8)</td>
<td>4 (16)</td>
<td></td>
</tr>
<tr>
<td>• &gt;95%</td>
<td>17 (68)</td>
<td>16 (64)</td>
<td></td>
</tr>
</tbody>
</table>

### Real-world challenges
Real-world challenges

Rx discontinuation and failures

• Rx Discontinuation (n=6):
  – 3/6 discontinued in Week 1
  – 3/6 discontinued beyond Week 4
  – 2/6 reported substance use in prior month

• Rx failures (SOF+R; n=7)
  – All reported substance use in the prior month
  – 5/7 had HCV RNA ≤LLOQ at EOT
  – 4 were GT3 and 3 were GT1
Sustained virologic response

SVR12 among those who completed treatment

- ITT*: 22/25
- AT**: 22/22

SOF+PR for 12 weeks
SOF+R for 24 weeks

*p=0.05; **p<0.01

SVR by genotype (AT)

SVR12 among those who completed treatment

- 1a: 1/4
- 3a: 14/18
- 6n: 1/1

SOF+PR for 12 weeks
SOF+R for 24 weeks
SVR by missed doses (AT)

SVR12 among those who completed treatment:
- <5% missed: 17/17
- 5-10% missed: 2/2
- >10% missed: 3/3

SVR by AUDIT (AT)

SVR12 among those who completed treatment:
- No/mild use: 12/12
- Harmful/hazardous use: 1/1
- Alcohol dependent: 9/9

*P=0.03
SVR by substance use (AT)

Conclusions

• Field-based DOT with minimal molecular monitoring was feasible for the delivery of HCV therapy to current and former substance using populations in India
  – 100% adherence was still challenging

• SOF+PR was superior to SOF+R particularly among those with ongoing substance use

• Role of PEG in shortening therapy worthy of further investigation particularly in settings where injections are viewed favorably
Acknowledgements

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• Research participants

THANK YOU