Intracellular 007-TP Concentrations are Associated with Gradients of Adherence to Ledipasvir/Sofosbuvir

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Abstract #2
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- I have no conflicts of interest to report
Background: Significance

- HIV/HCV infected persons who use drugs are an under-treated and under-represented population
  - Concern of low adherence
  - Re-infection potential especially for injection drug users
  - Restrictions on treatment eligibility

- Co-infected HIV/HCV patients are at a higher risk for liver failure, cirrhosis and death but are underrepresented in clinical trials with DAAs

- Knowledge gaps in the pharmacology of DAAs in this population

- Unknown relationship between adherence and PK
Sofosbuvir metabolism

- Sofosbuvir (SOF) is transported into cells and metabolized to a uridine-monophosphate analog and an active triphosphate analog inside cells (007-TP, originally GS-461203)
Aims of the study

1. Define 007-TP PK in a HIV/HCV co-infected, drug using population.
2. Determine the association between [007-TP] in DBS and PBMCs and adherence to LDV/SOF.
Study Design

N=60 HIV/HCV infected persons who use drugs

vDOT
N=19

WOT
N=20

LDV/SOF

Day 1  Wk 2  Wk 4  Wk 6  Wk 8  Wk 10  Wk 12  Off-drug
(pre, 1-18h, 24h)
Sample=Blood tube + DBS card

Adherence (ADH)=#doses taken/#prescribed between visits
Methods

*Quantification of 007-TP:
- LC-MS/MS in 50-50,000 fmol/sample range
- Sample=7mm punch or 1-2million PBMCs

Stats:
- Mixed models used to allow for repeated measures
- Final ADH results modeled as both as continuous and categorical (≤50%, >50-75%, and >75%)
- One-phase decay for \( t_{1/2} \) calculation

## Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Data N=39</th>
<th>%</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>M</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>non black</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>black</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td>Hispanic</td>
<td>77%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td><strong>Weight (Kg)</strong></td>
<td></td>
<td></td>
<td>71 (63, 78)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td>51 (46, 55)</td>
</tr>
<tr>
<td><strong>HCV GT</strong></td>
<td>1a</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td><strong>eGFR (mL/min/1.73^2)</strong></td>
<td></td>
<td></td>
<td>84 (43, 162)</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>DOT</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WOT</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td></td>
<td>21%</td>
<td></td>
</tr>
</tbody>
</table>
## Demographics: ADH

<table>
<thead>
<tr>
<th>N=39 subjects #ADH obs=227</th>
<th>N</th>
<th>#ADH Obs</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 50% \text{ ADH} )</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>&gt;50-75% ADH</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>&gt;75% ADH</td>
<td>38</td>
<td>191</td>
</tr>
</tbody>
</table>

ADH= number of doses taken/number prescribed between each visit

Overall ADH over 12 weeks: Median (range) 94\% (7\%, 100\%)
007-TP PK

DBS GM (95%CI): 616 (447, 783) fmol/punch

PBMCs GM (95%CI): 1820 (1212, 2596) fmol/10^6 cells

DBS t½ = 104 (59-182) hours

PBMCs t½ = 26 (15, 110) hours
Results: Adherence and DBS

- For every 10% increase in ADH, DBS 007-TP increased 7.0% (95% CI 3.8%, 10%)  
  P<0.0001
Results: 007-TP/punch by ADH category

Overall $P=0.002$
Results: Adherence and PBMCs

• For every 10% increase in ADH, PBMC 007-TP increased 23% (95% CI 15%, 31%) P<0.0001
Results: 007-TP PBMCs by ADH category

Overall p<0.0001
## Covariate Analysis DBS

<table>
<thead>
<tr>
<th>Effect variable</th>
<th>Univariate</th>
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<th></th>
<th>Multivariate</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>%Change 007-TP</td>
<td>P Val</td>
<td>%Change 007-TP</td>
<td>P Val</td>
<td>%Change 007-TP</td>
<td>P Val</td>
</tr>
<tr>
<td>*ADH</td>
<td>8.67%</td>
<td>&lt;.0001</td>
<td>8.66%</td>
<td>&lt;.0001</td>
<td>8.66%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Weight</td>
<td>-1.45%</td>
<td>0.014</td>
<td>-1.30%</td>
<td>0.019</td>
<td>-0.29%</td>
<td>0.396</td>
</tr>
<tr>
<td>eGFR</td>
<td>-0.68%</td>
<td>0.037</td>
<td></td>
<td></td>
<td>0.68%</td>
<td>0.037</td>
</tr>
<tr>
<td>Race</td>
<td>69.9%</td>
<td>0.002</td>
<td>24.9%</td>
<td>0.149</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>-20.3%</td>
<td>0.313</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>1.03%</td>
<td>0.270</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DOT vs WOT</td>
<td>-14.0%</td>
<td>0.382</td>
<td></td>
<td></td>
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</tbody>
</table>

ref group (0)=non-black, female, WOT

*ADH is per 10% increase, not winsorized
Covariate Analysis PBMCs

<table>
<thead>
<tr>
<th>Effect variable</th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%Change</td>
<td>P Val</td>
<td>%Change</td>
<td>P Val</td>
</tr>
<tr>
<td></td>
<td>007-TP</td>
<td></td>
<td>007-TP</td>
<td></td>
</tr>
<tr>
<td>*ADH</td>
<td>27.0%</td>
<td>&lt;.0001</td>
<td>23.8%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Weight</td>
<td>-0.62%</td>
<td>0.463</td>
<td>-0.68%</td>
<td>0.265</td>
</tr>
<tr>
<td>eGFR</td>
<td>-0.83%</td>
<td>0.057</td>
<td>-0.54%</td>
<td>0.155</td>
</tr>
<tr>
<td>Race</td>
<td>93.7%</td>
<td>0.006</td>
<td>9.67%</td>
<td>0.683</td>
</tr>
<tr>
<td>Sex</td>
<td>-57.8%</td>
<td>0.002</td>
<td>-44.9%</td>
<td>0.008</td>
</tr>
<tr>
<td>Age</td>
<td>0.22%</td>
<td>0.862</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOT vs WOT</td>
<td>-5.42%</td>
<td>0.810</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ref group (0)=non-black, female, WOT

*ADH is per 10% increase, not winsorized
Conclusions

- Half-life estimations support cumulative dosing of SOF (104 h in DBS, 26 h PBMC)

- ADH was the most significant predictor of 007-TP levels, remained after controlling for other covariates

- 007-TP levels were significantly lower in <50-75% ADH categories
Future directions

- Develop a PK model that can predict ADH based on 007-TP levels in both DBS and PBMCs

- Further exploration of univariate and multivariate predictors after study completion

- Determine relationship between cure and ADH
  - 3/36 subjects with SVR 12 visit were virologic failures
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  - Steven Johnson, MD
  - Sara Scherrrer, MD

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