Update on Hepatitis C Treatment in Special Populations

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DISCLOSURES

- Grants/Contracts to Institution
  - Abbvie
  - Anadys
  - BMS
  - Gilead
  - Merck
  - MedImmune
  - Vertex

- Advisory Board/Consulting
  - MedImmune
  - Merck

- DSMB
  - Janssen
  - MedPace
  - SynteractHCR

Non-FDA approved treatments will be discussed
FDA “Special Populations”

- Special populations listed in regulatory guidance on HCV drug development
  - Decompensated liver disease and/or pre-transplant
  - Post-transplant
  - HIV/HCV co-infected patients
  - Renal Disease
  - PEG-IFN and RBV intolerant patients
  - Patients with prior DAA experience
  - Pediatric patients

Special populations listed in regulatory guidance on HCV drug development

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DECOMPENSATED CIRRHOSIS

- Ascites
- Hepatic Encephalopathy (Overt)
- Bleeding Varices
- PT > 3 seconds over control (INR approx. >1.5)
Ledipasvir/Sofosbuvir + RBV in Patients with Decompensated Cirrhosis

- Randomized to SOF + LDV + RBV (600 mg w/ escalation) for 12 or 24 weeks
- Patients with G1 or 4 and decompensated cirrhosis
  - Most patients with MELD > 10 (MELD= 16-20 in 10-46%)
  - Median Albumin= 2.6- 3.0 g/L; Median platelets = 71-88 K

Ledipasvir/Sofosbuvir + RBV in Decompensated Cirrhosis: SAFETY

- Discontinuations- n=3
- SAE- Common but rarely treatment related
- Death= 5
  - Septic Shock- 4
  - Renal Failure/Cardiac- 1

## Target: Predictors of SVR4
### SOF/SMV ± RBV for 12 Weeks

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>Odd Ratio</th>
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<tbody>
<tr>
<td>Baseline ALB</td>
<td>2.3 (1.3, 3.9)</td>
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<tr>
<td>Baseline ALT</td>
<td>1.0 (1.0, 1.0)</td>
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<tr>
<td>Baseline AST</td>
<td>1.0 (1.0, 1.0)</td>
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<tr>
<td>Baseline CRCL</td>
<td>1.0 (1.0, 1.0)</td>
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<tr>
<td>Baseline CRE</td>
<td>1.3 (0.8, 2.3)</td>
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<tr>
<td>Baseline HCV</td>
<td>1.0 (1.0, 1.0)</td>
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</tr>
<tr>
<td>Baseline HGB</td>
<td>1.1 (0.9, 1.3)</td>
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<tr>
<td>Baseline PLT</td>
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<tr>
<td>Baseline TBIL</td>
<td>0.7 (0.5, 1.0)</td>
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<tr>
<td>Male</td>
<td>0.5 (0.2, 1.1)</td>
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<tr>
<td>Race White</td>
<td>0.6 (0.3, 1.5)</td>
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</tr>
<tr>
<td>Ethnicity</td>
<td>0.9 (0.7, 1.2)</td>
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</tr>
<tr>
<td>Genotype 1a</td>
<td>0.3 (0.1, 0.9)</td>
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</tr>
<tr>
<td>Cirrhotic</td>
<td>0.5 (0.2, 1.1)</td>
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<tr>
<td>Previous Treatment</td>
<td>0.6 (0.3, 1.3)</td>
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<tr>
<td>Age</td>
<td>1.0 (1.0, 1.1)</td>
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<tr>
<td>Prior Decomp</td>
<td>0.2 (0.1, 0.3)</td>
<td></td>
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<tr>
<td>Triple Failure</td>
<td>0.4 (0.2, 0.9)</td>
<td></td>
</tr>
<tr>
<td>Pegifi Failure</td>
<td>0.8 (0.4, 1.7)</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, sex, and genotype

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Days HCV RNA Negative Prior to LT and Rate of Recurrence

[Graph showing the distribution of days HCV RNA continuously TND prior to liver transplant, comparing 'No recurrence' (n = 30) and 'Recurrence' (n = 10).]

- Median days TND ($P < .001$):
  - No recurrence: 95.0
  - Recurrence: 5.5

POST-TRANSPLANT
Post-Transplant Solar-1: LDV/SOF + RBV in Post-Transplant

SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

Reddy, AASLD, 2014, Oral #8
POST-LIVER TRANSPLANT
AASLD/IDSA/IAS-USA Guidelines

- **RECOMMENDED**
  - Ledipasvir/Sofosbuvir FDC + Ribavirin (WB) x 12 Weeks for Genotype 1,4 including compensated cirrhotics (Lower Ribavirin in Decompensated)
  - Sofosbuvir + Ribavirin (WB) x 24 Weeks for Genotype 2, 3 including compensated cirrhotics (Lower ribavirin in Decompensated)

- **ALTERNATIVE**
  - Ledipasvir/Sofosbuvir FDC x 24 Weeks without ribavirin for Genotype 1,4 in ribavirin ineligible/intolerant or
  - Sofosbuvir + Simeprevir + Ribavirin x 12 weeks for Genotype 1 or
  - Paritaprevir/r/Ombitasvir + Dasabuvir + Ribavirin (WB) for Genotype 1 x 24 weeks with early (Metavir F0-2 fibrosis)

HCVGuidelines.org  Accessed 2/11/2015
HCV/HIV COINFECTION
What Features Make HCV/HIV “Special” or Unique

- Faster rates of fibrotic progression
- Increased risk of hepatic decompensation
- Higher viral loads
- Drug-drug interactions
- Potential for altered absorption
Rates of Liver Fibrosis Progression

Fibrosis Grades (METAVIR scoring system)

Duration of HCV Infection (Years)

- HIV positive (n = 122)
- Matched controls (n = 122)
- Simulated controls (n = 122)

Fibrosis Progression Rate by HIV Viral Load

- Retrospective analysis in 2 hepatitis C centers of 656 consecutive treatment-naïve patients who underwent liver biopsy
- 274 of these patients were coinfected with HIV (95.2% on HAART)

EFFECT OF cART

Sherman et al, SCIENCE TRANSLATIONAL MED, 2014
EFFECT of cART
Histology

Pre-cART  Post-cART

Sherman et al. SCIENCE TRANS MED, 2014
Effect of cART on Hepatic Decompensation in HCV/HIV Coinfection

- Retrospective cohort study at VHA of 4280 HCV/HIV coinfected patients who initiated ART and 6079 HCV-monoinfected patients receiving care between 1997 and 2010
- All patients had detectable HCV RNA and were treatment-naïve
HIV CONTINUUM OF CARE IN US

FIGURE 3. Number and percentage of HIV-infected persons engaged in selected stages of the continuum of HIV care — United States

- HIV-infected*: 1,178,350
- HIV-diagnosed*: 941,950
- Linked to HIV care†: 725,302
- Retained in HIV care§: 480,395
- On ART¶: 426,590
- Suppressed viral load (≤200 copies/mL)**: 328,475

*Per diagnosis
†Per diagnosis
§Per care engagement
¶Per ART
**Per viral load suppression
HCV Viral Load

Sofosbuvir Predictors of Relapse: Multivariate Regression Model

- Meta analysis of phase 2 and 3 trials of SOF + PEG-INF/RBV (ATOMIC, NEUTRINO) and SOF + RBV (FISSION, POSITRON, FUSION, VALENCIA)

- Populations
  - Treatment-naïve patients, G1, SOF + PEG-INF + RBV, 12 weeks (n=339)
  - Treatment-naïve and treatment-experienced patients, G2, SOF + RBV, 12 weeks (n=285)
  - Treatment-naïve and treatment-experienced patients, G3, SOF + RBV, 24 weeks (n=247)

DAAs (ALL ORAL REGIMENS) for HCV/HIV Coinfection

- Sofosbuvir (and ledipasvir)
- MK-5172 + MK-8742
- Daclatasvir + Sofosbuvir
- Paritaprevir/r/Ombitasvir + Dasabuvir ± Ribavirin

Clinicaltrials.gov
Sofosbuvir in HCV/HIV Coinfection: PHOTON-1 Trial

- Phase 3, open label
  - TN with G1 or G2/3
  - TE with G2/3
- N=224
- Treatment arms
  - SOF/RBV, 24 wks (TN GT1)
  - SOF/RBV, 12 wks (TN GT2/3)
  - SOF/RBV, 24 wks (TE GT2/3)
- EFV, ATA/R, DAR/R, RAL, RIL with TNF/EMT
  - Most on cART
- No resistance in virologic failures

Sułkowski MS et al, JAMA, 2014.
Sofosbuvir in HCV/HIV Coinfection
PHOTON-2

- N = 274
  - Genotype 1, 2, 3, 4
  - TN and TE
  - Compensated cirrhosis allowed
- Treatment
  - Sof 400 qd + Riba 1000/1200 (wb)
  - Duration: 24 weeks except TN Genotype 2 (12 Wks)
- Subgroups
  - Genotype 1 TN cirrhotic 65%
  - Genotype 2 TN cirrhotic 89%
  - Genotype 2 TE cirrhotic
  - Genotype 3 TN cirrhotic
  - Genotype 3 TE cirrhotic 78%
  - Genotype 4 TN cirrhotic 83%

Sofosbuvir/Ledipsavir in HCV/HIV Coinfection: ERADICATE Trial

- NIH phase 2, open label
- N=50 (13 w/o cART)
- SOF/LDV qd x 12 weeks
  - GT1
  - TN with or w/o cART
- “Difficult” cohort
  - G1a: 78%
  - A-A: 84%
  - F3: 26%
  - BMI: 26

Osinusi et al, JAMA 2015
ION-4

- N = 335 HCV/HIV
- Single Arm Sof/Ledip
- Duration 12 weeks
- Blacks with Slightly Lower Response Rate
  - Not explained by pK with sparse sampling

Naggie et al, CROI, 2015 Abs. 152LB
ALLY-2
Daclatasvir + Sofosbuvir in HCV/HIV

- Three arm Randomized Controlled Trial
  - TN n= 151
    - DCV 30/60/90 mg + SOF 400 mg qd x 12 Weeks or
    - DCV 30/60/90 mg + SOF 400 mg qd x 8 weeks
  - TE n=52
    - DCV 30/60/90 mg + SOF 400 mg qd x 12 weeks

(Standard Dose DCV= 60 mg but 30 mg with ritonavir-boosted PIs and 90 mg with NNRTI except rilpiverene)

Wyles et al, CROI 2015
MK-5172 + MK8742 +/- RBV: C-WORTHY Trial

- Phase 2, open label in genotype 1 patients
- N=59
  - Treatment-naïve
  - F0-F2
- Two arms HCV/HIV
  - MK-5172 100 mg + MK-8742 50 mg + RBV for 12 wks
  - MK-5172 100 mg + MK-8742 50 mg for 12 wks

3D + Ribavirin
TURQUOISE

- N= 63 HCV/HIV Geno 1
  - TN, TE
- 3D
  - ABT-450/ritonavir/ombitasvir (150/100/25 mg) qd + dasabuvir (250 mg) bid + ribavirin 1000-1200 qd
  - Duration 12 or 24 Weeks
  - Atazanavir or raltegravir based regimen
    - Undetectable HIV
    - CD4 >200 or CD4%>14

Sułkowski et al, JAMA, 2015
# ARV Interaction Score Card

<table>
<thead>
<tr>
<th></th>
<th>Simeprevir</th>
<th>Sofosbuvir</th>
<th>Ledipasvir</th>
<th>Daclatasvir</th>
<th>AbbVie 3D</th>
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<tr>
<td><strong>ATV/r</strong></td>
<td>No data</td>
<td>No data</td>
<td>↑ LDV, ↑ ATV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCV ↑&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ATV ↔; ABT450 ↑</td>
</tr>
<tr>
<td><strong>DRV/r</strong></td>
<td>SIM↑; DRV ↔</td>
<td>SOF↑; DRV ↔</td>
<td>↑ LDV, ↔ DRV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No data</td>
<td>DRV ↓/↑; 3D ↓</td>
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<tr>
<td><strong>LPV/r</strong></td>
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<td>LPV ↔; ABT450 ↑</td>
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<tr>
<td><strong>TPV/r</strong></td>
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<tr>
<td><strong>EFV</strong></td>
<td>SIM ↓; EFV ↔</td>
<td>SOF ↔; EFV ↔</td>
<td>LDV ↓; EFV ↓&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCV ↓&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No PK data&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>RPV</strong></td>
<td>SIM ↔; RPV ↔</td>
<td>SOF ↔; RPV ↔</td>
<td>LDV ↔; RPV ↔</td>
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<td>ABT450 ↑; RPV ↑</td>
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<tr>
<td><strong>ETV</strong></td>
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<td>No data</td>
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<tr>
<td><strong>RAL</strong></td>
<td>SIM ↔; RAL ↔</td>
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<td>3D ↔; ↑ RAL</td>
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<td><strong>ELV/cobi</strong></td>
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<tr>
<td><strong>TDF</strong></td>
<td>SIM ↔; TFV ↔</td>
<td>SOF ↔; TFV ↔</td>
<td>LDV ↔; ↑TFV</td>
<td>DCV ↔; TFV ↔</td>
<td>3D ↔; TFV ↔</td>
</tr>
</tbody>
</table>

<sup>a</sup>Watch renal function, TFV levels increased, <sup>b</sup>Decrease DCV dose to 30mg QD, Increase DCV dose to 90mg QD, <sup>c</sup>3D + EFV led to premature study discontinuation due to toxicities

COURTESY OF JEN KISER, PharmD, Univ. of Colorado
Antiretroviral Drug Switches Should be Done in Collaboration with HIV Practitioner

HCV/HIV Coinfected Persons Should Be Treated the SAME as those with HIV Infection
TREATMENT OF PATIENTS WITH RENAL DISEASE
Mild/Moderate Renal Impairment (CrCl > 30 ml/min)
- No dose adjustment when using
  - Sofosbuvir
  - Simeprevir
  - Ledipsavir/Sofosbuvir FDC
  - Paritaprevir/r/Ombitasvir + Dasabuvir

For CrCl < 30 Consult with Expert
SOFOSBUVIR IN RENAL FAILURE

- Open Label Study
- N = 10
  - Sof 200 mg + Riba 200 mg qd for 24 weeks
  - GT 1 or 3 Patients
  - Severe Renal Impairment or ESRD on Dialysis
- Sof and GS-331007 Metabolites Measured
  - GS-331007 Increased 4x
- SVR12 = 40%
- Ribavirin Adverse Events Seen

Gane et al, AASLD, Abs 966
HCV TREATMENT IN DIALYSIS PATIENTS
PegIFN/Riba

- Randomized Trial
  - PegINF 135/week + Riba 200 mg qd
  - Pegylated Interferon Monotherapy
- More epo used in combination arm

Liu CH et al, ANN INTERN MED, 2013
HCV TREATMENT IN RENAL FAILURE

- Simeprevir (from Label)
  - No dose adjustment needed in patients with mild, moderate or severe renal impairment
  - “Renal clearance plays an insignificant role in its elimination.”
  - NOT STUDIED IN PATIENTS WITH CrCl < 30

- Paritaprevir/r/Ombitasvir + Dasabuvir (from Label)
  - Single Dose Pharmacokinetics were studied in:
    - Mild (CrCl 60-89 mL/min)
    - Moderate (CrCl 30-59 mL/min)
    - Severe (CrCl 15-29 mL/min)
  - “Changes in exposure ...in non-HCV infected subjects with mild, moderate, and severe renal impairment are not expected to be clinically relevant.”

CONCLUSIONS & FINAL THOUGHTS

- Special Populations Remain Important, & Special
- Decompensated Disease Can Be Treated- However It is NOT Clear if Natural History is Altered by Treatment
- Post-transplant Patients have Excellent Treatment Outcomes
- HCV/HIV coinfection no longer is a “special population” With regard to Response in Highly Selected Patients
  - Results tend to be with limited array of cART regimens
- Renal Disease Patients Remain Complicated
  - Pre-Dialysis- Some options exist
  - Dialysis- No recommendations for treatment at this time