Potential issues in treating HIV/HCV co-infection with new HCV antivirals

Efficacy
Barriers to care
HCV Therapy in HCV/HIV
Access
Providers

Efficacy in HIV/HCV Co-Infection

<table>
<thead>
<tr>
<th></th>
<th>SVR4 (24w)</th>
<th>SVR12 (52w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 96%</td>
<td>Male 97%</td>
</tr>
<tr>
<td>Race</td>
<td>Black 19%</td>
<td>Black 25%</td>
</tr>
<tr>
<td>GT</td>
<td>GT1 75%</td>
<td>GT1 79%</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>48%</td>
<td>43%</td>
</tr>
<tr>
<td>Decompensated</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>SVR12 HCV (all)</td>
<td>87%</td>
<td>93%</td>
</tr>
<tr>
<td>SVR12 HIV</td>
<td>88%</td>
<td>93%</td>
</tr>
</tbody>
</table>

McGinnis J. #LBP-514.
Dieterich D. #SAT-134.
Montes ML. #SAT-206.
Impact of HIV co-infection on DAA response?

- Data from 2 prospective Spanish cohorts [HEPAVIR-DAA and GEHEP-MONO]

<table>
<thead>
<tr>
<th></th>
<th>HCV (N=404)</th>
<th>HCV/HIV (N=423)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>67%</td>
<td>82%</td>
</tr>
<tr>
<td>IDU</td>
<td>29%</td>
<td>84%</td>
</tr>
<tr>
<td>1a</td>
<td>29%</td>
<td>42%</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>52%</td>
<td>64%</td>
</tr>
<tr>
<td>Partial/Null</td>
<td>27%</td>
<td>33%</td>
</tr>
</tbody>
</table>

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Patient Case #1

- 64 yo African American male
- HIV-HCV coinfected
- DM2 diagnosed 2006 last A1c 6.0
  - Glipizide 10 mg bid + metformin 1g bid + insulin glargine 50u hs
- Seizure disorder dx 2007
  - Levetiracetam 1000 mg bid
- HTN dx 1990s
  - Hydrochlorothiazide 50 mg + lisinopril 20mg+ amlodipine 5mg
- Dyslipidemia
  - Rosuvastatin 5mg/day

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HIV History

- Most recent VL and CD4
  - HIV RNA not detected
  - CD4 769 cells/µL (33%)
- ARV History
  - Patient is a poor historian with poor health literacy and does not remember ARV history, previously received HIV care at a different facility with limited records
  - Documentation of exposure to AZT, 3TC, LPV/RTV
  - Current regimen Tenofovir DF/Emtricitabine + Darunavir + Ritonavir
    - Has been on this regimen since at least 2012 and viral load has been undetectable since that time
  - HLAB5701 not detected
HCV History

- Treatment history: Failed peginterferon/ribavirin x 2 (relapsed after 42 wks)
- Genotype 1A
- HCV RNA
  - 7,700,000 IU/mL (6.89 log_{10} IU/mL)
- Liver biopsy (2013):
  - Cirrhosis
- CTP A

What is your next step in preparation for HCV treatment for this patient?

1. Order Ledipasvir/Sofosbuvir x 24 weeks
2. Perform NS5A resistance testing
3. Plan to change patient’s ARVs prior to starting HCV treatment
4. Order Elbasvir/Grazoprevir x 12 weeks
5. Order PrOD + Ribavirin x 24 weeks

You decide to change the patient’s ARV regimen prior to starting HCV treatment. What regimen do you decide to initiate in this patient?

1. Order archived genotype prior to changing patient's ARVs
2. Change to abacavir/lamivudine/dolutegravir
3. Change to TAF/emtricitabine/elvitegravir/cobicistat
4. Change to TAF/emtricitabine + Darunavir + Ritonavir
5. Something else
You change the patient’s ARV regimen to TAF/emtricitabine® + Darunavir/Ritonavir and complete a NSSA resistance test which shows no baseline resistance. Which HCV treatment will you order for this patient.

1. Elbasvir/Grazoprevir x 12 weeks
2. Elbasvir/Grazoprevir + Ribavirin x 16 weeks
3. PrOD + Ribavirin x 24 weeks
4. Ledipasvir/Sofosbuvir x 12 weeks
5. Ledipasvir/Sofosbuvir x 24 weeks
6. Sofosbuvir + Daclatasvir + Ribavirin x 24 weeks
7. Something else

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**Carrier-Mediated Transport: Influx vs. Efflux**

- Influx Transporters – facilitate movement into cell
- Efflux Transporters – facilitate movement out of cell

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http://www.solvio.jp/solutions/instestine.html

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http://www.solvo.jp/solutions/instestine.html
Cytochrome P450 (CYP)

- Heme protein
- Located in the smooth endoplasmic reticulum (mitochondria) of all major organs and tissues
- Many P450 enzymes are inducible
- Genetic polymorphisms exist that may affect drug metabolism (+ or -)

CYP450 enzymes as a proportion of total drug metabolism

DAA potential interactions
LDV/SOF and Tenofovir

Table 5.10. Pharmacokinetic Parameters of Lopinavir, Sofosbuvir, GS-331007, and Tenofovir by ARV regimen and Overall

<table>
<thead>
<tr>
<th>Mean (%CV)</th>
<th>LDV/SOF + EFV/PTV-TOF 12 Weeks (N = 160)</th>
<th>LDV/SOF + RAL/FTC/TV 12 Weeks (N = 140)</th>
<th>LDV/SOF + RAL/FTC/TV 12 Weeks (N = 20)</th>
<th>LDV/SOF Total 12 Weeks (N = 300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng·h/mL)</td>
<td>3,608 (30.3)</td>
<td>4,010 (30.9)</td>
<td>4,288 (30.8)</td>
<td>3,838.5 (31.2)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>335.7 (20.2)</td>
<td>379.9 (20.9)</td>
<td>379.6 (25.4)</td>
<td>356.3 (28.5)</td>
</tr>
<tr>
<td>C_{tt} (ng/mL)</td>
<td>96.7 (47.5)</td>
<td>90.8 (49.1)</td>
<td>111.7 (42.4)</td>
<td>94.6 (46.5)</td>
</tr>
</tbody>
</table>

AUC of tenofovir 3000-3300 ng·h/mL

German et al. CROI 2015.

Vivancos - Gallego, et al. CROI 2016
Tenofovir alafenamide (TAF)  
Novel Prodrug of Tenofovir

- Tenofovir (TFV)
- Tenofovir disoproxil fumarate (TDF)
- Tenofovir alafenamide (TAF)

GI Tract  Blood  Lymphoid Cell

TFV  TDF  TAF  TFV

TFV

TFV-
MP = tenofovir monophosphate
TFV-
DP = tenofovir diphosphate
CatA = Cathepsin A

Modified from CROI 2015 - Sax et al. Abstract 143LB

LDV/SOF and TAF

Conclusions
- Safe to administer E/C/F/TAF with LDV/SOF – increases in COBI and EVG levels not considered clinically significant
- Garrison et al. 16th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy. 2015

LDV/SOF (+)  LDV/SOF (-)

Range of TFV exposures with safety data

STB  E/C/F/TAF  DTG  DRV+RTV  ATV+RTV  RAL  EFV  RPV

- LDV/SOF can be safely co-administered with E/C/F/TAF or R/F/TAF with no dose adjustment
- TFV exposures from E/C/F/TAF are lower compared to exposures from PI+RTV +TVD with LDV/SOF and with STB alone

German P, et al. CROI 2015. Seattle, WA. Oral #82

ION4 - Study Design

- Phase 3, multicenter, open-label study in US, PR, Canada, and New Zealand
- Broad inclusion criteria
  - Platelets ≥50,000/mm$^3$; hemoglobin ≥10 mg/dL, CrCl ≥60 mL/min
  - HIV-1 positive, HIV RNA <50 copies/mL; CD4 cell count >100 cells/mm$^3$

Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52 (7)</td>
<td>36</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>276 (82%)</td>
<td></td>
</tr>
<tr>
<td>Race (black)</td>
<td>115 (34%)</td>
<td></td>
</tr>
<tr>
<td>Race (Hispanic or Latino)</td>
<td>56 (17%)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>27 (6)</td>
<td></td>
</tr>
<tr>
<td>IL28B CC</td>
<td>81 (24%)</td>
<td></td>
</tr>
<tr>
<td>GT 1</td>
<td>327 (98%)</td>
<td></td>
</tr>
<tr>
<td>HCV treatment experienced</td>
<td>185 (55%)</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>67 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

SVR12 by Subgroup and Baseline Characteristics

- No difference in SVR in blacks vs. non-blacks in prior studies

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Overall SVR 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>99%</td>
</tr>
<tr>
<td>Male</td>
<td>276</td>
<td>99%</td>
</tr>
<tr>
<td>Female</td>
<td>59</td>
<td>96%</td>
</tr>
<tr>
<td>BL HCV</td>
<td>285</td>
<td>98%</td>
</tr>
<tr>
<td>BL HCV + BDEK</td>
<td>299</td>
<td>96%</td>
</tr>
<tr>
<td>GT 1a and 4</td>
<td>84</td>
<td>96%</td>
</tr>
<tr>
<td>GT 1b</td>
<td>222</td>
<td>100%</td>
</tr>
<tr>
<td>GT 4</td>
<td>11</td>
<td>100%</td>
</tr>
<tr>
<td>Non-black</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>448</td>
<td>99%</td>
</tr>
<tr>
<td>Male</td>
<td>431</td>
<td>99%</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
<td>100%</td>
</tr>
</tbody>
</table>

SVR 12 (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Overall SVR 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>538</td>
<td>99%</td>
</tr>
<tr>
<td>Black</td>
<td>115</td>
<td>96%</td>
</tr>
<tr>
<td>Non-black</td>
<td>423</td>
<td>96%</td>
</tr>
</tbody>
</table>

No treatment difference in non-cirrhotic patients

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>N</th>
<th>Overall SVR 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPV + RAL</td>
<td>87</td>
<td>99%</td>
</tr>
<tr>
<td>RAL + FTC + TDF</td>
<td>92</td>
<td>99%</td>
</tr>
</tbody>
</table>

Lennox et al. AASLD 2014 Oral abstract #237, Osinusi et al. JAMA 2015
What was different about African American patients in ION4?

- More black patients on EFV (53% vs. 46%)
- Predictors of relapse in black patients
  - IL28TT
  - Elevated baseline ALT (>1.5xULN)

Effect of EFV on LDV PK

- In healthy volunteers
  - EFV ↓ LDV ~34%

- In ION-4, by popPK analysis, LDV exposures similar in those on LDV/SOF with EFV vs. RAL and RPV

GWAS/Targeted gene analyses from ION-4

- GWAS (Human Cope BeadChip kit), >3 million SNPs
  - No genome-wide significant associations were observed
  - 2 SNPs in African-American-only analysis of possible relevance to treatment failure, but not statistically significant
- Targeted analyses of 52 “drug metabolism” genes identified modest associations with 3 non-coding SNPs in CYP3A4
  - Variant alleles for these SNPs more common in African Americans
  - Though not shown on the poster, investigators also looked at 2 SNPs in CYP2B6 known to impair EFV metabolism, but found no association

Kleinstein SE, et al. CROI, 2/22-2/25, 2016, Boston, MA, #601
**PrO D with RP V and RAL**

<table>
<thead>
<tr>
<th>OD Study of PiQO Regimen with</th>
<th>Effect of PiQO Drugs on Cmax and AUC of PiQO Regimen</th>
<th>Effect of PrQO regimen on Cmax and AUC of PiQO Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTC TDF</td>
<td>ART 450 vs. standard ART; ART 450 vs. standard ART</td>
<td>FTC vs. standard ART; ART 450 vs. standard ART</td>
</tr>
<tr>
<td>RAL</td>
<td>ART 450 vs. standard ART</td>
<td>RAL vs. standard ART</td>
</tr>
<tr>
<td>RLP</td>
<td>ART 450 vs. standard ART</td>
<td>RLP vs. standard ART</td>
</tr>
</tbody>
</table>

- EFV also contraindicated – EFV toxicity

**Comments**
- Not recommended due to theoretical concern for QTc prolongation


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**PrO D and HIV PI Interactions**

<table>
<thead>
<tr>
<th>OD Study of PiQO Regimen with</th>
<th>Effect of HIV PI on Cmax and AUC of PiQO Regimen</th>
<th>Effect of PiQO Regimen on Cmax and AUC of HIV PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV + RTV QR</td>
<td>DRV 450 vs. standard DRV; DRV 450 vs. standard DRV</td>
<td>DRV vs. standard DRV</td>
</tr>
<tr>
<td>DRV + RTV QR</td>
<td>DRV 450 vs. standard DRV; DRV 450 vs. standard DRV</td>
<td>DRV vs. standard DRV</td>
</tr>
<tr>
<td>DRV + RTV BID</td>
<td>DRV 450 vs. standard DRV; DRV 450 vs. standard DRV</td>
<td>DRV vs. standard DRV</td>
</tr>
<tr>
<td>LPV BID</td>
<td>DRV 450 vs. standard DRV; DRV 450 vs. standard DRV</td>
<td>DRV vs. standard DRV</td>
</tr>
</tbody>
</table>

- Not recommended due to too much RTV

Drop the ritonavir booster while on PrQO

Median DRV trough is 1330ng/mL without PrQO

Median DRV trough is 1330ng/mL without PrQO

• 2 and 3 patients from DRV QD and BID arms, respectively, experienced blips of intermittent viremia (HIV RNA >40 and <200 copies/mL) during treatment.

• Highest HIV-1 RNA recorded during treatment was 79 copies/mL.

Daclatasvir drug interactions:

• Substrate of Pgp and CYP3A4
  – Moderate Pgp inhibitor

• ATV/r- DCV 20mg: AUC: 0.70, C<sub>24</sub>: 1.21
  – 30mg (est): AUC: 1.05, C<sub>24</sub>: 1.83

• EFV- DCV 120mg: AUC: 1.37, C<sub>24</sub>: 0.83
  – 90mg (est): AUC: 1.03, C<sub>24</sub>: 0.62

• TDF- DCV 60mg: AUC: 0.10, C<sub>24</sub>: 1.17
Patient case #2

- JW is a 42 y/o AA male with HIV/HCV co-infection who comes to clinic for consideration of HCV treatment
- He has a history of dyslipidemia and depression
  - Atorvastatin 10mg daily, Fluoxetine 20mg daily
- HIV viral load – undetectable
- CD4 576 cells/µL
- HLA-B*5701 not present
- ARV history
  - Taking tenofovir DF/emtricitabine/efavirenz since 2010
  - 1st and only regimen, has maintained viral suppression since starting treatment
Patient Case #2

- JW HCV history
  - CMP: Na 138, K 4.5, BUN 10, SCr 1.2, Alk Phos 76, AST 58, ALT 47, Alb 3.9, T bili 0.7
  - CBC: Hgb 11.9, Plt 142k, wbc 3.4
  - HCV genotype: 2
  - HCV viral load: 4,567,386
  - Treatment naïve
  - Transient elastography in clinic 13.5 kPa

What is your recommendation to JW for treatment of his HCV?

- 27% 1. Start Sofosbuvir + Ribavirin x 12 weeks
- 31% 2. Start Sofosbuvir + Ribavirin x 24 weeks
- 12% 3. Start Sofosbuvir + Daclatasvir x 16 weeks
- 4% 4. Start Ledipasvir/Sofosbuvir x 12 weeks
- 27% 5. Wait for Sofosbuvir/Velpatasvir to be approved
- 0% 6. Something else

SOF/VEL geno 2

- 19 patients with cirrhosis in each arm
You decide to wait for approval of SOF/VEL to start HCV treatment. What do you do regarding JW's ARV regimen of TDF/FTC/EFV in preparation for HCV treatment?

35%. 1. No change, continue current regimen

6%. 2. Change to TDF/FTC + Darunavir/cobicistat

24%. 3. Change to abacavir/lamivudine/dolutegravir

35%. 4. Change to TAF/FTC/Rilpivirine

0%. 5. Something else

Velpatasvir Interactions with ARV

- Cannot be used with EFV
- Tenofovir Levels Increased

Mogalian E, et al. AASLD 11/13-11/17, 2015, Boston, MA #2265
**Velpatasvir**

**Effect of SOF/VEL on HIV ARV PK**

- No significant impact of SOF/VEL on TAF or TTV derived from TAF
  - TTV AUC ~40% lower when administered as TAF compared to boosted TDF containing TAF
- Modest increase in TTV exposure (~20-40%) when administered as TDF in the presence of SOF/VEL
- Mechanism likely inhibition of efflux transport (e.g., P-gp)
- No impact of SOF/VEL on FTC exposure (AUC: DMR range 100-150%)

**Conclusions**

- Study treatments were generally safe and well tolerated
- Efficacy data from this and previous studies support coadministration of SOF/VEL to coinfected patients on the following agents:
  - NNRTI
  - INI
  - HIV integrase inhibitor
  - PIs
  - FTC, TAF, TDF, MPV, DTG, ETV, RAL, ATV, DRV, LPV, Cobicistat, Indinavir

**Sofosbuvir/Velpatasvir for 12 Weeks in Patients Coinfected With HCV and HIV-1:**

**The ASTRAL-5 Study**

David Wyles, Norbert Brau, Shyam Kottilil, Eric Daar, Kimberley Workowski, Anis Anthony, Akanksha Amin, Peter Buon, Bruce Daley, R. G. Gancarz, Ana Oldemers, Jake Mcnally, Dana M. Brainard, John G. McHutchison, Susanna Naggie, Mark Sulkowski

Division of Infectious Diseases, University of California, San Diego, California, USA; Veterans Affairs Medical Center, New York, New York, USA; Institute of Human Virology, University of Maryland, Baltimore, Maryland, USA; Icahn School of Medicine at Mount Sinai, New York, New York, USA; David Geffen School of Medicine, University of California, Los Angeles, California, USA; Emory University, Atlanta, Georgia, USA; University of California, San Francisco, California, USA; Rush University Medical Center, Chicago, Illinois, USA; Ruane Medical and Liver Health Institute, Los Angeles, California, USA; Duke University, Durham, North Carolina, USA; Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
Study Design

ASTRAL-5 HIV/HCV Coinfection Study

- Open-label, single-arm, multicenter, Phase 3 study
- Broad inclusion criteria
  - HIV genotypes 1–6
  - Treatment naive or experienced
  - At least 30% with compensated cirrhosis
  - On stable ART for ≥8 weeks, CD4 cell count ≥100 cells/mm³, and
    HIV RNA ≤50 copies/mL
- Inclusion of non-nucleoside reverse transcriptase inhibitor (NNRTI), integrase inhibitor, and protease inhibitor (PI) regimens with TDF/FTC or ABC/3TC

Results: Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>N=106</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (range)</td>
<td>54 (25–72)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>91 (86)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>48 (45)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (range)</td>
<td>27 (19–43)</td>
</tr>
<tr>
<td>Cirrhosis, n (%)</td>
<td>19 (18)</td>
</tr>
<tr>
<td>Treatment experienced, n (%)</td>
<td>31 (29)</td>
</tr>
<tr>
<td>IL28B CC, n (%)</td>
<td>24 (23)</td>
</tr>
<tr>
<td>Mean HCV RNA, log_{10} IU/mL (range)</td>
<td>6.3 (5.0–7.4)</td>
</tr>
<tr>
<td>HCV genotype</td>
<td>1a / 1b 66 (62) / 12 (11)</td>
</tr>
</tbody>
</table>

Results: HIV Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>N=106</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CD4 count, cells/µL (range)</td>
<td>598 (183–1513)</td>
</tr>
<tr>
<td>ART backbone</td>
<td></td>
</tr>
<tr>
<td>TDF-based with boosted agent (RTV or Cobicistat)</td>
<td>56 (53)</td>
</tr>
<tr>
<td>TDF-based without boosted agent</td>
<td>10 (10)</td>
</tr>
<tr>
<td>ABC/3TC backbone</td>
<td></td>
</tr>
<tr>
<td>ART use combination</td>
<td></td>
</tr>
<tr>
<td>PI (lopinavir/ritonavir)</td>
<td>53 (50)</td>
</tr>
<tr>
<td>NNRTI (efavirenz)</td>
<td>31 (31)</td>
</tr>
<tr>
<td>Integrase inhibitor (raltegravir or elvitegravir)</td>
<td>36 (34)</td>
</tr>
<tr>
<td>Other (at least 1 of the above classes)</td>
<td>7 (7)</td>
</tr>
</tbody>
</table>
Results: SVR12 by Genotype

ASTRAL-5 HIV/HCV Coinfection Study

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Total</th>
<th>1a</th>
<th>1b</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12 (%)</td>
<td>95%</td>
<td>95</td>
<td>92</td>
<td>100</td>
<td>92</td>
<td>100</td>
</tr>
</tbody>
</table>

LTFU, lost to follow-up. Error bars represent 95% confidence intervals.

Results: Renal Function

ASTRAL-5 HIV/HCV Coinfection Study

- Non-boosted TDF
- Boosted TDF
- Non-TDF-containing regimen

Median Creatinine Clearance (mL/min)

- BL: 140
- FU-4: 120
- FU-12: 100

FU-4/12, follow-up Week 4/12; Creatinine Clearance calculated using the Cockcroft-Gault method, errors bars represent Q1, Q3.

High rate of HCV re-infection in HIV/HCV MSM in Western Europe

- 2nd (n=29), 3rd (n=4), and even 4th (n=1) re-infections were seen (2nd: 19.9/100py)
Questions?