Managing HCV in HIV-Infected People

Real-world clinical experiences

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University of California, San Diego
May 2014: I want you to treat my HCV immediately and without shots!

- 54 year old white male, HCV Gt1a, treatment naïve, cirrhosis with portal HTN without prior decompensation. HCV RNA 2.1 million
- EGD 8 months ago: No esophageal varices but portal gastropathy noted
- HIV+ with high degree of resistance on a salvage regimen with tenofovir/emtricitabine (TDF/FTC) daily, raltegravir (RAL) bid and ritonavir-boosted tipranavir bid. Of note, he was taking some of his medications inconsistently: RAL 400mg QD and TDF/FTC 1 tablet Q72hr
- Comorbidities: Mainly liver disease. Also chronic pain due to osteoarthritis of hip and shoulders: Oxycodone CR 20mg /day
Case #1-continued

- Housing: In a transitional home for sober independent living
- Substance/alcohol use: Tested positive for METH 4 months ago
  Drinks socially but sober for the last month
- Denied any depression, and/or related hospitalizations

- Insurance: Medical only (California equivalent of Medicaid)

- Physical exam:
  Normal vital signs. Distant appendectomy scar. Otherwise unremarkable. No evidence of liver stigmata. No skin rash
Significant laboratory tests:

CD4: \textbf{173 (16\%)} and HIV VL < 20 but detectable

\begin{align*}
\text{Na: 135} & \quad \text{BUN: 91} & \quad \text{Glucose: 101} \\
\text{K: 3.6} & \quad \text{Cr: 0.9} & \quad \text{ALT: 127} \\
\text{Hct: 40.5} & \quad \text{WBC: 2.2} & \quad \text{Platelets: 129K} \\
\text{Hb: 14.1} & \quad \text{INR: 1.3} & \quad \text{Albumin: 3.8} \\
\text{Total Protein: 8.1} & \quad \text{71} & \quad \text{CT May 2014: Nodular liver and splenomegaly}
\end{align*}

\text{Calculated Child-pugh score: A6, MELD: 14}
Visit #2: addressing his IFN-free treatment option(s)

- We discussed pros and cons of potential ‘Off label simeprevir and sofosbuvir (SMV/SOF)’ the only viable alternative at the time
- Discussed the need to adjust his antiretroviral regimen and assess his insurance requirements to get HCV medications
- Implications of proposed HCV regimen and need of liver function monitoring
- Encourage him strongly to wait few months for the foreseeable FDA approval of a new fixed-dose ledipasvir/sofosbuvir (LDV/SOF) to treat his HCV. Patient was unwilling to wait
Considerations of HCV and HIV drug interactions:

Viral failure (for both HIV and HCV)

Toxicity (HCV or HIV medications)

CYP P450

Transporters
Simeprevir is a substrate for liver CYP3A & intestinal P-gp and OATP1B1/3 transporters

Current HIV regimen: **TDF/FTC + RAL + tipranavir/ritonavir**

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<thead>
<tr>
<th></th>
<th>Simeprevir</th>
<th>Sofosbuvir</th>
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<tbody>
<tr>
<td>DRV/r</td>
<td>Simeprevir ↑&lt;br&gt; Darunavir ↔</td>
<td>Sofosbuvir ↑&lt;br&gt; Darunavir ↔</td>
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<tr>
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<tr>
<td>TPV/r</td>
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<td>Sofosbuvir ↔&lt;br&gt; Raltegravir ↔</td>
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<td>Tenofovir</td>
<td>Simeprevir ↔&lt;br&gt; Sofosbuvir ↔</td>
<td>Sofosbuvir ↔&lt;br&gt; Tenofovir ↔</td>
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Reality check: available HIV resistance test

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<tr>
<th>DRUG</th>
<th>PHENOSENSE™ SUSCEPTIBILITY</th>
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<tr>
<td><strong>NRTI</strong></td>
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<tr>
<td>Generic Name</td>
<td>Brand Name</td>
<td>Cutoffs (Lower - Upper)</td>
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<tr>
<td>Abacavir</td>
<td>Ziagen</td>
<td>(4.5 - 6.5)</td>
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<tr>
<td>Didanosine</td>
<td>Videx</td>
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<tr>
<td>Emtricitabine</td>
<td>Emtriva</td>
<td>(3.5)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>EpiVIR</td>
<td>(3.5)</td>
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<tr>
<td>stavudine</td>
<td>Zerit</td>
<td>(1.7)</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Retrovir</td>
<td>(1.9)</td>
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<td>Tenofovir</td>
<td>Viread</td>
<td>(1.4 - 4)</td>
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<td><strong>NRTI Mutations</strong></td>
<td></td>
<td>L74L/I/V, V75V/A/I/T, V118I, K219E</td>
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<td><strong>NNRTI</strong></td>
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<td>Delavirdine</td>
<td>Rescriptor</td>
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<td>Efavirenz</td>
<td>Sustiva</td>
<td>(3)</td>
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<td>Nevirapine</td>
<td>Viramune</td>
<td>(4.5)</td>
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<td><strong>NNRTI Mutations</strong></td>
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<td>K101E, Y181Y/C, G190C</td>
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<td><strong>PI</strong></td>
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<tr>
<td>Atazanavir</td>
<td>Reyataz</td>
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<td>Darunavir</td>
<td>Prezista / r</td>
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<td>Fosamprenavir</td>
<td>Lexiva</td>
<td>(2)</td>
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<td>Indinavir</td>
<td>Crizal</td>
<td>(2.1)</td>
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<td><strong>PI Mutations</strong></td>
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<td>L10F, 113V, K20R, L33F, M36I, I50V, L63P, A71V, 82A, L90M</td>
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<td><strong>Lower Clinical Cutoff (in bold)</strong></td>
<td><strong>Evidence of Drug Sensitivity</strong></td>
<td><strong>Highersusceptibility</strong></td>
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<td><strong>Upper Clinical Cutoff (in bold)</strong></td>
<td><strong>Biological Cutoff</strong></td>
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After discussing available HCV treatment options and taking into account his perceptions:

- We decided to apply for SMV + SOF approval
- Once HCV regimen is approved, we will switch his HIV regimen to:
  
  TDF/FTC + DTG + S.Q. T-20 ± DRV/r

- We decided to monitor carefully his liver function given concurrent use of a ritonavir boosted-protease inhibitor
HIV protease inhibitors increase levels of simeprevir: e.g. Darunavir/Ritonavir increases simeprevir exposures 2.6-fold. 

even after reducing the simeprevir dose by 2/3

Ouwerkerk-Mahadaven S, et al. IDWeek 2012
SMV levels ↑ in patients with hepatic impairment—concern is that with concurrent use of an HIV protease inhibitor could be significant.

FIGURE 1: Mean (± SD) plasma concentration-time curves for SMV on Day 7 up to 48 hours post-dose in volunteers with normal hepatic function, moderate hepatic impairment and severe hepatic impairment in this study.

09/2014: Insurance denied all attempts for SMV/SOF coverage and patient left clinic very frustrated.

12/2014: Call back patient to inform him that LDV/SOF was approved by the FDA to treat HCV. No response.
10 February 2015: patient returned for an HIV primary care visit

“ He was seen at an outside facility and was started on SOF/LDV for his HCV 11 days ago. He had previously been seen in the Owen HCV clinic and it is unclear how he established care outside with a private center. His ARVs have not been changed with the initiation of his HCV treatment”
Current HIV regimen: **TDF/FTC + RAL + tipranavir/r**

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<td>Sofosbuvir ↔ Raltegravir ↔</td>
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<td>Ledipasvir ↔ Tenofovir ↑</td>
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In contrast to SMV, Ledipasvir has little to no effect on CYP enzymes. Mostly a weak inhibitor of P-gp and BCRP.

Remember tipranavir: A Significant Inducer in particular at P-gp

The main concern is that Tipranavir, as a strong inducer of P-gp will decrease levels of both sofosbuvir and ledipasvir, and ultimately cause HCV treatment failure.

Given prior interaction considerations we proposed to change his HIV regimen to:

FTC/TDF qday + Dolutegravir 50mg/day + Darunavir 600mg bid, ritonavir 100mg bid + T-20 90mg SC bid
Wouldn’t it be nice if things in clinical practice were as ideal as in a book or a clinical trial report...?

He was told by HCV treating providers to:
A. take half dose of Tipranavir/rit, or
B. D/C all HIV medications. until he finishes HCV therapy. He chose “B”.

Patient called reporting extreme fatigue and feels ready to start new HIV regimen:
TDF/FTC + DTG + DRV/r + T-20

Patient d/c new HIV Meds and decides to re-start his former HIV regimen again!

Calls clinic reporting nausea/vomiting a new skin rash and request to be seen ASAP!

13 Feb 2015
2 March 2015
10 March 2015
20 March 2015
Follow-up & outcomes:

• Discontinuation of tipranavir/r broke its existing steady state that resulted from CYP-450 induction. Following reintroduction of tipranavir/r in the presence of established levels of LDV (a P-gp inhibitor) might have transiently increased tipranavir levels and contributed to his rash.

• Concurrent fungal endemic opportunistic and STD were ruled out with proper work up.

• Rash disappeared 4 days after tipranavir discontinuation.

• Completed 12 weeks of LDV/SOF and achieved HCV SVR-12.

• Patient has remained on TDF/FTC + DTG qday + DRV/r bid. His VL remains < 20 c/mL as of 10/15/2015.
To summarize...

- HIV/Hep C patients commonly have many years since time of infection with extensive HIV medication treatment
  - Associated with HIV drug resistance
  - Associated with greater number of comorbid conditions which increase number of medications increasing the potential for drug interactions
- Drug Interactions and management have become easier in HCV treatment but still exist
  - Multidisciplinary management with active pharmacist involvement will remain important!
Some useful online tools:

• HEPiChart (Liverpool: http://hep-druginteractions.org)
• IAS-USA HCV Resources app.
April 2015: I need your help to get my child back!


- He is HIV+ and treatment experienced on fixed-dose abacavir/lamivudine + atazanavir/r; trying to work on adherence issues

- He has [stage IV CKD](#) suspected due to long-standing hypertension and/or renovascular disease and further aggravated by distinct episodes of acute kidney injuries in the context of methamphetamine intoxication. He takes metoprolol 50mg q12hr + nifedipine 30mg q12hr for HTN.
Case #2-Continued

- Mainly inhales methamphetamine but no intravenous use. Currently assisting outpatient UCSD program. Sober for 70 days.
- Schizoaffective disorder, more stable on Wellbutrin SR 100mg + Zyprexa 7.5mg QHS
- Housing: Currently in recover facility until ~ January 2016.

‘I’m doing all of this for my 2 year old son who is under custody in a state-sponsored foster center in another city’.

**Insurance:** Ryan White

**Physical exam:**
Afebrile, BP 143/89, Pulse 56, Resp 18, Ht 5' 9" (1.753 m), Wt 81.5 kg
Besides a loud S2 his cardiopulmonary exam is unremarkable. He has no evidence of liver stigmata.
Significant laboratory tests as follows:

- **CD4**: 753 (16%) and HIV VL = 140 c/mL

- **Na**: 140
- **K**: 4.9

- **BUN**: 91
- **Cr**: 4.62
- **GFR**: 17 ml/min/1.73m²

- **Glucose**: 101

- **ALT**: 101
- **AST**: 122
- **TB**: 0.9

- **Alk phosp**: 72

- **Hct**: 30.3
- **WBC**: 4.3
- **Platelets**: 208K
- **Hb**: 9.8
- **INR**: 0.9

- **Albumin**: 4.5
- **Total Protein**: 8.2

We ordered an archived HIV genotype test; his HIV medications can be easily switched to abacavir/3TC/dolutegravir. Thus, there are no ARV restrictions for using DAA.
What would you have chosen to manage his HCV considering his CKD, HCV treatment history and personal circumstances?

1. PrOD (paritaprevir /ritonavir /ombitasvir plus dasabuvir) with 200mg RBV thrice weekly for 12 weeks

2. Wait until elbasvir/grazoprevir is approved in early 2016

3. Simeprevir plus sofosbuvir with 200mg RBV thrice weekly for 24 weeks

4. Ledipasvir plus sofosbuvir for 12 weeks with close monitoring
Current AASLD guidelines for treatment of HCV GT1a in people with creatinine clearance <30 mL/min

<table>
<thead>
<tr>
<th>Considerations</th>
<th>HCV regimen</th>
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<tbody>
<tr>
<td>Recommended</td>
<td>Elbasvir (50 mg)/grazoprevir (100mg) for 12 weeks</td>
</tr>
<tr>
<td>Alternative</td>
<td><strong>If Hemoglobin &gt; 10g/dL:</strong> Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with RBV at reduced doses (200 mg thrice weekly to daily) for 12 weeks</td>
</tr>
<tr>
<td>Sofosbusvir-containing regimens</td>
<td>Insufficient safety data</td>
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Available at: http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-renal-impairment
RUBY-I Multicenter, open-label, Phase 3b Study

Open-label Treatment

GT1b
- 3D (n=7)

GT1a
- 3D + RBV (n=13)

Day 1
- Week 12
- Week 24

SVR4

3D: Co-formulated OBV/PTV/r (25/150/100mg QD) and DSV (250mg bid)
- For GT1a: RBV 200mg QD
- For GT1b: No RBV

Pockros P, et al. Safety Of Ombitasvir/Paritaprevir/Ritonavir Plus Dasabuvir For Treating HCV GT1 Infection In Patients With Severe Renal Impairment Or End-stage Renal Disease: The RUBY-I Study. EASL 50th Annual meeting; April 22-26; 2015.
20 patients, majority were male, black race and CKD stage 5, including 14 on hemodialysis.

RUBY-I: ITT and mITT Virologic Response

HCV Gt1a: 11/13 pts achieved SVR12 84.6%

mITT population defines as those with post-treatment data available.

Pockros P, et al. Safety Of Ombitasvir/Paritaprevir/Ritonavir Plus Dasabuvir For Treating HCV GT1 Infection In Patients With Severe Renal Impairment Or End-stage Renal Disease: The RUBY-I Study. EASL 50th Annual meeting; April 22-26; 2015.
8/13 (61.5%) GT1a patients interrupted RBV while on treatment
1 patient had a hemoglobin value < 8 g/dL
No patients had blood transfusions
Of the 8 patients who interrupted RBV, 4 started EPO (week 1-7)
C-SURFER: Grazoprevir plus elbasvir in treatment-naïve and treatment experienced patients with HCV GT1 infection and chronic kidney disease

GZR 100mg/EBR50mg
N = 111

Placebo (n=113)

GZR 100mg/EBR50mg (PK)
n=11

*GZR 100mg/EBR50mg

D1 FW4 FW8 FW12 FW16
TW4 TW8 TW12

GZR = grazoprevir (NS 3/4A inhibitor), EBR = elbasvir (NS5A inhibitor)

Included CKD stage 4/5 (± hemodialysis dependence)
Naïve (80%) and Experienced (20%), compensated cirrhosis (6%)
36% DM2, 75% on hemodialysis

C-SURFER: SVR-12 immediate treatment group

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<tr>
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<th>Modified full Analysis set</th>
<th>Full Analysis set</th>
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<tr>
<td>Relapse</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Discontinue unrelated to Tx</td>
<td>0</td>
<td>6(^{a})</td>
</tr>
</tbody>
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\(^{a}\) = Lost to follow up (2), death (1), non-compliance (1), withdrawal by subject (1), withdrawal by physician due to pt violent behavior (1)

## C-SURFER: AE > 10% & laboratory: well tolerated

<table>
<thead>
<tr>
<th></th>
<th>GZR/EBR (ITG, n=111)</th>
<th>Placebo (DTG, n=113)</th>
<th>Difference in % estimate (95% CI)</th>
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<tbody>
<tr>
<td>AEs n (%)</td>
<td>84 (75.7)</td>
<td>95 (84.1)</td>
<td>-8.3 (-18.9,2.2)</td>
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<tr>
<td>Headache</td>
<td>19 (17.1)</td>
<td>19 (16.8)</td>
<td>0.3 (-9.6,10.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (15.3)</td>
<td>18 (15.9)</td>
<td>-0.6 (-10.3, 9.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (9.9)</td>
<td>17 (15.0)</td>
<td>-5.1 (-141, 3.7)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7 (6.3)</td>
<td>12 (10.6)</td>
<td>-4.3 (-12.2, 3.2)</td>
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<tr>
<td>Dizziness</td>
<td>6 (5.4)</td>
<td>18 (15.9)</td>
<td>-10.5 (-19.1,-2.6)</td>
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<tr>
<td>Diarrhea</td>
<td>6 (5.4)</td>
<td>15 (13.3)</td>
<td>-7.8 (-16.1,-0.2)</td>
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<tr>
<td>Serious AEs, n (%)</td>
<td>16 (14.4)</td>
<td>19 (16.8)</td>
<td>-1.5 (11.2,8.1)</td>
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<tr>
<td>D/c due to AE, n (%)</td>
<td>0 (0)</td>
<td>5 (4.4)</td>
<td>-4.4 (10.0,-1.0)</td>
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<tr>
<td>Deaths, n (%)</td>
<td>1 (0.9)</td>
<td>3 (2.7)</td>
<td>-1.8 (-6.7, 2.5)</td>
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<tr>
<td>ALT &gt; 2.5 -5.5x baseline</td>
<td>1 (0.9)</td>
<td>6 (5.3)</td>
<td>-4.4 (-10.3,-0.2)</td>
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<td>AST &gt; 2.5 x baseline</td>
<td>0 (0)</td>
<td>4 (3.5)</td>
<td>-4.6 (-11.3, -0.2)</td>
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<tr>
<td>Bilirubin &gt; 2.5-5x baseline</td>
<td>1 (0.9)</td>
<td>3 (2.7)</td>
<td>-1.8 (-6.7, 2.5)</td>
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1 SAE in the ITG group was considered drug-related (elevated lipase). 1 ITG patient died of cardiac arrest and 3 DTG patients died of Aortic aneurysm, pneumonia and unknown cause.  

Experience with SMV-SOF in CKD stage 4/5

• All patients were treated with SOF 400mg/day and SMV 150mg/day for 12 weeks.
• Overall well tolerated with no treatment discontinuations.
• Four (24%) patients reported mild adverse events: insomnia (n=2), headache (n=1), nausea (n=1), and worsening anemia requiring blood transfusion (n=1).
• All 17 patients reached SVR12

Nazario et al. Liver Int. 2015 [Epub ahead of print]
Our issue: Cross-resistance is widespread among NS3/4A protease inhibitors

### NS3 protease 180AA

**Boceprevir**

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**Telaprevir**

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**Simeprevir**

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**Paritaprevir**

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Sofosbuvir

Plasma

GS-566500

GS-606965

GS-331007

EXCRETED IN URINE

Hepatocyte

Sofosbuvir

GS-566500

GS-461203

GS-606965

GS-331007

ACTIVE FORM

hCE1, CatA

HINT1

SOF in renal impairment

Figure 1. Mean GS-331007 Concentration vs Time in Subjects with Normal Renal Function and All Renal Impairment Groups

Observations in Phase I studies in healthy volunteers

• At a dose three times the maximum recommended dose, Sofosbuvir does not prolong QTc to any clinically relevant extent.
• The highest documented dose of sofosbuvir was a single supratherapeutic dose of sofosbuvir 1200 mg administered to 59 healthy subjects. In that trial, there were no untoward effects observed at this dose level, and adverse events were similar in frequency and severity to those reported in the placebo and sofosbuvir 400 mg treatment groups. The effects of higher doses are not known.
• A 4-hour hemodialysis session removed 18% of the administered dose.

Available at: http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf
Downloaded 28 Feb 2016.
HCV TARGET: SVR-12 by baseline eGFR

Saxena V, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C infected patients with reduced renal function: real-world experience from HCVTARGET. EASL 50th Annual Meeting; April 22-26, 2015;
Our options placed in perspective:

• GZB + EBV → Ideal. Safe, effective (94%) but not available at the time. Unsure timeliness of coverage by his insurance. Theoretical: what is the role of cross-resistance with GZB?

• SMV+SOF → Some clinical evidence of efficacy and safety but concerns with HCV PI cross-resistance.

• ProD +RBV → Concern with anemia and RBV tolerability. Cross-resistance with paritaprevir?

• LDV/SOF → Unknown safety, but used by early reports arising documenting 88% efficacy and no major safety issues.

• His insurance would not cover any HCV resistance test.
Conversation with clear description of risks, ‘knowns’ and ‘unknowns’:

• Patient chose to start LDV/SOF right away
• Patient agreed to:
  - Weekly clinical and laboratory monitoring
  - Labs include CMP, CBC, EKG, lipase, uric acid, lactate, CPK and any symptom-driven work-up
Week 4 of therapy: Feels great but...

- **CPK:** 4,277 (Baseline 392 June 2014) Normal: 0-175 U/L
- **Aldolase:** 23.7 (no prior baseline), normal: 1.5-8.1 U/L

<table>
<thead>
<tr>
<th>Na: 139</th>
<th>Cl: 100</th>
<th>BUN: 50</th>
<th>Glucose: 66</th>
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<tr>
<td>K: 4.2</td>
<td>HCO₃: 25</td>
<td>Cr: 5.21</td>
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**Urine toxicology:** negative

- **Anion GAP:** 14
- **GFR:** 14 ml/min/1.73m²

- Concern with rhabdomyolysis and accelerating need for hemodialysis
- On further questioning, he had 2 prior episodes of AKI and mild rhabdomyolysis when admitted with acute methamphetamine intoxication in 2013 (CPK peak 4,916 U/L)
Clinical approach and follow-up

• Nephrology consult: ‘Instruct hydration with 2L oral fluid daily and continue HCV medications with close monitoring, as long as CPK below 10,000, low risk of tubular precipitation’

• Muscle enzymes peaked at week 12 of LDV/SOF: CPK 6,109 and aldolase 26.4 U/L. Patient remained asymptomatic. No change in acid-base status or urinary output. Creatinine and GFR were 5.0 and 15, respectively

• 16 February 2016. Patient achieved SVR12. At the same time his CPK and aldolase levels were normalizing: 943 and 5.8 U/L, respectively

• 1 March 2016: Considering his accomplishments, the court granted him a 6-month trial to look after his son. They have been reunited
To summarize ...#2

• Although clinical safety data of Sofosbuvir in patients with advanced renal disease remains limited, there are emerging cohort experiences of treatment success e.g. TARGET

• Our patient had significant asymptomatic CPK elevations without further renal function deterioration. However, it required intense close clinical monitoring. CPK values were normalizing 3 months after sofosbuvir-based treatment discontinuation

• It is unknown if a prior episode of rhabdomyolysis increases risk of muscle enzyme elevation as observed in our case
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