Financial Relationships With Commercial Entities

- Dr Marks was awarded research grants, paid to her institution, from Gilead Sciences, Inc, and Merck & Co, Inc. (Updated 11/4/16)

Learning Objectives

After attending this presentation, participants will be able to:

- Describe the options for initial treatment of hepatitis C virus (HCV) infection
- Describe when resistance testing should be done prior to initial treatment
- Describe current approaches to posttreatment monitoring
Newer strategy for HCV therapy: Direct acting antivirals target life cycle

---

- **PIs (Protease inhibitors)**
  - e.g. telaprevir, boceprevir, faldaprevir, simeprevir, danoprevir, asunaprevir, paritaprevir, grazoprevir, voxilaprevir

- **NUCs (Polymerase inhibitors)**
  - Nucleos(t)ide analogs: e.g. tegobuvir, sofosbuvir
  - Non-nucleoside: e.g. deleobuvir, dasabuvir

---

Currently used combinations of DAA classes

- **NUC + PI + RBV**
  - **NUC SPARING HCV**
    - Affordability
    - Provider preference
    - Refined insufficiency
    - Drug-drug interactions
  - **NUC SPARING RBV**
    - Toxicity
    - Resistance
    - Affordability

- **NUC + NS5A + RBV**
CASE
64 y.o. African American W with HIV, HCV Geno 1b and cirrhosis, HCV RNA 88,000 IU/mL

HCV Hx:
Treatment naive
Cirrhotic based on Bi 8 yrs ago
Transient Elastography 22 kPa
No decompensation events
EGD no varices
MRI no HCC
HIV Hx: CD4 264, HIV RNA UD, doing well on TDF/FTC + darunavir/r

Other med hx includes:
- HBVsAg+, eAb+ with HBV DNA not detected (had been elevated in distant past)
- HTN, high cholesterol, renal insufficiency (CrCl 45), past h/o heavy ETOH (none x 8 yrs)

LET'S CHOOSE AN HCV REGIMEN

Q1. Prior to HCV treatment she needs a switch in her ARVs for optimal management with most available HCV regimens. Which of the following switches should NOT be made in this patient?

1. TDF to TAF
2. TDF/FTC to ABC/3TC
3. Darunavir/r to dolutegravir
4. All of the above are fine

Q2. Testing for HCV resistance (RAVs) would be indicated in this patient with HIV/HCV geno 1b if...

1. She had failed PegIFN + RBV in the past
2. You plan to treat with sofosbuvir/velpatasvir
3. You plan to treat with grazoprevir/elbasvir
4. Nope! Resistance testing is not necessary here
5. Hmmm... What's a RAV?
Q3. A regimen with an 8 week duration SHOULD be used for this patient. (Because it is effective and it saves money.)

1. TRUE
2. FALSE

Minimum to Know Pre-Treatment

- HCV genotype/subtype
- HCV resistance (sometimes)
- Stage of fibrosis
  - Cirrhosis: yes/no
  - If yes, compensated? [e.g., ascites, encephalopathy, etc]
- Method?
  - Liver biopsy
  - Transient elastography
  - Laboratory biomarkers
  - Imaging
- Prior HCV treatment?
- Response?
- DAA used?

Medications
- To check for drug interactions
- Interferon, "eligibility," and/or willingness
- Comorbidities
  - Renal function
  - HIV status
- Patient preference
- Child-bearing potential of patient/partner
  - Ribavirin is a teratogen

HIV/Hepatitis C helpline
1-866-637-2342

Approved Drug Regimens
G1b vs G1a:
G1b Initial Treatment Recommended Regimens

IDSA/AASLD
www.hcvguidelines.org

**NO CIRRHOSIS:**
- Elbasvir/grazoprevir x 12 w
- Ledipasvir/sofosbuvir x 12w
- Paritaprevir/ritonavir/ombitasvir + dasabuvir x 12w
- Sofosbuvir/velpatasvir x 12 wks

**CIRRHOSIS:**
- Elbasvir/grazoprevir x 12 w
- Ledipasvir/sofosbuvir x 12w
- Paritaprevir/ritonavir/ombitasvir + dasabuvir + RBV x 12w*
- Sofosbuvir/velpatasvir x 12 wks

*Based on TURQUOISE-3 study results of PO4 w/o RBV - 100% SVR12 in G1b + cirrhosis

(BOLDED are regimens approved since last year!)
Elbasvir/grazoprevir x12w Results

- Overall study 95% SVR
- 144/157 (92%) G1a, 129/131 (99%) G1b, 18/18 G4, 8/10 G6
- 68/70 (97%) with cirrhosis

Baseline NS5A RAVs & SVR

<table>
<thead>
<tr>
<th>Population</th>
<th>Overall SVR</th>
<th>NS5A RAVs</th>
<th>NS5A RAVs with v1Aa</th>
<th>NS5A RAVs with v1Ac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>92/100 (92%)</td>
<td>89/95 (93%)</td>
<td>11/15 (73%)</td>
<td>11/15 (73%)</td>
</tr>
<tr>
<td>G1a</td>
<td>117/125 (94%)</td>
<td>111/119 (94%)</td>
<td>16/17 (94%)</td>
<td>16/17 (94%)</td>
</tr>
<tr>
<td>G1b</td>
<td>102/112 (91%)</td>
<td>96/103 (91%)</td>
<td>6/7 (86%)</td>
<td>6/7 (86%)</td>
</tr>
<tr>
<td>G4</td>
<td>18/18 (100%)</td>
<td>18/18 (100%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
</tr>
<tr>
<td>G6</td>
<td>8/10 (80%)</td>
<td>4/7 (57%)</td>
<td>1/3 (33%)</td>
<td>1/3 (33%)</td>
</tr>
</tbody>
</table>

RAV Testing prior to Treatment

- NS5A RAVs are relatively common (10-15%)
- Significance of NS5A RAVs may depend on the RAV, the genotype, the regimen used and whether prior NS5A treatment
- Use resistance testing prior to:
  - Treatment with grazoprevir/elbasvir for 1a
  - Treatment of G3 if cirrhosis
  - (DAA experienced)

What about 8 wk regimens?

Minimum criteria to be eligible:
- no cirrhosis, VL < 6mil, initial treatment

- Preliminary real-world (non-randomized) cohort data show conflicting results on the comparable effectiveness of 8 and 12 weeks in treatment-naive patients without cirrhosis.
- Based on available data, shortening treatment to less than 12 weeks is Not Recommended for HIV-infected patients, African-American patients, or those with known IL28B polymorphism CT or TT.
- For others, it should be done at the discretion of the practitioner.
Daclatasvir + Sofosbuvir x 8 or 12 wks in HIV/HCV

Wyles, NEJM, 2015

Sofosbuvir/velpatasvir x 12 wks in HIV/HCV
G1-6, Naive + Rx-exp

Wyles, EASL, 2016

N=106
20% Rx-exp
18% cirrhosis
12% NS5a RAVs
Of 2 relapses:
1 m-exp, D viremia, D baseline RAVS
Renal function unchanged in pts on boosted TDF

N=106
29% Rx-exp
18% cirrhosis
12% NS5a RAVs
Of 2 relapses:
1 m-exp, 0 m-cirrhosis, 0 baseline RAVS
Renal function unchanged in pts on boosted TDF

New York, New York: November 4, 2016
Drug-Drug Interactions with DAAS

- Acid-reducing drugs
- Anti-epileptics
- Antiretrovirals
- Amiodarone
- Lipid-lowering drugs

http://www.hep-druginteractions.org/

With SOF/LDV, TFV exposures are high in those on PIs

NRTI's

RTV-Boosted PIs

Range of TFV exposures with available safety data

- PIs exposures are higher when TFV is coadministered with a PIs/PIb compared to without a PIs/PIb, but
- Compared to the range of TFV exposures with available safety data
- For PIs or RTV; PIs exposures fall within the range
- For RTV-boosted PIs, PIs exposures partially exceed the range

Guidelines Recommendation about use of LDV or VEL with TDF

- SOF/LDV + TDF
  - CrCl < 60 mL/min: AVOID
  - CrCl > 60: MONITOR
- SOF/VEL + TDF
  - CrCl < 60 mL/min: AVOID
  - CrCl > 60: MONITOR
- SOF/LDV + TDF + cobi- or ritonavir-boosted PI
  - Any CrCl: AVOID if possible, consider TAF
- SOF/VEL + TDF + cobi- or ritonavir-boosted PI
  - CrCl < 60 mL/min: AVOID
  - CrCl > 60: MONITOR or consider TAF

* For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended. Rating: Class IIa, Level C.
TAF – Possible TDF Alternative in Patients on Cobicistat and Ritonavir

* TFV was increased by SOF/LDV in those on F/TAF/ELV/cobi by 27%, but TFV AUC with TAF only ~20% of AUC typically seen with TDF (~400 vs. 2000 ng*hr/mL).

Slide courtesy of J Kiser

G4 INITIAL TREATMENT RECOMMENDED REGIMENS

IDSA/AASLD

Grazoprevir/elbasvir x 12w
Ledipasvir/sofosbuvir x 12w
Paritaprevir/ritonavir/ombitasvir + RBV x 12w (note NO DASABUVIR)
Sofosbuvir/velpatasvir x 12w
Sofosbuvir + RBV x 24w

G2 INITIAL TREATMENT RECOMMENDED REGIMENS

IDSA/AASLD

NO CIRRHOSIS:
Sofosbuvir/velpatasvir x 12 wks
Sofosbuvir + RBV x 12w
Sofosbuvir + deoxycytidine x 12w if cannot tolerate RBV

CIRRHOSIS:
Sofosbuvir/velpatasvir x 12 wks
Sofosbuvir + RBV x 24w
Sofosbuvir + deoxycytidine x 12-24w if cannot tolerate RBV
**Sofosbuvir/velpatasvir x 12 wks for G2 (ASTRAL-2)**

14% cirrhosis
14-15% Rx-exp

**G3 INITIAL TREATMENT RECOMMENDED REGIMENS**

NO CIRRHOSIS:
- Sofosbuvir + daclatasvir x 12 w
- Sofosbuvir/velpatasvir x 12 w
- Sofosbuvir + PegIFN+ RBV x 12w

CIRRHOSIS:
- Sofosbuvir/velpatasvir x 12 w*
- Sofosbuvir + daclatasvir +/-RBV x 24w*
- Sofosbuvir + PegIFN+ RBV x 12w

*RAV testing for Y93H
and add RBV if present

**Sofosbuvir + Daclatasvir for G3 (ALLY-3)**

All-Oral 12-week Combination of Daclatasvir and Sofosbuvir in Patients with Genotype 3: ALLY-3

- Key demographics: Cirrhosis 31%, Prior Sof failure = 7%
- 0 DAs related to treatment, 5 AE causing DIs of treatment
- Most AE mild fatigue, headache, nausea, diarrhea
- Relapse occurred in 16/102 (16%), most relapses were cirrhotic

Sofosbuvir/velpatasvir x 12 wks for G3 (ASTRAL-2)

Most of the 1% with cirrhosis

Foster, NEJM, 2015

FDA Drug Safety Communications: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C

2013-16 FDA ADverse event reporting
- 24 cases HBV reactivation associated with DAA treatment
- 3 decompensated – 2 died, 1 transplant. Delays in diagnosis and treatment.
- Most wks 4-8 of treatment

Who’s at risk:
- 7 had detectable HBV at baseline
- 4 sAg+ and undetectable HBV DNA
- 1 sAg- and undetectable HBV DNA
- 10 unknown

[风险: sAg+ DNA+/ > sAg- cAb+ sAb- > sAg- cAb+ sAb+]
No risk: sAg- cAb- sAb+

Screen at HBsAg and anti-HBc. In patients with serologic evidence of HBV infection, measure baseline HBV DNA prior to DAA treatment.

Monitor patients who show evidence of current or prior HBV infection for clinical and laboratory signs (i.e., HBsAg, HBV DNA, serum aminotransferase levels, bilirubin) of hepatitis flare or HBV reactivation during DAA treatment and posttreatment follow-up.

Counsel patients to contact health care professional immediately if they develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools, as these may be signs of serious liver injury.

Q1. Prior to HCV treatment she needs a switch in her ARVs for optimal management with most available HCV regimens. Which of the following switches should NOT be made in this patient?

1. TDF to TAF
2. TDF/FTC to ABC/3TC
3. Darunavir/r to dolutegravir
4. All of the above are fine

New York, New York: November 4, 2016
Q1. Prior to HCV treatment she needs a switch in her ARVs for optimal management with most available HCV regimens. Which of the following switches should NOT be made in this patient?

- TDF to TAF: 4%
- TDF/FTC to ABC/3TC: 1%
- Darunavir/r to dolutegravir: 2%
- All of the above are fine: 27%
- All of the above are not fine: 5%

Q2. Testing for HCV resistance (RAVs) would be indicated in this patient with HIV/HCV geno 1b if...

- She had failed PegIFN + RBV in the past: 11%
- You plan to treat with sofosbuvir/velpatasvir: 43%
- You plan to treat with grazoprevir/elbasvir: 43%
- Nope! Resistance testing is not necessary here: 12%
- Hmmm... What's a RAV? 0%
Q3. A regimen with an 8 week duration SHOULD be used for this patient. (Because it is effective and it saves money.)

1. TRUE
2. FALSE

After Successful Treatment:
- Manage liver disease
- Monitor for HBV reactivation (sAg+ > cAb+)
- HCCs expected (continue screening)
- Reinfections expected (e.g. MSM)
Acute HCV treatment in HIV+ MSM

- LDV x SOF x 6wks (n=26)
  - 69% 1a, 31% G4
  - Any ARVs

- SVR4 85%, SVR12 77%
  - 4 failures, 2 LTFU by wk 12

- Relapses with High baseline RNA

- 1 reinfection by Wk 12

COMING SOON results from ACTG 5327: SOF/LDV x 8 wks for acute HCV in HIV-infected persons

---

Is this as good as it gets?

- Treatment coverage inadequate
- Shorter treatment
  - Triples coming... e.g. SOF/VEL/voxilaprevir
  - Do we need them for initial treatment?
- Long–acting formulations
  - Will PEP for HCV ever make sense?

---

Summary

- Remarkable advances in terms of HCV treatment tolerability & efficacy
  - SVRs for HCV now mirror monoinfection
  - Continued refinement of therapies without significant drug interactions & those that can be used in varied populations (ESRD, G3+cirrhosis, acute HCV, etc)
  - Successful treatment prevents cirrhosis, end stage liver disease, and hepatocellular cancer
- Post SVR – continue liver disease management and consider HCV screening
Resources

- HCVguidelines.org
- nynjaetc.org
- http://www.hep-druginteractions.org

Thank you