Staging liver disease

- A hepatologist, ID doc, primary care provider, and insurance executive go to a bar…
Staging liver disease

- A hepatologist, ID doc, primary care provider, and insurance executive go to a bar…
- to discuss whether a 58 year old HCV infected woman with well controlled HIV has cirrhosis.
Which is right?

1. The hepatologist says she can’t have cirrhosis because he did a biopsy 2 years earlier that was F2
2. The ID doctor says she has to have cirrhosis because her elastography is 12.5 kPa
3. Her primary care practitioner says she probably has cirrhosis because her Fib-4 is 5.2 and she’s HIV pos
4. Her insurance executive says it doesn’t matter because she can’t have the meds anyway
Liver disease staging is a necessary inexact art

- Stage to detect cirrhosis and get approvals
Liver disease staging is a necessary inexact art

- Stage to detect cirrhosis and get approvals
- 3 approved tests are liver biopsy, blood fibrosis tests, and elastography
Liver disease staging is a necessary inexact art

High sensitivity for excluding cirrhosis is with FIB-4 plus transient elastography

<table>
<thead>
<tr>
<th>Cutoff Level (kPa)</th>
<th>$\geq 11.8$</th>
<th>$\geq 14.5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>False positive</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>True negative</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>False negative</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100 (80.5–100)</td>
<td>88.2 (63.6–98.5)</td>
</tr>
<tr>
<td>Specificity</td>
<td>92.7 (82.4–98.0)</td>
<td>96.4 (87.5–99.6)</td>
</tr>
<tr>
<td>PPV</td>
<td>81 (58.1–94.6)</td>
<td>88.2 (63.6–98.5)</td>
</tr>
<tr>
<td>NPV</td>
<td>100 (93–100)</td>
<td>96.4 (87.5–99.6)</td>
</tr>
<tr>
<td>PLR</td>
<td>13.8 (5.35–35.3)</td>
<td>24.3 (6.2–95.6)</td>
</tr>
<tr>
<td>NLR</td>
<td>0</td>
<td>0.12 (0.03–0.45)</td>
</tr>
</tbody>
</table>

de Ledinghen et al. JAIDS 2006
Elastography also can tell you something about how bad the cirrhosis is

Complications of cirrhosis among 144 with F3-4

\[
\begin{align*}
y &= 1.5952x + 2.037 \\
r^2 &= 0.61 \\
p &< 0.0001
\end{align*}
\]
Liver disease staging is a necessary inexact art

- High sensitivity for excluding cirrhosis is with FIB-4 plus transient elastography

<table>
<thead>
<tr>
<th>FIB4 Index</th>
<th>F0-F1-F2</th>
<th>F3-F4</th>
<th>Total</th>
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<tbody>
<tr>
<td>&lt;1.45</td>
<td>94.7% (n = 521)</td>
<td>5.3% (n = 29)</td>
<td>550</td>
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<tr>
<td>1.45-3.25</td>
<td>73.0% (n = 168)</td>
<td>27.0% (n = 62)</td>
<td>230</td>
</tr>
<tr>
<td>&gt;3.25</td>
<td>17.9% (n = 12)</td>
<td>82.1% (n = 55)</td>
<td>67</td>
</tr>
<tr>
<td>Total</td>
<td>82.8% (n = 701)</td>
<td>17.2% (n = 146)</td>
<td>847</td>
</tr>
</tbody>
</table>

Sterling Hepatology 2006; Vallet-Pichard
Hepatology 2007
Liver disease staging is a necessary, inexact art

- Stage to detect cirrhosis and get approvals
- Blood tests and elastography (or biopsy)
- High sensitivity for excluding cirrhosis with FIB-4 plus transient elastography
- When discrepant use higher
- MRE terrific but expensive
- Vibration-controlled equivalent to transient elastography and gives US to rule out HCC
Highest-paid insurance executives

Salary: $1,000,000
Stock awards: $3,575,396
Nonequity incentive: $7,347,200
Other: $514,354
Total: $12,436,950
Change: (22.9%)
Question 2

Your patient is on elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate and presents for initial treatment of 1b HCV infection with F0 disease. She has a GFR of 32/min. Which option would you choose:

1. Elbasvir and grazoprevir
2. Sofosbuvir, velpatasvir, and voxilaprevir
3. Sofosbuvir and ledipasvir
4. Glecaprevir and pibrentasvir
5. Change ART
HCV treatment can vary
HCV treatment in the HIV infected person

• No differences (no 8 week SOF/LDV)
HCV treatment in the HIV infected person

- No differences (no 8 week SOF/LDV)
- Drug interactions
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir (RAL)</td>
<td>▶️ LDV ▶️ RAL</td>
<td>▶️ VEL ▶️ RAL</td>
<td>▶️ ELB ▶️ GRZ ▶️ RAL</td>
<td>▶️ GLE ▶️ PIB ▶️ RAL</td>
<td>ND</td>
</tr>
<tr>
<td>Cobicistat-boosted elvitegravir (COB)</td>
<td>▲ LDV ▲ COB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>▲ VEL ▲ COB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>▲ ELB ▲ GRZ ▲ COB</td>
<td>▲ GLE ▲ PIB ▲ COB</td>
<td>▲ VOX ▲ COB&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dolutegravir (DTG)</td>
<td>▶️ LDV ▶️ DTG</td>
<td>▶️ VEL ▶️ DTG</td>
<td>▶️ ELB ▶️ GRZ ▶️ DTG</td>
<td>▶️ GLE ▶️ PIB ▶️ DTG</td>
<td>ND</td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td>▶️ LDV ▶️ RPV</td>
<td>▶️ VEL ▶️ RPV</td>
<td>▶️ ELB ▶️ GRZ ▶️ RPV</td>
<td>▶️ GLE ▶️ PIB ▶️ RPV</td>
<td>▶️ VEL ▶️ VOX ▶️ RPV</td>
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<td>---------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>▲ LDV ▲ RAL</td>
<td>▲ VEL ▲ RAL</td>
<td>▲ ELB ▲ GRZ</td>
<td>▲ GLE ▲ PIB</td>
<td>ND</td>
</tr>
<tr>
<td>Cobistat-booster elvitegravir (COB)</td>
<td>▲ LDV ▲ COB^a</td>
<td>▲ VEL ▲ COB^a</td>
<td>▲ ELB ▲ COB</td>
<td>▲ GLE ▲ COB</td>
<td>▲ VOX ▲ COB^a</td>
</tr>
<tr>
<td>Dolutegravir (DTG)</td>
<td>▲ LDV ▲ DTG</td>
<td>▲ VEL ▲ DTG</td>
<td>▲ ELB ▲ GRZ</td>
<td>▲ GLE ▲ PIB</td>
<td>ND</td>
</tr>
<tr>
<td>Tenofovir (TFV) disoproxil fumarate</td>
<td>▲ LDV ▲ TFV^c</td>
<td>▲ VEL ▲ TFV</td>
<td>▲ ELB ▲ GRZ</td>
<td>ND</td>
<td>▲ TFV^b</td>
</tr>
<tr>
<td>Tenofovir (TFV) alafenamide</td>
<td>▲ LDV ▲ TFV^d</td>
<td>▲ VEL ▲ TFV^d</td>
<td>ND</td>
<td>▲ GLE ▲ PIB</td>
<td>▲ TFV^b</td>
</tr>
<tr>
<td>HIV Drug Combination</td>
<td>Ledipasvir/ Sofosbuvir (LDV/SOF)</td>
<td>Sofosbuvir/ Velpatasvir (SOF/VEL)</td>
<td>Elbasvir/ Grazoprevir (ELB/GRZ)</td>
<td>Glecaprevir/ Pibrentasvir (GLE/PIB)</td>
<td>Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)</td>
</tr>
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<td>---------------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Ritonavir-boosted atazanavir (ATZ)</td>
<td>▲ LDV ▲ ATZ&lt;sup&gt;a&lt;/sup&gt;</td>
<td>▲ VEL ▲ ATZ&lt;sup&gt;a&lt;/sup&gt;</td>
<td>▲ ELB ▲ GRZ ▲ ATZ</td>
<td>ND</td>
<td>▲ ATZ</td>
</tr>
<tr>
<td>Ritonavir-boosted darunavir (DRV)</td>
<td>▲ LDV ▲ DRV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>▲ VEL ▲ DRV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>▲ ELB ▲ GRZ ▲ DRV</td>
<td>ND</td>
<td>▲ VOX ▲ DRV</td>
</tr>
<tr>
<td>Ritonavir-boosted lopinavir (LPV)</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt; ▲ VEL ▲ LPV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>▲ ELB ▲ GRZ ▲ LPV</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Ritonavir-boosted tipranavir (TPV/r)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>▼ LDV ▼ EFV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>▼ VEL ▼ EFV</td>
<td>▼ ELB ▼ GRZ ▼ EFV</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>
Management of Unique Populations

The following pages include guidance for management of unique populations.

- Patients With HIV/HCV Coinfection
- Patients With Decompensated Cirrhosis
- Patients Who Develop Recurrent HCV Infection Post Liver Transplantation
- Patients With Renal Impairment
- Kidney Transplant Patients
- Management of Acute HCV Infection
- HCV in Pregnancy
- HCV in Children
HCV treatment with cirrhosis

- F3 or F4
HCV treatment with cirrhosis

- F3 or F4
- G/P is always 12 (vs 8) weeks

Forns Lancet ID 2017

N=146
HCV treatment with cirrhosis

- F3 or F4
- G/P is always 12 (vs 8) weeks
- Screen HCC and varices
HCV treatment with cirrhosis

- F3 or F4
- G/P is always 12 (vs 8) weeks
- Screen HCC and varices
- Treatment helps with decompensation (CAUTION)
HCV treatment in persons with decompensated cirrhosis

Study Design: SOLAR-1 and SOLAR-2

Pretransplant
- CPT B (7–9)
- CPT C (10–12)
- Fibrosis (F0–F3)
- CPT A (5–6)
- CPT B (7–9)
- CPT C (10–12)
- FCH

Posttransplant
- LDV/SOF + RBV

SVR12

CPT, Child-Pugh-Turcotte; FCH, fibrosing cholestatic hepatitis; SVR12, sustained virologic response 12 wk after treatment end.

Manns Lancet ID 2016; Charlton Gastro 2015
Change in MELD score baseline to post treatment week 12 in those with SVR

Pre-transplant
Recommendation 2.1
We suggest that HCV-infected patients with decompensated cirrhosis with CTP Class B and/or MELD less than 20 on the waiting list for liver transplantation, who are without refractory portal hypertensive symptoms or other conditions requiring more immediate transplantation, should be treated with antiviral therapy.
Q3. Which is right?

Which regimen is recommended for a patient with cirrhosis and HCV genotype 1a with GFR of 15/min?

1. Elbasvir/grazoprevir x 12 wks
2. Glecaprevir and pibrentasvir x 8 wks
3. Sofosbuvir and ledipasvir x 12 wks
4. Sofosbuvir and ribavirin x 24 wks
Management of Unique Populations

The following pages include guidance for management of unique populations.

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- HCV in Pregnancy
- HCV in Children
Grazoprevir/Elbasvir in genotype 1 or 4 and ESRD: C-SURFER

- 73% male, 46% AA, 80% naïve, 52% 1a, 6% cirrhosis
- 81% CKD stage 5 (GFR <15 or HD)
- 6 stopped treatment early + 11 in pK group (mITT N=116)

Roth Lancet 2015
Grazoprevir/Elbasvir in genotype 1 or 4 and ESRD: C-SURFER

- No serious drug related AE
- NS5 RAS in 17 (14.8%)
- ITT SVR12 – 115/122 (94%)
- 1 relapse in 1b with L31M baseline
- RAS testing not recommended

Roth Lancet 2015
Glecaprevir and pibrentasvir for 12 weeks in patients with stage 4-5 renal impairment

**EXPEDITION 4**

- N=104, 19% F4
- 82% dialysis
- GT1=54; GT2=17; GT3=11; GT4=20; GT5/6=2
- NS5A RAS 24/96
- No serious drug-related AE
- No relapse
- REC same as not ESRD

**% SVR 12**

<table>
<thead>
<tr>
<th>% SVR 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
</tr>
</tbody>
</table>

Source: NEJM 2017
Treatment of patients with renal insufficiency

• When should you treat?
Treatment of patients with renal insufficiency

• When should you treat?

HCV treatment can vary...
Treatment of acute hepatitis C

• How?
  - Treat the same as with chronic hepatitis C
Treatment of acute hepatitis C

How?
- Treat the same as with chronic hepatitis C
- Can it be shorter?
  - 63 with acute HCV (<24 weeks)
  - All but 3 HIV pos; GT 1 or 4
  - Single arm open label, grazoprevir/elbasvir qd for 8 weeks
  - SVR 12 in 52/53

Boerekamps CROI 2018; Abstract 128
Treatment of acute hepatitis C

• How?
  - Treat the same as with chronic hepatitis C
  - Can it be shorter?
    - 27 HIV infected with acute hepatitis C treated with 8 weeks of SOF/LDV
    - 100% SVR12

Naggie AASLD 2017; Abstract 196
Treatment of acute hepatitis C

- How?
  - Treat the same as with chronic hepatitis C

- When/whom?
  - not acute any more (6 months)
  - not likely to clear (HIV pos, IFNL4, male, Black, stable high HCV RNA)
  - might transmit
HCV is growing problem in pregnancy

Number of reported cases of HCV among women in the USA

“estimated 29,000 women who gave birth to 1700 infants with HCV infection each year”
HCV infection is growing problem in pregnancy

- Risk of mother infant transmission is 4-8% if HIV neg and 10-20% if HIV positive
- DAAs not known to be harmful to fetus
- No recommendation for routine testing
- No recommended prevention
  - No C section or maternal or infant treatment
- Test infants born to HCV pos moms
Treatment of the patient over 65 years of age is fine

- Pooled analysis of G/P in 328 >65 yrs vs 2041 <65 yrs
  - No difference in adverse events
  - SVR12 was 97.9% >65 yrs vs 97.3 in <65 yrs
Summary of HCV management

- List the 3 approved methods of liver staging
- Identify the top interactions between HCV and HIV drugs
- List the medications that are approved to treat HCV in renal disease
- Compare treatment of HCV in persons with cirrhosis to those without
Question-and-Answer
Changes

- Slide 1: added “Virus (HCV)” after Hepatitis C, updated degrees (MPH)
- Slide 3: “Top interactions” to “most important interactions”
- Slide 6: Inserted “care practitioner” after “primary”, deleted “who”
- Slide 28: Rephrased “which of the following regimens” to “which regimen”, added slash (“Elbasvir/grazoprevir”)
- Slide 36-39, 42: increased font size