Overview of Hepatitis B & C: Current Concepts and Changing paradigms

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Disclosures
I have received research grant support to UCSF related to HCV from the following:
• AbbVie
• Gilead
• Merck
• ACTG (NIH)

Overview

• HCV
  – Screening and selection of patients to treat
  – Changing treatment landscape
• HBV
  – HBV treatment
  – HBV reactivation
  – New HBV agents
• HCC screening

Your patient

• 49 yo man, HCV Ab+, establishing care with you
• PMH: depression
• Meds: paroxetine, Methadone maintenance x 3 years with intermittent IDU and smoked methamphetamine
• Social history
  – Prior IDU heroin
  – Alcohol- few beers/day, binge drinks on occasion
  – Sexually active with men (MSM), condoms use inconsistent
HCV Ab+: next steps

- Confirm viremia with HCV RNA
- Screen and vaccinate if indicated for HAV & HBV
- Reduce alcohol consumption
- Reduce forward transmission risk
  - Drug use – avoid sharing needles or nasal straws
  - Sexual counseling: MSM or HIV infected partner
  - Household precautions: no shared toothbrushes or razor
- Fibrosis Assessment: serologic markers (ex: APRI, Fibrotest) and/or imaging
  - Impacts decision to screen for HCC and varices
  - Affects treatment response, choice of therapy, and treatment initiation timeline
- HCV Genotype: 1-6, determines choice of therapy (for now)

Case #1 continued

- HCV RNA: 3 million IU/ml
- Genotype 1a
- AST 35/ALT 33 Alb 3.9. INR 1.1 Platelets 210
- HIV Ab negative
- APRI= 0.4 (suggests non-cirrhotic)
- HAV Immune
  - Hep B S Ab neg, S Ag neg, Core Ab Positive
- Ultrasound: no evidence of cirrhosis

ARS Question

Would you offer HCV treatment to this non-cirrhotic patient, with ongoing alcohol use, prior substance use?
1) No, I would not treat until evidence of advanced fibrosis or frank cirrhosis as no benefit
2) No, I am worried about reinfection via MSM route
3) Yes, I would pursue treatment now if he is motivated to be treated
4) Yes, but only after he demonstrates 6 months of sobriety from speed and alcohol

Whom to treat

Recommendations for Testing, Managing, and Treating Hepatitis C

WHEN AND IN WHOM TO INITIATE HCV THERAPY

“Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.”

www.hcvguidelines.org
What about alcohol?

- Alcohol and HCV are negatively synergistic
- Data support successful interferon-based HCV treatment in active drinkers
- Benefit of HCV cure despite continued alcohol in most patients (Russell 2012, Costenin 2013)
- Successful HCV cure can be a springboard for other positive health changes.

**Take-home:** Counsel regarding alcohol reduction but don’t withhold treatment due to alcohol use alone.

What about active drug use?

- ≈ 96% cure rate in HCV+ methadone clinic attendees, many with active substance use

DAA Prescribing Restrictions

- 2016 Medicaid Liver Disease Requirements for HCV Treatment


DAA Prescribing Restrictions

- 2016 Medicaid Sobriety Requirements for HCV Treatment

HCV Arsenal & Principals of therapy

Direct Acting Agents (DAA)

- **Protease inhibitors**
  - Target viral protease
  - "previr"
  - Grazoprevir (Opviux)
  - Paritaprevir (Viekira)

- **NS5b Inhibitors**
  - Target viral RNA polymerase
  - "buvir"
  - NS5b Nucleotide i.e. Sofosbuvir
  - NS5b Non Nucleotide i.e. Dasabuvir

- **NS5a Inhibitors**
  - Target viral assembly and release
  - "asvir"
  - Ledipasvir
  - Velpatavir
  - Ombitasvir (Viekira)
  - Elbasvir (Zepatier)
  - Daclatasvir

- **“P” = Previr**
- **“B” = Buvir**
- **“A” = Asvir**

• **NS5a based therapy**
  - NS5a Backbone
  - One drug from 2nd class
  - Sofosbuvir
  - Protease inhibitor
  - Ribavirin

• **Triple therapy without a NS5b Nuke**
  - NS5a
  - NS5b Non-Nuke
  - Protease inhibitor

• **NS5a based therapy**
  - NS5a Backbone
  - One drug from 2nd class
  - Ledipasvir/Sofosbuvir (Harvoni): GT 1 & 4
  - Velpataivir/Sofobuvir (Epclusa): Pangenotype
  - Daclatasvir + Sofosbuvir: Pangenotype

• **Triple therapy without a NS5b Nuke**
  - NS5a
  - NS5b Non-Nuke
  - Protease inhibitor
• **NS5a based therapy**

**NS5a Backbone**

- NS5a

**One drug from 2nd class**

- Ledipasvir/Sofosbuvir (Harvoni) GT 1 & 4
- Velpatasvir/Sofosbuvir (Epclusa)
- Daclatasvir + Sofosbuvir

**Triple therapy without a NS5b Nuke**

- NS5a

**Protease inhibitor**

- Ribavirin

for hard to treat:
- Decompensated
- Retreatment
- GT3

**Pangenotype**

- Elbasvir/Grazoprevir (Zepatier): GT 1&4
- Pibrentasvir/glecaprevir (in development): Pangenotype

• **NS5a based therapy**

**NS5a Backbone**

- NS5a

**One drug from 2nd class**

- Ledipasvir/Sofosbuvir (Harvoni) GT 1 & 4
- Velpatasvir/Sofosbuvir (Epclusa)
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**Triple therapy without a NS5b Nuke**

- NS5a

**Protease inhibitor**

- Ribavirin

Ribavirin for hard to treat:
- GT1A with NS5a resistance (Zepatier)

**PrOD**: Paritaprevir/ombitasvir/ritonavir, dasabuvir (Viekira Pak)
• NS5a based therapy
  - NS5a Backbone
    - One drug from 2nd class
  - NS5a + Sofosbuvir + Protease inhibitor
    - Ribavirin for hard to treat: • GT1A

• Triple therapy without a NS5b Nuke
  - NS5a + Non-Nuke + Protease inhibitor

Current options: Genotype 1a, non-cirrhotic, treatment naive

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Dose</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Ledipasvir/Sofosbuvir “Harvoni”</td>
<td>One FDC pill daily</td>
<td>x12 weeks (8 weeks if HCV RNA &lt; 6 million IU/ml)</td>
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<tr>
<td>Velpatasvir/Sofosbuvir “Epclusa”</td>
<td>One FDC pill</td>
<td>x12 weeks</td>
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<tr>
<td>Elbasvir/Grazoprevir “Zepatier”</td>
<td>One FDC pill daily*</td>
<td>x 12 weeks (16 weeks +RBV if resistance)</td>
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*NS5a resistance testing required for GT1a

For treatment of other genotypes, treatment experienced and cirrhotics, please see www.hcvguidelines.org

Coming soon
• “Next generation” dual therapy
  - NS5a + Protease inhibitor

• Triple therapy
  - NS5a + NS5b Nuke + Protease inhibitor

• (Almost) One size fits all, pangenotypic regimens
• 8 weeks for non-cirrhotic, treatment naive
• Triple therapy effective for NS5a failures, regardless of presence of resistance
• Caveat: Protease inhibitors lead to more drug interactions, particular with ART
  “More is not better, better is better”

Back to our patient
• Hepatitis B Serologies:
  - Hep B S Ab (-)
  - Hep B s Ag (-)
  - Hep B core Ab (+)
• What does this mean?
HBV reactivation

- FDA warning about risk of HBV reactivation during HCV treatment: 24 cases
  - none on HBV active treatment before HCV treatment
- Transaminitis on therapy weeks 4-8 of HCV treatment
  - 2 died, 1 transplant, 3 decompensated
  - Transaminitis mistakenly attributed to DAA initially (8)
- Baseline HBV serologies:
  - HBV DNA detectable: 7
  - HBsAg(+), DNA (-): 4
  - HBsAg(-), DNA (-): 3
  - HBV serologies unknown: 10

http://www.fda.gov/Drugs/DrugSafety/ucm522932.htm

HBV reactivation

- Mechanism- ? Viral interference
  - HCV can have known suppressive effect on HBV in dually infected patients
- Check HBV serologies before HCV treatment (HBsAb, sAg, core Ab)
- Very unlikely in HIV+ patients on HBV active ART (3TC/FTC +/- Tenofovir )
<table>
<thead>
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<th>HBsAg</th>
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<th>Action</th>
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<td>NEG</td>
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<td>NEG</td>
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<td>Active HBV infection</td>
<td>• Check HBV DNA</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>• Treat HBV according to guidelines (US)</td>
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<tr>
<td>POS</td>
<td>NEG</td>
<td>NEG</td>
<td>Possible occult infection (vs waned Ab, false +, or window period)</td>
<td>• Check DNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Consider treatment if DNA+ (EASL)</td>
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• Consider treatment even if low/undetectable HBV DNA (EASL)  
• Monitor transaminases (q 4 weeks) |
| POS       | NEG   | NEG   | Possible occult infection | • Check DNA  
• Consider treatment if DNA+ (EASL)  
• Vaccinate if DNA negative |
| POS       | POS   | NEG   | Immune recovery | • Monitor transaminases on therapy  
• Consider HBV reactivation if ↑ |

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**Risk of HBV reactivation**

- Notably: High dose steroids, rituximab, TNF-alpha blockers, chemotherapy

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**Back to our patient**

- Insurance approves velpatasvir/sofosbuvir x 12 weeks
- You work with his methadone counselor to co-administer his HCV treatment with methadone
- Your pharmacist checks in with him every 2 weeks regarding adherence
- Week 4 lab check:
  - HCV RNA at week 4 is < limit of detection, LFTs have normalized
- 12 weeks after completing treatment, HCV RNA is undetectable -> Cured!

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**Entecavir or Tenofovir preferred over lamivudine**

- DiBisceglie Hepatology 2015
After the cure...

• HCV Ab may remain positive for life
  – Future HCV screening will need to be HCV RNA
• Counsel about Reinfection
  – Drug use: shared needles, injecting equipment ("works"), straws used for snorting
  – Sexual contact through men having sex with men (MSM): risk highest in HIV+ men but occurs in HIV-
• If cirrhotic, continue to screen for hepatocellular carcinoma with q 6-12 month imaging

HCV conclusion

• We have tools to cure HCV in the majority of HCV patients, including those with most complex disease
• HCV treatment is well tolerated and relatively straightforward for most patients
• Next steps: improved pangenotype regimens and treatment for hardest to treat groups.
• We need primary care providers to identify HCV and discuss treatment readiness as well as large cadre of HCV treaters, including primary care based treatment.
• Stay vigilant in this rapidly changing field: HBV reactivation

HBV Potpourri

Treating HBV
HBV infection: Dynamic & Lifelong

- Latent HBV (S Ag negative, core Ab+)
  - HIGH DNA
  - Elevated AST/ALT
  - S Ag+

- Immune Tolerant Phase
  - Immune Active Phase
  - Inactive Carrier Phase
  - Cirrhosis
  - Hepatocellular Carcinoma

- Immune Tolerant Phase
  - Immune Active Phase
  - Inactive Carrier Phase
  - Cirrhosis
  - Hepatocellular Carcinoma

- Low/no DNA
- Normal AST/ALT
- S Ag+
HBV infection: Dynamic & Lifelong

- Latent HBV (S Ag negative, core Ab+)
  - DNA (-)
  - Normal AST/ALT

Indications for HBV treatment

<table>
<thead>
<tr>
<th>Treat</th>
<th>HBV DNA threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compensated cirrhotics</td>
<td>HBV DNA &gt; 2000 IU</td>
</tr>
<tr>
<td>Decompensated cirrhotics</td>
<td>Any detectable DNA</td>
</tr>
<tr>
<td>Immune Active (E Ag Positive or Negative)</td>
<td>HBV DNA &gt; 2000 IU, AST &gt; 2x ULN (DNA threshold varies by guideline)</td>
</tr>
</tbody>
</table>

HBV treatment arsenal

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Considerations</th>
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<tr>
<td>PEG-Interferon</td>
<td>• Finite (6 -12 months)</td>
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<tr>
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<td>• E antigen loss higher than oral therapy but still low (&lt;30%)</td>
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<td></td>
<td>• Poorly tolerated</td>
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PEG-Interferon

- Finite (6 -12 months)
- E antigen loss higher than oral therapy but still low (<30%)
- Poorly tolerated

Oral Nucleo(s)tides

- Tenofovir disoproxil fumarate (TDF) & entecavir have emerged as first line (over lamivudine)
- Well tolerated
- Very low E antigen loss
- Indefinite
Tenofovir Alanafemide (TAF)

- Tenofovir prodrug (like tenofovir disproxil)
- Approved in combination therapy for HIV
- TAF/emtricitabine and TAF (“Velmidy”) standalone now approved for HBV

The future looks bright….

Today

HCC screening in HBV

<table>
<thead>
<tr>
<th>Population Group (HBV+ carrier or Active disease)</th>
<th>Annual HCC Incidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis, any etiology</td>
<td>1.5-8%</td>
<td>Screening recommended</td>
</tr>
<tr>
<td>HBV, noncirrhotic Asian male &gt;40 y</td>
<td>0.4-0.6%</td>
<td>Screening recommended</td>
</tr>
<tr>
<td>HBV, noncirrhotic Asian female &gt;50 y</td>
<td>0.3-6%</td>
<td>Screening recommended</td>
</tr>
<tr>
<td>HBV, noncirrhotic African/Black</td>
<td></td>
<td>Screening recommended</td>
</tr>
<tr>
<td>HBV, family history HCC</td>
<td></td>
<td>Screening recommended</td>
</tr>
<tr>
<td>(HBV + HIV)</td>
<td></td>
<td>Screening recommended*</td>
</tr>
<tr>
<td>HBV, noncirrhotic, age &lt;40 (&lt;50)</td>
<td>&lt;0.2%</td>
<td>Benefit uncertain</td>
</tr>
<tr>
<td>HCV, stage 3 fibrosis</td>
<td>&lt;1.5%</td>
<td>Benefit uncertain</td>
</tr>
<tr>
<td>NAFLD, noncirrhotic</td>
<td>&lt;1.5%</td>
<td>Benefit uncertain</td>
</tr>
</tbody>
</table>

* Not in AASLD guidelines but expert consensus

Note courtesy of J. Guy

Thank you!
Resources

• AASLD HBV treatment guidelines:

• EASL HBV management guidelines:

• AASLD/IDSA HCV Guidelines:
  http://www.hcvguidelines.org

• University of Liverpool HCV Drug interaction database: http://www.hep-druginteractions.org

• Patient education resources