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
- Bristol Myers Squibb (BMS)
- Gilead
- Pfizer
- Merck
- ACTG (NIH)

Overview
- HCV
  - Screening and selection of patients to treat
  - Changing treatment landscape
- HBV
  - New HBV agents
  - HBV pipeline
  - Prophylaxis for HBV reactivation

Your patient
- 42 yo man, HCV Ab+, establishing care with you
- PMH: depression
- Meds: paroxetine, Methadone maintenance x 3 years
- Social history
  - Prior IDU heroin, none currently
  - Alcohol- few beers/day, binge drinks on occasion
  - Sexually active with men, 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

**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 Neg
- 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

**Whom to treat**

Recommendations for Testing, Managing, and Treating Hepatitis C

“When evidence clearly supports treatment in all HCV-infected persons except those with limited life expectancy (less than 12 months) due to non liver related comorbid conditions”
Hepatic Benefits of HCV cure

- Reduce hepatic decompensation, liver transplant and HCC
- Avert MORE liver disease complication in those with LESS fibrosis

Non-Hepatic Benefits of HCV Cure

HCV is a systemic, inflammatory viral infection associated with non-hepatic complications

- Renal disease (Chen 2014)
- Lymphoproliferative disease (Feld 2013)
- Insulin resistance
- Vascular disease (CAD & CVA) (Maria 2014)
- Cognitive impairment
- Bone Disease & Fracture (Lo Re 2014)
- Skin disease including porphyria cutanea tarda

HCV cure reduces all cause mortality, including non-hepatic, as well as these co-morbidities

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?

- C-Edge CO-STAR; HCV-infected patients stable on methadone or buprenorphine x ≥ 3 months and kept at least 80% of scheduled appointments
- 12 weeks of HCV treatment (one pill daily)

Despite substantial drug use during treatment, 96.5% of patients missed ≤ 3 doses during 12 weeks
What about the COST??!
- Current oral medications remain extraordinarily expensive
- Despite the cost, many models find universal HCV treatment cost effective
- Cost effective ≠ cheap
  - If 50% of US HCV+ treated at base price ≈ $53 billion

Direct Acting Agents (DAA)

Protease inhibitors
- Target viral protease
  - "previr"
  - Simeprevir
  - Paritaprevir
  - Grazoprevir

SSN-Inhibitors
- Target viral RNA polymerase
  - "-buvir"
  - NS5b Nucleotide
  - Sofosbuvir
  - NS5b Non-nucleotide
  - Dasabuvir

SSA-Inhibitors
- Target viral assembly and release
  - "-asvir"
  - Ledipasvir
  - Ombitasvir
  - Dasabuvir
  - Elbasvir

Current DAA combinations
- NS5b Nucleotide based therapy
- Triple therapy without a NS5b Nuke
- HCV protease inhibitor + NS5a

>90-95% cure rate for most patients
Current DAA combinations

- **NS5b Nucleotide based therapy**
  - NS5b Nuke Backbone
  - One drug from 2nd class
  - Sofosbuvir
  - Ledipasvir
  - FDC

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

- **HCV protease inhibitor + NS5a**
  - Protease inhibitor
  - NS5a

Increasingly 2nd line

- **NS5b Nucleotide based therapy**
  - NS5b Nuke Backbone
  - One drug from 2nd class
  - Sofosbuvir
  - Daclatasvir
  - (Pangenotypic NS5a)

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

- **HCV protease inhibitor + NS5a**
  - Protease inhibitor
  - NS5a
Current DAA combinations

- **NS5b Nucleotide based therapy**
  - NS5b Nuke Backbone
  - One drug from 2nd class
  - Ribavirin

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

- **HCV protease inhibitor + NS5a**
  - Protease inhibitor
  - NS5a

Options: Genotype 1a, non-cirrhotic, treatment naive

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>One FDC pill daily</td>
<td>x12 weeks (8 weeks if HCV RNA &lt; 6 million IU/ml)</td>
</tr>
<tr>
<td>PTV/RTV/OBV + DSV + RBV</td>
<td>One FDC pill + one BID pill + weight based ribavirin BID (4-6 pills day)</td>
<td>x12 weeks</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>One FDC pill daily*</td>
<td>x 12 weeks (16 weeks +RBV if resistance)</td>
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</table>

*NS5a resistance testing required for GT 1a

For treatment of other genotypes, treatment experienced and cirrhotics, please see [www.hcvguidelines.org](http://www.hcvguidelines.org)

Back to our patient

- Insurance approves LDV/SOF x 8 weeks (HCV RNA < 6 million)
- 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!
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, 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 to 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

HBV Potpourri
Treating HBV

Indications for HBV treatment

<table>
<thead>
<tr>
<th>Treat</th>
<th>HBV DNA threshold</th>
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<tbody>
<tr>
<td>Compensated cirrhotics</td>
<td>HBV DNA &gt; 2000 IU</td>
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<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>
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</tbody>
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EASL Guidelines 2012, AASLD Guidelines 2009

Viral Life Cycle

HBV infection: Dynamic & Lifelong
HBV treatment arsenal

Regimen Considerations

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 disoproxil)
- Approved in combination therapy for HIV
- TAF/emtricitabine and TAF standalone under evaluation

Monotherapy in HBV

- **Gilead Study 108: HBeAg negative**
  - Randomized 2:1 to receive TAF (n=285) or TDF (n=140)
  - TAF: 94% vs TDF 92.9% with HBV DNA< 29 IU/ml at week 48 (CI -3.6% to +7.2%, p=0.47)

- **Gilead Study 110: HBeAg Positive**
  - Randomized 2:1 to receive TAF (n=581) or TDF (n=292)
  - TAF: 63.9% vs TDF 66.8% with HBV DNA <29 IU/mL at week 48 (CI -9.8% to +2.6%, p=0.25)

ARS question

When should prophylactic HBV therapy be considered prior to immunosuppressive therapy (such as chemotherapy or rituximab)?

- Only in patients with detectable HBV DNA
- Only in patients with HBsAg +, regardless of HBV DNA
- In patients with HBcAb+
- All patients should receive HBV therapy if undergoing severe immunosuppression
Viral Life Cycle - “latent or recovered” HBV

Immune system considers this “recovered” BUT cccDNA is template for viral replication

- HBsAg neg
- Anti-HBs
- Anti-HBc

Risk of HBV reactivation

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

Entecavir or Tenofovir preferred over lamivudine

DiBisceglie Hepatology 2015
PREP & HBV

• Pre-exposure prophylaxis to prevent HIV with Truvada (tenofovir DF/emtricitabine)

• Good news: Protective effect against HBV acquisition (Heulft AIDS 2014)

• Bad news: risk of flares with discontinuation

Remember to screen PREP patients for active and latent HBV

Resources


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

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

• Patient education resources http://www.hepatitis.va.gov/provider/hcv/index.asp