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

Annie Luetkemeyer
HIV/AIDS Division
San Francisco General Hospital

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

• HBV
  – HBV as a dynamic, lifelong disease
  – Indications for treatment
  – Prophylaxis for HBV reactivation
  – Hepatocellular carcinoma screening in HBV

• HCV
  – Screening for HCV
  – Initial Evaluation of HCV+ patients
  – Changing treatment landscape
  – HCC screening in HCV

True or false?

Once a person has developed HBV Surface Antibody, they have been cured of HBV infection?

A. True
B. False
Viral Life Cycle

HBV

Entry → ER → Budding → Recycling → Transcription → Translation

S, C, P, e synthesis → Reverse transcriptase → P protein

cccDNA → Replication → Pre-genomic RNA → RNA packaging (encapsulation)

Host RNA pol → Plus strand synthesis → Minus strand synthesis → HBsAg (+)

Important diagnostic tests:
- HBsAg
- HBsAg (anti-HBs)
- Anti-HBc
- Anti-HBx (anti-HBe)
**Viral Life Cycle- “latent or recovered” HBV**

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

**HBV infection: Dynamic & Lifelong**

- **Mother to Child Transmission**
- **Person to Person Transmission**
- **Clearance of HBsAg**

- **Immune Tolerant Phase**
- **Immune Active Phase**
- **Inactive Carrier Phase**

- **Cirrhosis**
- **Hepatocellular Carcinoma**
HBV infection: Dynamic & Lifelong

- **Mother to Child Transmission**
  - Immune Tolerant Phase
  - Immune Active Phase
  - Inactive Carrier Phase
  - Clearance of HBsAg

- **Person to Person Transmission**
  - Immune Tolerant Phase
  - Immune Active Phase
  - Inactive Carrier Phase

**Immune Tolerant:** High HBV DNA, E Ag+, normal transaminases

**Immune Active:** Moderate to High HBV DNA, elevated transaminases

- Cirrhosis
- Hepatocellular Carcinoma
HBV infection: Dynamic & Lifelong

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

**Mother to Child Transmission**

**Person to Person Transmission**

**Clearance of HBsAg**

Inactive Carrier
Low-undetectable HBV DNA, Normal transaminases, S Ag+

E Antigen Negative
Low HBV DNA, Elevated transaminases (both may fluctuate), associated with progressive disease

**Inactive Carrier**
Low-undetectable HBV DNA, Normal transaminases, S Ag+
HBV infection: Dynamic & Lifelong

Immunologic Control (Latent)
Low-undetectable HBV DNA, Normal transaminases, S Ag+

Progression of Fibrosis: Generally driven by viremia
# Hepatitis B Serologies

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>HbcAb</th>
<th>sAb</th>
<th>eAg/Ab</th>
<th>DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Chronic HBV</strong></td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Latent</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-/+</td>
</tr>
<tr>
<td><strong>Vaccinated</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Occult (or window)</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

- Isolated Core Ab positive = Waned sAb vs. false positive

# Indications for HBV treatment

<table>
<thead>
<tr>
<th><strong>Treat</strong></th>
<th><strong>HBV DNA threshold</strong></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 (&lt;DNA threshold varies by guideline&gt;)</td>
</tr>
<tr>
<td>HIV-HBV coinfected</td>
<td>All patients. Avoid lamivudine or FTC monotherapy</td>
</tr>
</tbody>
</table>

### HBV Disease state

<table>
<thead>
<tr>
<th>HBV Disease state</th>
<th>Treatment considerations</th>
</tr>
</thead>
</table>
| **Immune Tolerant** |  | • < 30 years old: Generally don’t treat  
- HBV suppression not associated with E ag loss  
- Low risk of fibrosis w/o treatment  
• Patients > 30 years old: consider biopsy and possible treatment  
• Ongoing controversy: treatment to reduce risk of HCC associated with high HBV viral load |
| **Inactive Carriers** | Treatment not recommend |
| **Latent Disease** (Core Ab +, Surface Antibody +) | Treatment not recommended, except in setting of immunocompromise |

Tseng 2015 J Viral Hepatology

---

### Reactivation of Latent HBV

- High rate of reactivation in immunosuppressed patients  
  – Chemotherapy  
  – Post organ transplant  
  – Biologic response modifiers: rituximab (anti-CD20), TNF-α inhibitors  

- Prophylaxis with oral anti-HBV recommended.

<table>
<thead>
<tr>
<th>Patients With Event, No. (%)</th>
<th>Entecavir (n = 61)</th>
<th>Lamivudine (n = 60)</th>
<th>Difference (95% CI), %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV-related hepatitis</td>
<td>0 (0.0)</td>
<td>8 (13.3)</td>
<td>13.3 (4.7 to 21.9)</td>
<td>.003</td>
</tr>
<tr>
<td>HBV reactivation</td>
<td>4 (6.6)</td>
<td>18 (30.0)</td>
<td>23.4 (10.2 to 36.6)</td>
<td>.001</td>
</tr>
<tr>
<td>Chemotherapy disruption</td>
<td>1 (1.6)</td>
<td>11 (18.3)</td>
<td>16.7 (6.4 to 27.0)</td>
<td>.002</td>
</tr>
<tr>
<td>Treatment-related adverse events</td>
<td>15 (24.6)</td>
<td>18 (30.0)</td>
<td>5.4 (-10.5 to 21.3)</td>
<td>.50</td>
</tr>
</tbody>
</table>

Huang JAMA 2014
What to treat with

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| PEG-Interferon   | • Finite (6 -12 months)  
                  | • E antigen loss higher than oral therapy but still low (<30%)  
                  | • Poorly tolerated                                                       |
| Oral Nucleo(s)tides | • Indefinite                    
                        | • Very low E antigen loss       
                        | • Well tolerated               
                        | • Tenofovir (or entecavir) has emerged as first line over lamivudine |

HCC Screening

HBV
• Asian men over the age of 40 years
• Asian women over the age of 50 years
• All cirrhotics
• Africans and North American blacks
• Patients with a family history of HCC

In contrast, HCV:
• Cirrhotics only

HOW to SCREEN
• Imaging q 6-12 months.
• Ultrasound is reasonable first step for most patients.
• AFP no longer recommended in most guidelines

AASLD HCC Guidelines 2010
HBV Vaccination

- Vaccination recommended: all newborns, adult higher risk groups (including MSM, IDU, immunocompromised, travelers, healthcare workers)
- 0, 1 and 6 months
  - Twinrix (HAV/HBV) alternative: 0, 7, 30 days, 12 months
- “Double-dose” vaccine for hemodialysis/immunocompromised
- 95% effective: post vaccination testing only for healthcare workers or immunocompromised

Common HBV vaccine questions

- Vaccination of isolated core antibody positive?
  - Yes
- What to do with vaccine non-responders?
  - Repeat full series of three vaccines (consider double dose)
  - If 2nd full series, generally would not revaccinate
- Does anyone need a “booster”?
  - Not recommended for general population
  - Target HBs Ab > 10 miu/ml in hemodialysis patients
  - Consider in new patient with HBsAb+ but < 10 miu/ml
**HCV: The big picture in 2015**

**The future is now: We can cure the majority of patients with well tolerated, all oral medication**

- Initial Testing and Staging
- Benefits of HCV cure
- Who should be treated for HCV
- Our current HCV arsenal:
  - Overview of the current classes and characteristics
  - How many drugs are necessary?
  - How short can successful HCV treatment be?

---

**HCV treatment Cascade 2003-13**

- Up to 50% of American with HCV unaware of their infection
- 45% with HCV report no known risk factor
- 75% of US HCV infections are in “Baby Boomers” born 1945-1965

Yehia PLOS One 2014

<table>
<thead>
<tr>
<th>Chronic HCV-Infected</th>
<th>Diagnosed and Aware</th>
<th>Access to Outpatient Care</th>
<th>HCV RNA Confirmed</th>
<th>Underwent Liver Biopsy</th>
<th>Prescribed HCV Treatment</th>
<th>Achieved SVR**</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>50%</td>
<td>43%</td>
<td>27%</td>
<td>17%</td>
<td>16%</td>
<td>9%</td>
</tr>
</tbody>
</table>

* Chronic HCV-infected; N=3,500,000.
† Calculated as estimated number chronic HCV-infected (3,500,000) x estimated percentage diagnosed and aware of infection (49.8%); n=1,743,000.
‡ Calculated as estimated number diagnosed and aware (1,743,000) x estimated percentage with access to outpatient care (86.9%); n=1,514,667.
§ Calculated as estimated number with access to outpatient care (1,514,667) x estimated percentage HCV RNA confirmed (90.9%); n=532,726.
¶ Calculated as estimated number with access to outpatient care (1,514,667) x estimated percentage who underwent liver biopsy (88.4%); n=581,632.
Screening for HCV

- **Initial HCV antibody test to screen**
  - Screen all people born between 1945-65 as well as those at risk, including IDU, MSM, Hemodialysis
- **Confirm with HCV RNA**
  - Up to 20% will spontaneously clear without treatment -> no longer infected with HCV
- **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

**Genotypes 1-6**

- Can impact disease progression
  - Genotype 3: associated with steatohepatitis
- Impacts selection and response to therapy
  - Easiest to Cure: 2\(>\)3\(>\)4\(\geq\)1 (1b\(>\)1a)
- Genotype 1: most common in US (70%)
- Send genotype if considering HCV treatment
Fibrosis assessment

- **Serologic markers**
  - Platelets, INR, Albumin
  - Serologic tests: APRI, Fib-4, FibroSure/Test

- **Physical Exam**
  - Palmar erythema, telangectasia, gynecomastia, splenomegaly

- **Imaging**: Ultrasound reasonable first step
  - CT and MRI usually unnecessary - would avoid radiation and save as follow-on tests

- **Transient Elastography**: Fibroscan
  - Excellent option when available - now FDA approved

- **Biopsy**: rarely necessary

- **When cirrhosis present**: HCC screening, EGD for varices

---

Once a patient has frank cirrhosis, curing HCV can lead to regression of cirrhosis

A. Cirrhosis can regress after HCV cure in about half of patients

B. Cirrhosis can regress but very rarely (<5%)

C. Once you have cirrhosis, it cannot regress

D. We don’t know

![Graph showing 25% 25% 25% 25%]

25% 25% 25% 25%
Hepatic Benefit of HCV Cure

- **Cirrhotics** - not too late to benefit from cure
  - Regression of cirrhosis in up to 50%
  - Reduced risk of liver related death
  - Reduced *(but not eliminated)* risk of hepatocellular carcinoma

- **Non-cirrhotics**: Reduction of fibrosis progression, risk of HCC and liver related death

Poynard J Hep 2013 59: 673

Benefit of treatment in early fibrosis

- Reduction of fibrosis progression, risk of HCC and liver related death

Aijaz AASLD Abstract # 1751
Benefit of HCV Cure: Non-hepatic

- Reduces risk of death, including due to non-hepatic causes, in all populations

5-year risk of death (all-cause) by SVR

<table>
<thead>
<tr>
<th>Group</th>
<th>Studies</th>
<th>Participants</th>
<th>Avg. FU (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>18</td>
<td>n=29,989</td>
<td>4.6</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>9</td>
<td>n=2,734</td>
<td>6.6</td>
</tr>
<tr>
<td>HIV/HCV</td>
<td>5</td>
<td>n=2,060</td>
<td>5.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SVR</th>
<th>No SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.3%</td>
<td>10.5%</td>
</tr>
<tr>
<td>3.6%</td>
<td>11.3%</td>
</tr>
<tr>
<td>1.3%</td>
<td>10.0%</td>
</tr>
</tbody>
</table>
“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”

**Priority for HCV therapy**

**HIGHEST PRIORITY**
- Advanced Fibrosis (F3) or compensated cirrhosis (F4)
- Cryoglobulinemia with end organ manifestations
- Renal complications of HCV infection

**HIGH PRIORITY**
- Fibrosis (F2)
- HIV Coinfection
- HBV Coinfection
- Other liver disease (e.g. NASH)
- Debilitating Fatigue
- Diabetes
- Porphyria cutanea Tarda
- *HIGH HCV Transmission Risk* (includes MSM, IDU)
In the US, how many HCV infected patients are not in these highest or high priority group for HCV treatment?

A. 10%
B. 25%
C. 40%
D. 75%

Patients Meeting "Highest" or High" priority for HCV Treatment in the Chronic Hepatitis C Cohort Study (CHeCS)

- Treatment recommendations have suggested prioritizing patients for treatment based on disease severity, risks of progression, co-morbidities, and extrahepatic manifestations
- Aim: To determine treatment priority status in a large, multicenter patient cohort

<table>
<thead>
<tr>
<th>Priority status</th>
<th>N=8504</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIGHEST PRIORITY</strong></td>
<td>32.9%</td>
</tr>
<tr>
<td>F3 or higher by biopsy or FIB4 score &gt;2.5</td>
<td>30%</td>
</tr>
<tr>
<td>&lt;F3 with chronic kidney disease</td>
<td>2.9%</td>
</tr>
<tr>
<td><strong>HIGH PRIORITY</strong></td>
<td>28.9%</td>
</tr>
<tr>
<td>F2 by biopsy or FIB4 score &lt; 2.5</td>
<td>22.7%</td>
</tr>
<tr>
<td>&lt;F2 with HIV co-infection</td>
<td>0.7%</td>
</tr>
<tr>
<td>&lt;F2 with HBV coinfection</td>
<td>0.2%</td>
</tr>
<tr>
<td>&lt;F2 with NASH</td>
<td>0.4%</td>
</tr>
<tr>
<td>&lt; F2 with diabetes</td>
<td>4.9%</td>
</tr>
<tr>
<td><strong>NOT MEETING &quot;HIGHEST&quot; or &quot;HIGH PRIORITY&quot;</strong></td>
<td>38.2%</td>
</tr>
</tbody>
</table>
AASLD Position on Treating Patient with HCV:

“Our Guidance is not intended to be used by payers to deny access to treatment. In no way does this position contradict the evidence evaluated to produce the Guidance and the recommendation made in the Guidance to treat the sickest first, but recognizes need to treat all.”

http://www.aasld.org/aboutus/publicpolicy/Pages/aasldhcyposition.aspx

Cost & Cost Effectiveness

• Current oral medications extraordinarily expensive
• Despite the cost, many models find HCV cure cost effective
• Optimism about near future
  – New regimens to be approved- competition should improve pricing
  – Treatment is getting shorter
  – Commitment to compassionate pricing in resource limited setting
HCV Arsenal & Principals of therapy

Current DAA combinations

- **NS5b Nucleotide based therapy**
  - **NS5b “Nuke” Backbone**
  - **One drug from 2nd class**
    - SOFOSBUVIR
    - NS5a
    - Protease inhibitor
    - Ribavirin

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

- **Other approaches**
  - Protease inhibitor
  - NS5a
Current Treatment principles

- HCV Genotype matters (for now)
  - Many regimens not pan-genotypic
  - Easiest to Cure: 2>3>4≥1 (1b>1a)

- Harder to treat populations need longer therapy or addition of ribavirin
  - Cirrhotic patients
  - Prior Treatment failures (even if not with DAA)

- Treatment now possible for almost everyone including decompensated cirrhotics, HCC and post liver transplant
  - Still need better options for severe renal disease, dialysis, and Genotype 3

- HIV coinfection does not seem to matter*

---

Genotype 1, Treatment naïve, non-cirrhotic

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir/Ledipasvir (“Harvoni”)</td>
<td>All Genotypes: 12 weeks (8 weeks if HCV&lt;6 million)</td>
</tr>
</tbody>
</table>
| Ombitasvir/ritonavir, paritaprevir daily with dasabuvir BID (“Viekira Pak”) | GT1a: 12 weeks with weight-based ribavirin  
GT1b: 12 weeks without weight-based ribavirin |

*For treatment of other Genotypes, treatment experienced and cirrhotics, please see www.hcvguidelines.org*
How short can HCV treatment be?

Treatment naïve, non-cirrhotics

- **8 weeks with 2 drugs:**
  - NS5b+NS5a (Sofosbuvir/ledipasivir), HCV RNA <6 million IU/ml: 97% SVR (ION-3)

- **6 weeks with 3 drugs:**
  - NS5b+NS5a (Sofosbuvir/ledipasivir) with Nonnucleoside or PI: 95-100% SVR (SYNERGY)

Kohil, CROI 2014, 27LB, Lawitz AASLD 2014 #236

---

How short can HCV treatment be?

- **4 weeks with 3 drugs? Too Short for now**
  - Not successful with Merck PI+NS5a+ Sofosbuvir (C-SWIFT) or with Sofosbuvir/ledipasivir + 3rd agent (NNI or HCV PI)

- **All 4 drug classes x 4 weeks (or less?) Stay tuned.**
  - BMS FOURward study

BMS FOURward study:
- NS5a
- Protease inhibitor
- NS5b Non-Nuke
- SOFOSBUVIR

Stay tuned….
When should HCV resistance testing should be obtained?

A. Same as HIV: prior to treating all HCV patients and at time of treatment failure
B. Only after oral regimen failure
C. Only if planning to retreat with the same class of medications
D. D) HCV resistance testing is currently rarely indicated
E. E) I don’t know

HCV resistance testing

• Baseline resistance testing for treatment naïve: generally unnecessary
• Resistance testing after treatment failure: generally not necessary
• Retreatment strategies for SOF-failure under evaluation: sofosbuvir-based strategies promising
Conclusions

HCV

• We finally have tools to cure HCV in the majority of HCV patients
• This is the beginning: Future regimens will be even shorter (and hopefully cheaper) and address remaining gaps (such as treatment in ESRD and Genotype 3)
• While we need to prioritize treatment of those with most advanced disease, all benefit from HCV cure

HBV

• Cure of HBV is the next frontier- current treatments control viremia and at best, induce latent state
• HBV is vaccine preventable
• Vigilence regarding risk of reactivation with immunocompromise
• HCC screening as HBV patients age

Resources

• AASLD/IDSA HCV Guidelines: http://www.hcvguidelines.org
• University of Liverpool HCV Drug interaction database: http://www.hep-druginteractions.org
• Patient education resource HCV Advocate: www.hcvadvocate.org