HIV/HCV Co-infection: Are we there yet?

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9/27/17
Disclosures

- **Speaker’s Bureau**: Janssen, Gilead, Merck, AbbVie
- **Scientific Advisor**: Gilead, Janssen, BMS
- **Grant/Research/Contracted Support**: CDC/HRSA, NWAETC, Pacific AETC, HealthHIV, Project ECHO, National Cancer Institute, Gilead Sciences

  **Mention will be made of therapeutic combinations not fully evaluated/approved by the FDA (‘off-label’ combinations)**
Learning Objectives

• Review the prospects of HCV elimination within the HIV+ community
• Address elements of the HCV Care Continuum from the HIV perspective
• List strategies to overcome challenges in HIV/HCV care
The Concept of ‘No Co’
Is HIV/HCV Elimination Possible?
Why ‘No-Co’?

• HCV easier to eliminate in the co-infected than general population
  – Liver disease recognized as a major cause of death in HIV patients
  – Better knowledge of HCV status
  – Higher levels of linkage to care
  – Support systems in place (case mgmt mental health, insurance, adherence support)
  – Often better medication access
  – Comfort with adherence counseling, DDI’s
  – High SVR rates
HIV/HCV Co-infection Epidemiology

1.2 million HIV-infected persons in US

- HIV Monoinfection (900,000) - 75%
- HIV-HCV Coinfection (300,000) - 25%

Which is TRUE regarding HCV transmission in HIV+ individuals?

A. New HCV infections are driven mostly by IVDU
B. Sexual HCV transmission only occurs in HIV+ MSM
C. CD4+ cell count is an important factor in sexual HCV transmission
D. Most HCV transmission in HIV+ cohorts occurs via inhaled stimulant paraphernalia
Risk Factors for Transmission of Hepatitis C

- Heterosexual Sex
- Mother to Child
- Male-Male Sex
- Blood Products
- Injection Drug Use
- Needlestick Injury
Hepatitis C Prevalence in HIV+ Patients

Hopkins HIV Cohort (N=1955)

- Overall: 45.1%
- IVDU: 85.1%
- Heterosexual: 14.3%
- MSM: 9.8%

Sulkowski et al Ann Int Med 2003; 138: 197-207
High Incidence of HCV Infection Is Associated With HIV-Positive Status and Risky Sexual Behavior

Incident HCV Infection in 5310 MSM: A Prospective Cohort Analysis (MACS), 1984-2011

- Among HIV-positive patients, every 100 cell/mm³ increase in CD4 cell count was associated with a 7% ($P = .002$) decrease in the HCV incidence rate

MSM, men who have sex with men. $^a P < .001$.
The HCV Care Continuum
HCV Care Continuum

- Chronic HCV-Infected: 100%
- Diagnosed and Aware: 50%
- Access to Outpatient Care: 43%
- HCV RNA Confirmed: 27%
- Underwent Liver Biopsy: 17%
- Prescribed HCV Treatment: 16%
- Achieved SVR: 9%

Prevention of Reinfection
HCV Screening Guidelines
How do you screen for HCV in your HIV+ patients?

A. HCV Ab on entry to care
B. HCV Ab on entry to care and annually
C. HCV Ab on entry to care and annually (if risk)
D. HCV Ab on entry to care and annually (if ↑ALT)
E. HCV Ab on entry to care and thereafter as dictated by risk behaviors
HCV Screening in HIV Patients

• AASLD/IDSA Guidelines:
  Because of the high incidence of HCV infection among persons who inject drugs and among HIV-infected MSM who have unprotected sex at least annual HCV testing is recommended in these subgroups

• DHHS Guidelines:
  On entry into HIV care, all HIV-infected patients should undergo routine HCV screening. For at risk HCV-seronegative individuals, HCV antibody testing is recommended annually or as indicated by risk exposure.

www.hcvguidelines.org; www.aidsinfo.nih.gov
Linkage to Care
Linkage to Care Challenges in HIV/HCV

- Mental Health issues
- Homelessness
- Ongoing Substance Abuse
- Maladherence to HIV regimen
- Insurance restrictions
- Lack of access to HCV-treating provider
Pre-Treatment Evaluation
Natural History of Hepatitis C

Exposure (Acute Hepatitis)

Resolution

15-25%

Persistence (chronic)

75-85%

20-30%

Cirrhosis

ESLD

HCC

3%/yr

4%/yr

Accelerated by Hep B, EtOH, HIV

Time (yrs): 10 20 30

Transplant Death

Death

Mandell: Principles & Practice of Infectious Disease, 7th Ed;
HCV: Diagnostic tools used in Initial Evaluation

- **HCV Ab, RNA** – Defines active infection
- **Liver Enzymes (AST/ALT)**
  - surrogate measure of necro-inflammation
  - may fluctuate through time
- **Albumin, PT-INR**
  - Surrogate markers of productive liver capacity
- **Complete Blood Count**
  - Platelets are clue to underlying hypersplenism/portal hypertension
  - CBC+Liver Enzymes allows for APRI, Fib-4 calculation
- **Rheumatoid Factor, Cryoglobulins**
  - Diagnose extrahepatic manifestations
- **HCV Genotype** – helps to refine treatment regimen
- **Liver Fibrosis Assessment** – APRI, Fibrotest, Elastography, biopsy
- **Other:** Ultrasound, AFP, Esophagogastroduodenoscopy (EGD)
Histologic Staging - METAVIR

Stage 0

Stage 1

Stage 2

Stage 3

Stage 4
Histologic Staging – Ishak vs. METAVIR

<table>
<thead>
<tr>
<th>Ishak</th>
<th>0</th>
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<th>2</th>
<th>3</th>
<th>4</th>
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<tr>
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Alternatives to Liver biopsy

• Basic Ultrasound

• APRI score = \( \frac{\text{AST}/40}{\text{Plts}} \times 100 \)

• Fib-4 score = \( \frac{\text{AST} \times \text{Age}}{\text{Plts} \times \sqrt{\text{ALT}}} \)

• Fibrosure/Fibrotest – blood test

• Fibroscan – ‘Transient Elastography’

• AIXPlorer – ‘Shear Wave Elastography’

• MRE – Magnetic Resonance Elastography
HCV: Transient Elastography

- $V_S = 1.0 \text{ m/s}$
  - $E = 3.0 \text{ kPa}$
  - **F0**

- $V_S = 1.6 \text{ m/s}$
  - $E = 7.7 \text{ kPa}$
  - **F2**

- $V_S = 3.0 \text{ m/s}$
  - $E = 27.0 \text{ kPa}$
  - **F4**

HCV: Shear Wave Elastography – F4 Fibrosis

Average Liver Elasticity
Avg Elast: 21.6 kPa

Elasticity (kPa) METAVIR Fibrosis

- >7.1 F2
- >8.7 F3
- >10.4 F4
AST to Platelet Ratio Index (APRI) Calculator

This is an AST to Platelet Ratio Index (APRI) calculator tool. Enter the required values to calculate the APRI value. The APRI Score will appear in the oval on the far right (highlighted in yellow). Most experts recommend using 40 IU/L as the value for the AST upper limit of normal when calculating an APRI value.

\[
\text{APRI} = \frac{\text{AST Level (IU/L)}}{\text{AST (Upper Limit of Normal) (IU/L)}} \times 100 = \frac{\text{Platelet Count (10^9/L)}}{}
\]

**Interpretation:**

In a meta-analysis of 40 studies, investigators concluded that an APRI score greater than 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis. In addition, they concluded that APRI score greater than 0.7 had a sensitivity of 77% and specificity of 72% for predicting significant hepatic fibrosis.\(^1\)

For detection of cirrhosis, using an APRI cutoff score of 2.0 was more specific (91%) but less sensitive (46%). The lower the APRI score (less than 0.5), the greater the negative predictive value (and ability to rule out cirrhosis) and the higher the value (greater than 1.5) the greater the positive predictive value (and ability to rule in cirrhosis); midrange values are less helpful. The APRI alone is likely not sufficiently sensitive to rule out significant disease. Some evidence suggests that the use of multiple indices in combination (such as APRI plus FibroTest) or an algorithmic approach may result in higher diagnostic accuracy than using APRI alone.\(^2\)
Ultrasound Criteria for Diagnosing Cirrhosis

• A very **specific** but not very **sensitive** tool

• (Many with Cirrhosis will have normal Ultrasounds)

• **Useful Findings:**
  - Ascites
  - Nodular Liver
  - Scalloped hepatic contour
  - Splenomegaly (> 12 cm)
  - Enlarged Portal Vein diameter (> 12 mm)
  - Small R lobe, Large L lobe
  - Coarsened or Heterogeneous Hepatic echotexture
  - Varices: splenic, gastric, esophageal
Drug-Drug Interactions
Your 61 yo HIV/HCV (GT-1, non-cirrhotic) pt is preparing for treatment. Meds include FTC/TDF/EFV, Amiodarone, Simvastatin, Omeprazole. Which HCV DDI would be most concerning?

A. ELB/GRZ with Efavirenz
B. SOF/LDV with TDF
C. SOF/LDV with Omeprazole
D. SOF/VEL with Amiodarone
E. GLE/PIB with Simvastatin
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<tr>
<th></th>
<th>Elbasvir/Grazoprevir</th>
<th>Glecaprevir/Pibrentasvir</th>
<th>Ledipasvir/Sofosbuvir</th>
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- **Do Not Coadminister**
- **Potential Interaction**
- **Potential Weak Interaction**
- **No Interaction Expected**
- **No Clear Data**
A. ELB/GRZ with Efavirenz → decreased ELB/GRZ AUC 54-83% (CYP 3A/P-gp induction)
B. SOF/LDV with TDF → increased TDF AUC 98%
C. SOF/LDV with Omeprazole → decreased LDV absorption (pH-dependent solubility of LDV)
D. SOF/VEL with Amiodarone → SOF+Amiodarone symptomatic bradycardia (Ca++ metabolism)
E. GLE/PIB with Simvastatin → increased Simvastatin AUC by 132%, rhabdomyolysis (OATP1B1/3, P-gp, and BRCP inhibition)
Tenofovir (TFV) Exposures: Coadministration of LDV/SOF with E/C/F/TAF or R/F/TAF vs Other ARVs

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<tr>
<td>HIV/HCV (+)</td>
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<tr>
<td>HIV (-)</td>
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Mean TFV AUC\(\text{tau}\) ng·h/mL, (SD)

- LDV/SOF can be safely co-administered with E/C/F/TAF or R/F/TAF with no dose adjustment
- TFV exposures from E/C/F/TAF are lower compared to exposures from PI+RTV +TVD with LDV/SOF and with STB alone


### ‘Allowable’ ART with HCV DAA’s

- **Daclatasvir** - dose may need to be adjusted (30-60-90)
- **Simeprevir** - ABC, FTC/3TC, TDF, TAF, MVC, RAL, DTG, RPV
- **Elbasvir/Grazoprevir** - ABC, FTC/3TC, TDF, TAF, RAL, DTG, RPV
- **Glecaprevir/Pibrentasvir** - ABC, FTC/3TC, TDF, TAF, RAL, DTG, RPV
- **Sofosbuvir/Velpatasvir** - All OK but EFV, ETR, NVP, (caution TDF)
- **Sofosbuvir/Ledipasvir** - All OK but caution TDF+PI
- **Sofosbuvir/Velpatasvir/Voxilaprevir** - TAF, FTC/3TC, RAL, DTG, RPV, (caution TDF), (avoid PI, Cobi, Ritonavir)
- **Paritaprevir/ritonavir/Ombitasvir/Dasabuvir** - TAF, FTC/3TC, RAL, DTG, ATZ (hold concomitant ritonavir)
Acid-Reducing Agents

• **Ledipasvir** and **Velpatasvir** - both sensitive to gastric pH
  - Antacids - separate by 4 hours
  - H-2 blockers - simultaneous or separate by 12 hrs
  - PPI’s - avoid, or concurrent (LDV) or 4 hrs prior (VEL) dosing if necessary

• **Sofosbuvir/Velpatasvir/Voxilaprevir** - Due to complex interactions, no PPI effect

• **Glecaprevir** - AUC decreased 29% by omeprazole 20 mg; 51% by omeprazole 40 mg
Other important Drug Interactions

- **Amiodarone** - avoid Sofosbuvir
- **Anticonvulsants** - phenytoin, phenobarbital, oxcarbazepine,
- **Statins** - idiosyncratic interactions
- **Herbal Agents** - Milk Thistle, St. John’s Wort
- **Oral Contraceptives** - depend on regimen
DAA Efficacy in HIV/HCV Co-infection
Extensive HIV/HCV Clinical Trials Experience

- SOF/LDV: ION-4 (n=335, 96% SVR)
- PrOD: TURQOISE (n=63, 90-93% SVR)
- ELB/GRZ: C-EDGE (n=218, 96% SVR)
- SOF/VEL: ASTRAL-5 (n=106, 95% SVR)
- GLE/PIB: EXPEDITION-2 (n=137, 98% SVR)
- SOF+DCV: ALLY-2 (n=203, 97% SVR)

**however limited clinical trial participants with AIDS**
Post-Treatment Monitoring
Long-term Cirrhosis Management

• U/S for long-term HCC surveillance recommended if F3-F4 pre-treatment
• EGD recommended if F4 and Plt <150, elastography > 15 kPa
• Clinical assessment for decompensation events, portal HTN encephalopathy
HCV Re-infection
Risk of HCV re-infection in low and high risk groups

Meta-analysis of 66 studies in 11,071 patients

Low risk
- 43 studies; N=9,419
- FU=4.1±2.1 years

High risk (PWID/prisoners)
- 16 studies; N=819
- FU=2.9±1.6 years

HIV/HCV co-infected
- 7 studies; N=833
- FU=3.1±1.2 years

Recurrence rate/100 patient years

- Low risk: 0.23 (95%CI 0.18–0.28)
- High risk: 2.80 (95%CI 2.06–3.71)
- HIV/HCV co-infected: 4.78 (95%CI 3.97–5.71)

HCV Re-infection Rates

Young J et al CID 2017 May 1;64(9):1154-1162. doi: 10.1093/cid/cix126
Summary

• HCV infection in the HIV+ community can be eliminated using existing care structures
• Liver disease is still a major cause of morbidity/mortality in HIV+ patients
• HCV DAA therapies yield high efficacy in HIV/HCV co-infected populations, must be careful with drug-drug interactions