Advances in Hepatitis C Treatment for People with HIV Coinfection

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Disclosures

• Dr. Graham has joined Trek Therapeutics, a benefits corporation
Barriers to HCV Care

• Patients may harbor beliefs about hepatitis C that make them reluctant to seek care:
  – The treatment is worse than the HCV
    • Interferon almost killed someone I know
  – Everyone has to get a liver biopsy
    • Someone I knew almost died from a biopsy
  – Doctors don’t like to treat people like me
    • I feel judged by hepatitis doctors
  – Treatment is too expensive

• Patients may not realize that their HIV provider does not provide HCV treatment and/or GI docs are not comfortable with HIV
  – Late recognition of severe liver disease
  – Inappropriately labeled as poor treatment candidate
HIV/HCV Coinfection: Epidemiology

• About 25% of people living with HIV are co-infected with HCV (300-400,000)
• About 80% of people with HIV who inject drugs are also infected with HCV
• Rates of sexual transmission of HCV in HIV-positive people: ?
• HIV accelerates HCV disease: Faster rates of cirrhosis, higher risk of liver failure and liver cancer
• HCV is the leading cause of non-AIDS death in people living with HIV
• Increased risk of other co-morbidities (kidney disease, heart disease, bone disorders, etc)
Everyone with HIV needs to be tested for hepatitis C.

Some people need to be retested once a year or more frequently.
Screening for HCV in HIV-Infected Persons

• Screen at least annually in those with risk factors for ongoing exposure (3-6 months for people with higher risk exposures)
  – Sharing injection equipment
  – Sex (if HIV+ and/or engaged in sex with blood)
  – Sharing equipment for intranasal drug use (“snorting”)
  – Other blood-to-blood contact (e.g., sharing tattoo needle)

• Patients who are severely immuno-compromised may not be able to produce HCV antibodies; perform HCV RNA testing

• Acute HCV is common: If a patient has elevated ALTs and no history of liver disease, check for acute HCV infection with HCV antibody and RNA
Positive HCV Antibody Results Must be Followed by HCV RNA Test

• HCV Ab positive, HCV RNA detected
  – Patient has active HCV infection
  – They need referral to a hepatitis C providers for further evaluation
  – Counsel on transmission risks

• HCV Ab positive, HCV RNA not detected
  – Person was previously infected, but their body got rid of the virus (either through spontaneous clearance or from cure)
  – Patients can get re-infected with HCV—antibodies do not offer protection!
Chronic HCV Infection May Lead to Chronic Liver Disease and Liver Cancer

Chronic HCV infection can lead to the development of fibrous scar tissue within the liver. Over time, fibrosis can progress, causing severe scarring of the liver, restricted blood flow, impaired liver function, and eventually liver failure. Cancer of the liver can develop after years of chronic HCV infection.

Fibrosis
- Chronic HCV infection can lead to the development of fibrous scar tissue within the liver.

Cirrhosis
- Over time, fibrosis can progress, causing severe scarring of the liver, restricted blood flow, impaired liver function, and eventually liver failure.

Hepatocellular Carcinoma (with cirrhosis)
- Cancer of the liver can develop after years of chronic HCV infection.

Decompensated cirrhosis:
- Ascites
- Bleeding gastroesophageal varices
- Hepatic encephalopathy
- Jaundice

Chronic liver disease includes fibrosis, cirrhosis, and hepatic decompensation; HCC=hepatocellular carcinoma.
Initial Approach to Patients Diagnosed with Hepatitis C
Address Alcohol Use in HCV

- The CDC recommends brief alcohol intervention for all patients with HCV
- There is no “safe” amount of alcohol consumption
- Insist on absolute abstinence if patient has bridging fibrosis or cirrhosis
- Assess for risky alcohol use
  - Men: >2 drinks/day (>14/week) or more that 4 in one day
  - Women: >1 drink/day (>7/week) or more than 3 in one day
- Screen for alcohol misuse
  - How many times in the past year have you had X or more drinks in a day?”, where X is 5 for men and 4 for women, and a response of >1 is considered positive

Moyer et al. Screening and Behavioral Counseling Interventions in Primary Care to Reduce Alcohol Misuse: USPSTF Recommendation Statement. Annals Int Med; 14 May 2013 online
Determine Likelihood of Cirrhosis

- Noninvasive test results increase the likelihood of cirrhosis, especially if more than one are present:
  - APRI > 1.5 or FIB-4 > 3.25 (use on-line calculators)
    - FIB-4 more predictive of ESLD than liver biopsy (CROI 2014)
  - Hepascore or Fibrotest > 0.74
  - Fibroscan > 12.5
  - Platelets < 150,000
  - Albumin < 3.5
- Splenomegaly on exam or ultrasound
- Any signs of liver decompensation
- MELD and Child-Pugh scores (use on-line calculators)

FibroScan - Transient Elastography

- Ultrasound determines velocity of shear wave in m/s, which is proportional to liver stiffness in kilopascal (kPa)
- Entire process requires 15 to 20 minutes, provides immediate results
- Falsely elevated results: 
  - High ALT (>100)
  - Eating within 2 hours

Continuum of scores (in kPa)

<7 kPa = Stage 0-1
7-9.5 kPa = Stage 2
9.5-12.5 kPa = Stage 3
>12.5 kPa = Cirrhosis

>20 kPa = Increased risk liver-related complications

70+ kPa

Continuum of Fibrosis/Cirrhosis in HCV

Management of Patients with Hepatitis C and Cirrhosis

- Every 6 month screening for liver cancer
  - Usually ultrasound
  - Consider CT or MRI if highly nodular liver; first exam
- Screening for esophageal varices
  - Repeat every 1 - 3 years depending on results
- Counsel on symptoms of hepatic encephalopathy
- Vaccination for pneumococcus
- Counseling around medication use to avoid overdose or adverse events (including common drugs like Tylenol and NSAIDS)
- Counseling about complete abstinence from alcohol
- Evaluation for antiviral treatment
  - Cure of HCV can reduce liver failure and liver cancer, even in patients with cirrhosis (+/- HIV coinfection)
- Possible referral for liver transplant services

http://www.aasld.org/practiceguidelines/pages/guidelinelisting.aspx
SVR Associated With Reduced 5-Yr Risk of Death and HCC in All Populations

- SVR on IFN-based therapy was associated with substantial benefit vs no SVR
  - 62% to 84% reduction in all-cause mortality, 90% reduction in liver transplantation, 68% to 79% reduction in HCC

Recent Treatment Data and Guidelines
Multiple Validated Drug Targets

Graphic courtesy of Dr John Link, Not all-inclusive
Key Issues in HIV/HCV Coinfection

- Most people are candidates for HCV treatment with the proper support
- Most will have genotype 1 infection
- Most will be offered Harvoni or Viekira Pak
  – Will likely depend on insurance coverage
- In most cases follow guidelines for HCV monoinfection
  – Hcvguidelines.org
- Drug interactions with HIV medications most important difference
Journey to HCV Treatment

• Basic workup: HCV antibody, genotype/subtype, viral load, CBC, SCr, LFTs, PT/INR, albumin, liver fibrosis staging, height, weight, co-morbidities, current medication list and allergies, HCV treatment history, Rx insurance plan

• Select treatment candidate: social history, assess readiness and compliant, insurance status

• Select the best treatment regimen for each individual patient based on the clinical and insurance exclusivity information

• Establish a working relationship with a specialty pharmacy of your choice to work through prior authorization and drug obtaining process (note that some insurance plans may have their own preferred specialty pharmacy)

• Create an excel spreadsheet to keep track of all HCV patients’ treatments activities
Step 1:

- Complete assessment form for each treatment candidate
- Screen for drug-drug interactions and develop management plan
- Recommend having alternative treatment option (if applicable)
<table>
<thead>
<tr>
<th>Concurrent Medication</th>
<th>Harvoni allowed</th>
<th>Viekira Pak allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/ritonavir (Reyataz®/Norvir®)</td>
<td>Yes; inc tenofovir levels; monitor renal fx</td>
<td>Yes; no additional RTV and dose ATV with AM Pak</td>
</tr>
<tr>
<td>Darunavir/ritonavir (Prezista®/Norvir®)</td>
<td>Yes; inc tenofovir levels; monitor renal fx</td>
<td>No; (lowers DRV levels)</td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir (Lexiva®/Norvir®)</td>
<td>Yes; inc tenofovir levels; monitor renal fx</td>
<td>No</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (Kaletra®)</td>
<td>Yes; inc tenofovir levels; monitor renal fx</td>
<td>No</td>
</tr>
<tr>
<td>Efavirenz (Sustiva®)</td>
<td>Yes; inc tenofovir levels; monitor renal fx. May decrease LDV levels</td>
<td>No</td>
</tr>
<tr>
<td>Rilpivirine (Edurant®)</td>
<td>Yes</td>
<td>No (prolonged QT)</td>
</tr>
<tr>
<td>Tenofovir (Viread®)</td>
<td>Yes; See boosted PI notes</td>
<td>Yes</td>
</tr>
<tr>
<td>Raltegravir (Isentress®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Elvitegravir (in Stribild®)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dolutegravir (Tivicay®)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Abacavir (Ziagen)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Ledipasvir/Sofosbuvir: Genotype 1 Approved Indications

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommended Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naive with or without cirrhosis</td>
<td>12 wks*</td>
</tr>
<tr>
<td>Treatment experienced† <em>without</em> cirrhosis</td>
<td>12 wks</td>
</tr>
<tr>
<td>Treatment experienced† <em>with</em> cirrhosis</td>
<td>24 wks</td>
</tr>
</tbody>
</table>

*8-wk duration can be considered in treatment-naive pts without cirrhosis or HIV coinfection who have pretreatment HCV RNA < 6 million IU/mL.*

†Treatment-experienced pts who have failed treatment with pegIFN/RBV ± HCV PI.

- One pill once a day
- Can be taken with or without food
- Can be used in people with liver failure (decompensation)
- Cannot be used in people with more severe kidney disease (GFR <30 ml/min)
- Common side effects include headache, fatigue
- Ledipasvir needs stomach acid for solubility/absorption

Results: SVR12 by Prior Treatment Experience and Cirrhosis Status
HIV-HCV (ION-4)

Overall

Naïve vs Experienced

Cirrhosis Status

LDV/SOF 12 Weeks

No Cirrhosis

Cirrhosis

SVR12 (%)

321/335

179/185

258/268

63/67

96

95

97

96

94

Error bars represent 95% confidence intervals.
Naggie, CROI 2015; NEJM 2015

-HIV regimens: TDF/FTC, Efavirenz, Raltegravir, Rilpivirine
**Results: SVR12 in Subgroups**

**HIV-HCV (ION-4)**

<table>
<thead>
<tr>
<th>Overall</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>Black</td>
<td>Non-Black</td>
</tr>
<tr>
<td>HCV Genotype</td>
<td>1a</td>
<td>1b</td>
</tr>
<tr>
<td>Baseline HCV RNA (IU/mL)</td>
<td>&lt;800,000</td>
<td>≥800,000</td>
</tr>
<tr>
<td>Baseline BMI (kg/m²)</td>
<td>&lt;30</td>
<td>≥30</td>
</tr>
<tr>
<td>IL28B</td>
<td>CC</td>
<td>CT</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Prior HCV Treatment</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>ARV Regimen</td>
<td>EFV + FTC + TDF</td>
<td>RAL + FTC + TDF</td>
</tr>
<tr>
<td>Baseline CD4 (cells/μL)</td>
<td>&lt;350</td>
<td>≥350</td>
</tr>
</tbody>
</table>

**LDV/SOF 12 Weeks, N=335**

- Statistically significant in multivariate analysis

**SVR12, % (95% CI)**
# Characteristics of Relapsers

**HIV-HCV (ION-4)**

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
<th>BMI (kg/m²)</th>
<th>HCV GT</th>
<th>BL CD4 Count (cells/µL)</th>
<th>Cirrhosis</th>
<th>IL28B GT</th>
<th>BL HCV RNA ($log_{10}$ IU/mL)</th>
<th>HCV RNA &lt;LLOQ (Wk)</th>
<th>Timing of VF (FU wk)</th>
<th>Prior HCV Treatment</th>
<th>ARV Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>M</td>
<td>Black</td>
<td>24.1</td>
<td>1a</td>
<td>308</td>
<td>No</td>
<td>CT</td>
<td>7.3</td>
<td>2</td>
<td>4</td>
<td>N/A</td>
<td>EFV+FTC+TDF</td>
</tr>
<tr>
<td>58</td>
<td>M</td>
<td>Black</td>
<td>28.2</td>
<td>1a</td>
<td>553</td>
<td>No</td>
<td>TT</td>
<td>7.5</td>
<td>2</td>
<td>4</td>
<td>PEG+RBV</td>
<td>EFV+FTC+TDF</td>
</tr>
<tr>
<td>61</td>
<td>M</td>
<td>Black</td>
<td>22.4</td>
<td>1a</td>
<td>504</td>
<td>Yes</td>
<td>TT</td>
<td>7.0</td>
<td>4</td>
<td>4</td>
<td>N/A</td>
<td>EFV+FTC+TDF</td>
</tr>
<tr>
<td>61</td>
<td>F</td>
<td>Black</td>
<td>26.8</td>
<td>1a</td>
<td>144</td>
<td>Yes</td>
<td>CT</td>
<td>6.4</td>
<td>1</td>
<td>12</td>
<td>PEG+RBV</td>
<td>RAL+FTC+TDF</td>
</tr>
<tr>
<td>51</td>
<td>M</td>
<td>Black</td>
<td>30.0</td>
<td>1a</td>
<td>964</td>
<td>No</td>
<td>TT</td>
<td>6.5</td>
<td>2</td>
<td>4</td>
<td>NS5A+PEG+RBV</td>
<td>EFV+FTC+TDF</td>
</tr>
<tr>
<td>65</td>
<td>F</td>
<td>Black</td>
<td>24.8</td>
<td>1b</td>
<td>904</td>
<td>Yes</td>
<td>TT</td>
<td>7.0</td>
<td>2</td>
<td>4</td>
<td>N/A</td>
<td>EFV+FTC+TDF</td>
</tr>
<tr>
<td>60</td>
<td>M</td>
<td>Black</td>
<td>32.3</td>
<td>1a</td>
<td>435</td>
<td>No</td>
<td>TT</td>
<td>7.4</td>
<td>2</td>
<td>4</td>
<td>N/A</td>
<td>RAL+FTC+TDF</td>
</tr>
<tr>
<td>63</td>
<td>M</td>
<td>Black</td>
<td>42.7</td>
<td>1a</td>
<td>690</td>
<td>No</td>
<td>TT</td>
<td>7.3</td>
<td>4</td>
<td>12</td>
<td>PEG+RBV</td>
<td>EFV+FTC+TDF</td>
</tr>
<tr>
<td>55</td>
<td>M</td>
<td>Black</td>
<td>32.5</td>
<td>1a</td>
<td>933</td>
<td>No</td>
<td>CT</td>
<td>6.7</td>
<td>1</td>
<td>4</td>
<td>PEG+RBV</td>
<td>EFV+FTC+TDF</td>
</tr>
<tr>
<td>58</td>
<td>M</td>
<td>Black</td>
<td>24.8</td>
<td>1b</td>
<td>2069</td>
<td>No</td>
<td>TT</td>
<td>7.3</td>
<td>4</td>
<td>4</td>
<td>PEG+RBV</td>
<td>EFV+FTC+TDF</td>
</tr>
</tbody>
</table>

*Prohibited regimen (protocol violation).
BL, baseline; FU, follow-up; VF, virologic failure.
Ledipasvir Solubility Decreases as pH Increases: Products that Increase Gastric pH are Expected to Decrease Concentration of Ledipasvir

- Caltrate (all forms)
- Os-Cal (all forms)
- Tums (all forms)
- Viactiv
- Wellesse calcium/vitamin D
- Citracal (all forms)
- Alka-Mints®
- Calel-D®
- Calcid®
- Chooz®
- Miralac®
- Rolaids®
- Gas-X® with Maalox® (containing Calcium Carbonate, Simethicone)
- Rolaids® Plus Gas Relief (containing Calcium Carbonate, Simethicone)
- Titralac® Plus (containing Calcium Carbonate, Simethicone)
- Alamag®
- Alumina and Magnesia®
- Gen-Alox®
- Kudrox®
- M.A.H.®
- Maalox (all forms)
- Magagel®
- Magnalox®
- Maldroxal®
- Mylanta®
- Ri-Mox®
- Rulox®
- Mag-Ox®
- Maox®
- Uro-Mag®

Separate these OTC products and Harvoni administration by at least 4 hours.
# H2 Blockers and Proton Pump Inhibitors with Harvoni

<table>
<thead>
<tr>
<th>H2 blockers</th>
<th>H2 blocker may be administered at the same time with Harvoni OR 12 hours apart from Harvoni at a dose that does not exceed doses comparable to famotidine 40mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Famotidine 40mg BID</td>
<td></td>
</tr>
<tr>
<td>Ranitidine 150mg BID</td>
<td></td>
</tr>
<tr>
<td>Tagamet 800mg BID</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proton Pump Inhibitors</th>
<th>PPI doses comparable to omeprazole 20mg or lower can be administered at the same time with Harvoni under fasted conditions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole 20mg daily</td>
<td></td>
</tr>
<tr>
<td>Prevacid 30mg daily</td>
<td></td>
</tr>
<tr>
<td>Aciphex 20mg daily</td>
<td></td>
</tr>
<tr>
<td>Protonix 40mg daily</td>
<td></td>
</tr>
<tr>
<td>Nexium 20 to 40mg daily</td>
<td></td>
</tr>
</tbody>
</table>

[https://www.medicines.org.uk/emc/medicine/29471](https://www.medicines.org.uk/emc/medicine/29471)
BIDMC Acid-Blocker Strategy

• Thoroughly assess all prescription and over-the-counter use of all products
• Attempt one month trial off all acid blockers prior to starting Harvoni
• Provide counseling around non-pharmacological ways to reduce acid reflux
  – Eat at least 2-3 hours before bedtime
  – Avoid acidic or spicy foods
  – Use two pillows when sleeping
• Ensure avoidance of the “stomach aisle” in pharmacies
• If acid blockers are required, review exactly how to take them in oral and written form
• Document in notes so other providers do not prescribe these agents
Paritaprevir/RTV, Ombitasvir, Dasabuvir aka “Viekira Pak”

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment*</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a, without cirrhosis</td>
<td>VIEKIRA PAK + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a, with cirrhosis</td>
<td>VIEKIRA PAK + ribavirin</td>
<td>24 weeks**</td>
</tr>
<tr>
<td>Genotype 1b, without cirrhosis</td>
<td>VIEKIRA PAK</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1b, with cirrhosis</td>
<td>VIEKIRA PAK + ribavirin</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

- Viekira Pak only studied with ribavirin in HIV/HCV coinfection
- Avoid in liver failure
- Take with food twice a day
- No dose change needed in people with chronic kidney disease
- Common side effects include fatigue, nausea, itching, insomnia
Special Considerations with Ribavirin

- Common side effects include nausea, rash, fatigue, cough and irritability
  - Warn patients of “Riba-Rage”
- Ribavirin causes hemolytic anemia
  - Close monitoring of Hgb
  - Folic acid can be added
  - Avoid in patients with bad cardiac or pulmonary disease who may not tolerate anemia well
  - Dose reduction used for significant drops in Hgb
- Ribavirin is a teratogen
  - Female patients and female partners of male patients must use two forms of birth control while on therapy and for 6 months after
- If dose reduction required for anemia, decrease to 600 mg once a day (in the morning)
Paritaprevir/r+Ombitasvir+Dasabuvir+RBV in HIV/HCV genotype 1 Infection

- HIV regimens: TDF/FTC, Atazanavir, Raltegravir
- Cirrhosis = 19%
- Peg-IFN/RBV relapse, partial and null responder, 33%

12 week arm: one subject withdrew consent at week 10 (viral load UD); one subject relapsed
24 week arm: One subject had viral breakthrough, and two had re-infection after SVR

Wyles AASLD 2014; Lancet 2015
African American Patients Have Similar Cure Rates as Caucasians with All-Oral Treatment

Graham, JAMA 2015
Genotype 2

Naïve, with or without cirrhosis or Treatment experienced, no cirrhosis

- Sofosbuvir+RBV x 12 weeks

Treatment experienced, with cirrhosis

- Sofosbuvir+RBV x 12-16 weeks
- Sofosbuvir+Peg-IFN+RBV x 12 weeks

2014 IDSA/AASLD Recommendations: www.hcvguidelines.org
SVR in Genotype 2 Patients Treated with Sofosbuvir+Ribavirin for 12 Weeks

Treatment experienced, cirrhotic patients only had a 78% SVR with 16 weeks SOF+LDV. May wait for sofosbuvir + daclatasvir.
Genotype 3

Naïve, with or without cirrhosis or Treatment experienced, no cirrhosis

Sofosbuvir+RBV x 24 weeks

Sofosbuvir+Daclatasvir

Sofosbuvir+Peg-IFN+RBV x 12 weeks

Sofosbuvir+Daclatasvir

www.hcvguidelines.org + Product label for Daclatasvir
Daclatasvir + Sofosbuvir x 12 weeks in Genotype 3 HCV Infection

<table>
<thead>
<tr>
<th>Stage of Liver Disease</th>
<th>Treatment Naïve SVR Rate (%)</th>
<th>Treatment Experienced SVR Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cirrhosis</td>
<td>98%</td>
<td>92%</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>58%</td>
<td>69%</td>
</tr>
</tbody>
</table>

Presence of the baseline NS5A polymorphism Y93H further reduces SVR rates

Daclatasvir product label
Critical Role of Advocacy

• Share new information about advances in hepatitis C treatment

• If mental health or addiction is an issue, ensure that patient is engaged in services and is as stable as possible
  – Help them look like a treatment candidate
  – Have a back up plan if they become unstable

• If possible, go to at least one visit and describe support services (adherence, monitoring, help with appointments and transport, etc)