HIV, Hepatitis B and Hepatitis C

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Hepatitis B and C in PLWH

The goal of this talk is to use a cased-based format to discuss:

– Serologies
– Vaccinations
– Treatment
– Outcomes
Case #1: Patient AM

- 55 year old man diagnosed with HIV ten years ago in Puerto Rico.
- Never on meds
- CD4 count is 150, HIV VL is 1 million.
- Hepatitis A IgG negative
- Hepatitis B
  - HBV Surface Antigen negative
  - HBV Surface Antibody negative
  - HBV Core Antibody positive
- Hepatitis C Antibody Positive
Vaccinations

• HAV IgG negative: Hepatitis A Vaccine needed
• What do you think about HBV?
  – Further testing?
  – Vaccination?
Hepatitis B Testing

<table>
<thead>
<tr>
<th>Susceptible to Hep B</th>
<th>HepB sAg</th>
<th>HepB sAb</th>
<th>HepB cAb</th>
</tr>
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Needs Vaccination
Hep B Vaccination

• 3 doses of 20 µg HBsAg at 0, 1 and 6 months
• Testing of Hep B sAb 6-8 weeks after last dose
• If not >10 IU/L, consider revaccination
• 3 doses of 20 µg or 3 doses of 40 µg
# Hepatitis B Testing

<table>
<thead>
<tr>
<th></th>
<th>HepB sAg</th>
<th>HepB sAb</th>
<th>HepB cAb</th>
<th>Hep B VL</th>
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<tbody>
<tr>
<td>Active Infection</td>
<td>+</td>
<td>-</td>
<td>+ or -</td>
<td>Need to check</td>
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# Hepatitis B Testing

<table>
<thead>
<tr>
<th></th>
<th>HepB sAg</th>
<th>HepB sAb</th>
<th>HepB cAb</th>
<th>Hep B VL</th>
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<tbody>
<tr>
<td>Previous infection</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>? Need to check</td>
</tr>
</tbody>
</table>

If planning on treating for Hep C in future, would check Hep B VL now
## Isolated HBV Core Antibody

<table>
<thead>
<tr>
<th>Four options</th>
<th>HepB sAg</th>
<th>HepB sAb</th>
<th>HepB cAb</th>
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</thead>
<tbody>
<tr>
<td>1.) Acute HBV</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>2.) Distant infection</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3.) False positive cAb</td>
<td></td>
<td></td>
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<tr>
<td>4.) Chronic HBV infection</td>
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</tbody>
</table>

50% of people PLWH with negative Hep B sAb and negative Hep BsAg had positive HBV core Antibody

1/42 (2.4%) of PLWH with Isolated Hep B cAb had positive HBV VL
Clinical Debate

• Do you vaccinate this patient for Hep B in the patient with isolate Hep B core antibody positivity?
Vaccination Against Hepatitis B Virus (HBV) in HIV-1–Infected Patients With Isolated Anti–HBV Core Antibody: The ANRS HB EP03 CISOVAC Prospective Study

- 54 PLWH with isolated core antibody
- Vaccinated: Week 4 after vaccination 25 (46%) showed Hep B sAb >10
  - 24 people followed, and at month 18, 50% lost their sAb
- 27 people received Double-Dose HBV at Week 5, 9, and week 24
  - At week 28: 24 of the 27 people (89%) had + HepB sAb
  - 18 months later, 81% still had Hep B sAb
Vaccination Against Hepatitis B Virus (HBV) in HIV-1–Infected Patients With Isolated Anti–HBV Core Antibody:

“Thus, it can be suggested that all patients with isolated anti-HBc profile who do not present with an anti-HBs titer of >100 mI/mL 4 weeks after single recall HBV vaccine dose should be further vaccinated with triple double-dose reinforced scheme given its better efficacy and its good tolerance.
Hep B Vaccination: Summary

• Check Hep B VL in people who have positive isolated Hep B core antibody
• Probably a good idea to vaccinate people with isolated Hep B core antibody
• Start vaccination with 20 μg and if no response consider moving to 40 μg
Case #2: Patient JL

- 55 year old Haitian Male with HIV and HBV
  - Hep BeAg+, HepBeAb negative
- Also has CKD 3, diabetes, cardiovascular disease, severe back pain
- Was on 3TC/ABC + Lopinavir/R and switched to FTC/TDF + Lopinavir/R
HBV and HIV: US Health and Human Services: Updated 7/14/2016

- If PLWH has +HepBsAg, do a HBV VL
- ART should be initiated with TDF/FTC or TAF/FTC (or TDF and 3TC)
- If TDF or TAF can’t be used, add entecavir to a fully suppressive HIV regimen
- Peg-interferon alfa monotherapy may be used in certain patients.
Hepatitis B Virus in Patient with HIV

FTC/TDF + Lopinavir/R + Entecavir

HBV Resistance: Resistant to 3tc PreCore Mutation Detected
Hepatitis B Virus in Patient with HIV

Log Hepatitis B Viral Load

2011 2012 2013 2014 2015

FTC/TDF + Lopinavir + Entecavir

Peg Interferon

FTC/TDF + Raltegravir + Entecavir
Hepatitis B Virus in Patient with HIV

Log Hepatitis B Viral Load

FTC/TDF + Lopinavir + Entecavir
FTC/TDF + Raltegravir + Entecavir
Dolutegravir + TAF/FTC + Entecavir

Peg Interferon

HBV VL = 56
Efficacy and Safety of Switching to a Single-Tablet Regimen of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in HIV-1/Hepatitis B–Coinfected Adults

Joel Gallant, MD, MPH,* Jason Brunetta, MD,† Gordon Crofoot, MD,‡ Paul Benson, DO,§ Anthony Mills, MD,‖ Cynthia Brinson, MD,¶ Shinichi Oka, MD,# Andrew Cheng, MD, PhD,** Will Garner, PhD,** Marshall Fordyce, MD,** Moupal Das, MD, MPH,** and Scott McCallister, MD,** the GS-US-292-1249 Study Investigators

- 100 adults with HIV/HBV
- High rates HIV and HBV suppression
- Improved renal function
- Reduced biomarkers of bone turnover

(J Acquir Immune Defic Syndr 2016;73:294–298)
Long Term Care: Hep B in HIV

• Liver imaging every 6 months
  – Five to six fold increase in HCC incidence in HIV compared to no HIV
  – People with HBV do not need to have cirrhosis to get HCC (unlike people with HCV, who need cirrhosis first before HCC is a risk)
  – If you find HCC, consider transfer to liver transplant center.

• Make sure patient knows that the HIV meds are also treating their HBV
Case #3: PM

- 42 year old man presented to GI clinic with 3 months of diarrhea after travelling in Greece
- Works as an accountant in Boston
- Did not see a doctor since 2005
- MSM
- Reported monogamous relationship
- History of cocaine use (none recently)
- Heavy ETOH use
Case #3: PM

- GI tested for enteric pathogens and recommended HIV testing
- Microsporidia infection found
- HIV Ab positive, CD4 count 20
- Referred to ID clinic
- Hep A IgG+, Hep BsAb+, Hep C Ab negative
- Originally on ATZ/r → Atripla → Complera
- CD4 count rose to 200 within one year
RUQ u/s showed fatty liver
<table>
<thead>
<tr>
<th>Month/Year</th>
<th>RPR</th>
<th>HCV RNA</th>
<th>HCV Ab</th>
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<tbody>
<tr>
<td>Jan 2011</td>
<td>Non Reactive</td>
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<td>Non Reactive</td>
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<td>May 2012</td>
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<tr>
<td>August 2014</td>
<td></td>
<td>Reactive</td>
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<tr>
<td>October 2014</td>
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<td>&gt;7,700,000</td>
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HCV exposure

Symptomatic hepatitis (10–15%)
- Chronic infection: 48–75%
- Spontaneous clearance: 25–52%

Asymptomatic infection (85–90%)
- Chronic infection: 85–90%

Incubation period 2–12 weeks
HIV/HCV Co-Infection

• 1/3 of people with HIV have HCV co-infection
• Rates of spontaneous clearance of HCV less (5% vs. 20%) if have HIV infection
• Until recently, main risk factor for HCV in people living with HIV (PLWH) was IDU
• Epidemiology is changing to involve more sexual transmission, especially in MSM
2004 IDSA Guidelines for Primary Care for people with HIV

• At first visit, all patients should have Anti-HCV
• HCV RNA should also be measured for HCV-negative persons with unexplained liver disease, because \(~6\%\) of HIV-positive persons do not develop HCV antibodies
• RPR recommended yearly

Aberg J et al CID 2004
All HIV-infected patients should be screened for hepatitis C at diagnosis & on an annual basis.

HIV-infected patients should be screened for hepatitis C virus (HCV) infection upon initiation of care by a test for HCV antibody and annually thereafter for those at risk.
Tufts MC: HCV testing in PLWH

Retrospective Study:
- 9% of the clinic had no record of Hep C testing
- < 2/3 of PLWH who tested Hep C Ab negative were re-tested
- >85% had repeat RPR testing

Quality Improvement Study
- Electronic prompt to remind providers about annual Hep C testing
- New identification of 8 new cases of incident Hep C

Wurcel A et al OFID Feb 2016;
Wurcel A et al OFID May 2017
HCV Testing Take Home

- Test Hep C Ab every year in PLWH who have negative Hep C Ab
- If they have tested positive in the past, and cleared, then should consider yearly HCV RNA testing or ALT/AST testing
HCV Treatment: An Evolution

Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, 2011 meeting. Slide borrowed from Dr. Hannah Lee, modified by Danna Nisai
Welcome to the New HCVGuidelines.org
The AASLD and IDSA in partnership with the panel have created an updated web experience to facilitate easier and faster access to this important resource. Please select a patient profile from the menu above, click on a Guidance section below, or use the search box to begin.

Search the Guidance
Enter your keyword:  Search

Recent Announcements
Gilead's Glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir have been approved by the FDA; update coming soon.
In addition to updates

+ Contents and Introduction - Select a Page

+ Testing, Evaluation, and Monitoring of Hepatitis C - Browse Topics

+ Initial Treatment of HCV Infection - Choose Patient Genotype

+ Retreatment of Persons in Whom Prior Therapy Has Failed - Choose Patient Genotype

+ Management of Unique Populations - Review Recommendations
HCV Treatment in HIV

• In the age of Interferon, PLWH were less likely to clear HCV than people without HIV.

• In the era of all oral medication:

No difference in viral clearance rates between people with HIV and people who don’t have HIV!
Active Drug Use

• Active drug use should not be a barrier to treating HIV.

• HIV viral load suppression is a sign that people with HIV who use drugs can take meds consistently.

• If patient has active drug use and can show up for 2 consecutive appointments, that says to me that they can be engaged in HCV treatment.
HCV Meds (June 2017)

• Sofosbuvir (NS5B Polymerase Inhibitor): Sovaldi™
• Daclatasvir (NS5A Inhibitor): Daclatasvir™
• Ledipasvir (NS5A Inhibitor) + Sofosbuvir = Harvoni™
• Velpatasivir (NS5A Inhibitor) + Sofosbuvir = Epclusa™
• Elbasvir (NS5A)/Grazoprevir (NS3/4A Protease): Zepatier™
• Paritaprevir (PI), ombitasvir (NS5A Inhibitor), dasabuvir (non-nuc NS5B polymerase inhibitor): Viekira Pak™
HCV Meds

- Sofosbuvir (NS5B Polymerase Inhibitor): Sovaldi™
- Daclatasvir (NS5A Inhibitor): Daclatasvir™
- Ledipasvir (NS5A Inhibitor) + Sofosbuvir = Harvoni™
- Velpatasivir (NS5A Inhibitor) + Sofosbuvir = Epclusa™
- Elbasvir Grazoprevir (NS5A Inhibitor) / NS3/4A Protease Inhibitor): Zepatier™
- Paritapraivir (PI), ombitasvir (NS5A Inhibitor), dasabuvir (non-nuc NS5B polymerase inhibitor): Viekira Pak™

Just Approved July 2017:

- Glecaprevir/Pibrentasvir: Mavyret™
- Sofosbuvir/Velpatasvir/Voxilaprevir: Vosevi™
My Decision Tree for Initial DAA Treatment

Does Patient have active Hep C?

YES

Geno 1, 4
Sofosbuvir+ Ledipasvir

Geno 2, 3
Sofosbuvir+ Velpatasvir
My Decision Tree for Initial DAA Treatment

Does Patient have active Hep C?

**YES**

- Geno 1, 4: Sofosbuvir+ Ledipasvir
- Geno 2, 3: Sofosbuvir+ Velpatasvir
- Geno 5,6
Why not the other Hep C meds?

• Potential interactions
• No additional testing needed
• Pill Burden
• The ID pharmacist has successfully negotiated with insurance companies to get which medications I want for PLWH
Resistance Testing

- Correct term: Resistance-Associated Mutations (RAs)
- Test for RAs with NS5A test
  - Geno1a and need to use elbasvir/grazoprevir
    - If NS5 RA mutation present, need 16 weeks and RBV
  - Geno 3 cirrhotic:
    - If Y93 mutation there (if it is, add RBV)
How Long To Treat:

• Treatment course of less than 12 weeks is not recommended for PLWH
• May need 16 or 24 weeks depending on the patient and the medication.
Ribavirin?

• There are certain times when RBV is recommended:
  – Geno1a with NS5A RA treated with E/G
  – Geno3 cirrhotics treated with sof/vel NS5A RA
  – More complex patients (decompensation, treatment experienced, etc).
Patient DC

• 56 year old male I saw in 2014
  – HIV
  – Lymphoma 2001 (remission)
  – PVD (stents in left and right leg)
  – CAD (stents 2007, 2009)
  – HCV Geno 1a, cirrhosis
  – DM (7.6 HgbA1c)
May 2014

- HIV meds: Atazanavir/r + Truvada
- Other: Crestor 20 mg
- CD4 507 and HIV RNA undetectable

We wanted to treat him with LDV/SOF but we were concerned about drug interactions.
Med Interactions: Concerns in the early days

• Main concern: TDF + LDV
  – LDV inhibits the P-glycoprotein efflux pump expressed in the gut
  – Extra TDF gets absorbed leading to increased TDF levels and potential for renal impairment

• PI/r + TDF + LDV
  – Tenofovir levels increased by 40-60% in healthy controls taking PI/r + SOF/LDV
  – ATZ levels increased by 63%

German P, CROI 2015, Abstract 82
Interactions: SOF/LDV+ TDF

Virologic Response Following Combined Ledipasvir and Sofosbuvir Administration in Patients With HCV Genotype 1 and HIV Co-infection

- Open label single center trial
- 50 people with HIV/HCV
- Most people on HIV meds including TDF/FTC
- No Protease Inhibitors allowed
- No changes in renal function
- All but one had SVR

Osinusi A, JAMA 2015
Interactions: SOF/LDV+ ATZ+ TDF

- Study of 96 HIV/HCV co-infected on darunavir/r OR atazanavir/r + TDF/FTC + SOF/LEDIP
  - 95/96 completed study
  - Most adverse events (AEs) were Grade 1 or 2.
    - Ocular icterus with ATV (22%)
    - Headache (19%)
    - Nausea (18%).
    - One SAE of abdominal pain (Grade 3) was concluded related to ATV/r+TDF by the investigator

German P, CROI 2015, Abstract 82
HCV Drug-Drug Interactions

• HIV
  – Absolutely no tipranivir
  – Etravirine has not been studied but is not recommended
  – Efavirenz reduces velpatasvir levels so co-administration is not recommended.
  – If using boosted PI, try to switch TDF to TAF

• Remember to ask about antacids!
  – Drop omeprazole dose to 20 mg
  – 4 hours between meds and antacids
Non-Sofosbuvir HCV regimens

• **Viekira Pak™**: Geno 1, 4
  – Has ritonavir in it, so if patient on ritonavir ask them to stop
  – No efavirenz or rilpilvirine
  – Safe with Ataz/R combinations (Turquoise 1) but not darunavir/R
  – Think about methadone and buprenorphine

• **Zepatier™**: Geno 1
  – If 1a: need to do NS5A testing looking for resistance associated mutations and if present extend to 16 weeks
  – Meds:
    – Yes: Dolutegravir, Raltegravir, Rilpivirine
    – No efavirenz; No ritonavir boosted PI
HBV Reactivation Risk

• October 2016, FDA release black box warning about potential for HBV reactivation upon treatment for HCV.
  – 24 cases of reactivation, 2 people died, one needed a liver transplant
  – None of them had HIV

• People with HIV and history of HBV will likely be on 2 meds for HBV treatment
On treatment monitoring

• Check creatinine 2-4 weeks after treatment

• Check HCV VL after 4 weeks and then 12 weeks after treatment
  – If HCV RNA is undetectable 12 weeks out from treatment, can tell patient they are cleared.
Follow Up Patients of PLWH After SVR

- Annual testing for HCV by HCV VL or AST/ALT
- Cirrhosis related screening: endoscopy, HCC monitoring with ultrasounds every 6 months
- Risk reduction counseling
  - Risk of reinfection
    - Study of 606 MSM with HIV and HCV in Europe
    - After viral clearance, 24.5 % presented with new HCV infection
  - Alcohol
  - Fatty Liver Disease

Ingiliz, P. Journal of Hepatology 2017
What is the evidence for DAAs?

• High cost of medications
• What is the evidence that these medications are safe and lead to increased lifespans, less disease and increased quality of life?
• We could not reliably determine the effect of DAAs on the market or under development on our primary outcome of hepatitis C related morbidity or all-cause mortality.
• There is very low quality evidence that DAAs on the market or under development do not influence serious adverse events.
• None of the 138 trials provided useful data to assess the effects of DAAs on the remaining secondary outcomes (ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy, and hepatocellular carcinoma).
IDSA/AASLD Response

We are ... troubled by the implications of this Review for the ongoing international efforts to halt the HCV epidemic, and to give patients back their futures....we believe that the Cochrane Review does a grave disservice to these efforts and to patients living with chronic HCV infection, a disease responsible for tens of thousands of deaths around the world each year.
SVR and All-cause Mortality in CHC Patients with Advanced Fibrosis

530 patients followed for a median of 8.4 years

- Baseline factors significantly associated with all-cause mortality:
  - Older age
  - Genotype 3 (2-fold increase in mortality and HCC)
  - Higher Ishak fibrosis score
  - Diabetes
  - Severe alcohol use

Clearance of HCV with DAAs has been associated with:

- Improved liver function
- Decreased risk for HCC
- Improved glycemic control
- Improved cutaneous manifestations of HCV

HCV: What the future holds:

• Shorter courses?
  – Mavyret™ pan-genotypic 8 weeks

• Treatment of Re-Infection
  – Vosevi™ recommended, but has a PI in it so need to watch with boosted regimens.

• Emergences of Resistance

• Do we need to test HCV genotype?

• Will cost go down with market competition?
What does the future hold in the world of HCV treatment?

• Shorter courses?
  – Mavyret™ is 8 week regimen

• Treatment of Re-Infection
  – Vosevi™ recommended, but has a PI in it so need to watch with boosted regimens.

• Emergences of Resistance

• Do we need to test HCV genotype?
  – Mavyret™ pan-genotypic

• Will cost go down with market competition?
Thank you for your time!

• Acknowledgements:
  – Sarah Perez, PharmD
  – Katie Foss
  – Deirdre Burke MPH

Please feel free to email me with questions/thoughts: awurcel@tuftsmedicalcenter.org