Liver Disease and HIV Infection

Marion G. Peters, MD
Professor of Medicine
Northwestern University
Chicago, Illinois

Financial Relationships With Commercial Entities

Dr. Peters has served as an advisor to Abbott, Antios, Aligos, and Atea. Her spouse is employed by Hoffman-La Roche. (Updated 7/30/20)

Learning Objectives

After attending this presentation, learners will be able to:

▪ Describe most common causes of liver disease in people living with HIV (PLWH)
▪ Determine how to evaluate abnormal liver tests in PLWH
▪ Discuss new issues with HBV, HCV and fatty liver disease in PLWH
Drug-related Hepatotoxicity

Liver Disease in PLWH

- Alcohol
- Drug Mediations
- HCV / HBV Other Liver Diseases
- NAFLD
- Antibiotics: TB, fungal, bacterial
- NSAIDS
- Neuropsychiatric medications
- OTC e.g. herbal medications

Evaluation of Abnormal LFTs in PLWH

- Liver Tests:
  - Function: Albumin, bilirubin, INR
  - Inflammation: AST, ALT
  - Cholestasis: Alk Phos, bilirubin
  - portal HTN: platelets, WBC

- Common liver diseases:
  - HBV: HBsAg, anti-HBs, anti-HBc
  - HCV: HCV Ab, HCV RNA
  - NAFLD: Fasting glucose, TG, cholesterol, Hgb A1c

- Less common:
  - Metabolic: iron, Tt, ferritin (hemochromatosis), Ceruloplasmin (Wilson Disease)
  - Autoimmune diseases: AMA, IgM (for PBC), ASMA, ANA, IgG (for AIH)

- Hepatotoxicity
  - Fibrosis: APRI (AST/Platelet ratio)
  - FIB-4 (AST, ALT, plt, age)

- Vaccination status for HAV (IgG) and HBV
- Liver imaging and fibrosis assessment

Worse outcomes with HBV-HIV coinfection

- HIV HBV vs HBV
  - higher % HBeAg positivity
  - Lower loss of HBsAg after acute infection (79% vs >95%)
  - higher HBV DNA levels
  - longer duration of viremia
  - lower aminotransferase levels
  - more rapid progression to cirrhosis

- HIV HBV vs HIV
  - 14-fold higher liver-related mortality
  - higher risk of progressing to AIDS or death
HBV-HIV still a problem in this decade

- Analysis of 72,584 HBV; 133,880 HIV; and 8,155 HBV/HIV

**Compared to HIV monoinfection**
- Higher liver related admissions: HBV/HIV patients (48%) vs HIV (28%, P<0.001)

**Compared to HBV monoinfection**
- HBV/HIV higher liver-related mortality (OR 1.73, 95% CI 1.20-2.48)
- HBV/HIV higher all cause mortality (OR 1.50, 95% CI 1.10-2.04)
- Longer length of stay HBV/HIV (+1.41 days, 95% CI 0.84-1.99)

2011 US Nationwide Inpatient Sample

Rajbhandari JVH 2018

Treatment of HBV HIV

- ART including agents with activity against HIV and HBV is recommended for all patients co-infected with HIV and HBV, regardless of CD4 cell count or need for HBV treatment
- ART must include **two drugs active against HBV**, preferably tenofovir and emtricitabine, regardless of the level of HBV DNA. Such a regimen will
  - reduce the likelihood of immune reconstitution inflammatory syndrome (IRIS) against HBV
  - reduce risk of resistance which could occur with newer regimens without HBV active drugs or with 3TC or FTC alone

DHHS Guidelines 2017

With current therapies

HBsAg loss in HBV monoinfection is a high bar...

<table>
<thead>
<tr>
<th>Time (yrs)</th>
<th>Entecavir</th>
<th>Tenofovir</th>
<th>Peginterferon</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 Yr</td>
<td>2.0%</td>
<td>9.3%</td>
<td>1.0%</td>
</tr>
<tr>
<td>1.5-2.0 Yrs</td>
<td>7.5%</td>
<td>37.5%</td>
<td>0%</td>
</tr>
<tr>
<td>3.0-4.0 Yrs</td>
<td>6.0%</td>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*HBsAg is sustained undetectable HBV DNA*
With current therapies HBsAg loss is a high bar...

Not head-to-head trials; different patient populations and trial designs
Extended Treatment With Nucleos(t)ides* vs 1 Yr Peginterferon

*With sustained undetectable HBV DNA.

Loss of HBsAg in HIV/HBV with ART therapy

<table>
<thead>
<tr>
<th>Country</th>
<th>N</th>
<th>% HBsAg loss</th>
<th>Predictor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zambia</td>
<td>284</td>
<td>10.2 % at 2 years</td>
<td>BL CD4 &lt; 350 OR 4.94 (1.02-23.8)</td>
<td>Chirwa et al 2020</td>
</tr>
<tr>
<td>Germany</td>
<td>359</td>
<td>18% median 4 yrs</td>
<td>Less robust CD4 response associated with non-seroconversion</td>
<td>Boesecke et al CROI 2019</td>
</tr>
</tbody>
</table>

CROI 2019: not clear if adult acquired (20% chronic) HBV or perinatal (95% chronic) Increase in clearance with ART- Matthews
Protection of ART: HBV PrEP

HBV in PLWH Summary

- HIV increases HBV chronicity after acute HBV infection
- HBV increases antiretroviral-related hepatotoxicity
- HIV/HBV co-infection increases the risk of end stage liver disease compared to HBV alone
- Tenofovir based therapy can be HBV PrEP
- ART can lead to loss of HBsAg especially in first 1-2y
- Screen all HBV patients for HCC not just those with severe fibrosis
- There are new drugs on the horizon
  (Virologic failures may indicates poor adherence)
  (Reactivation of HBV can occur with immune suppression)

HCV in PLWH

- DAA are highly effective in HIV/HCV co-infection
- Treatment of HCV is same regardless of HIV but
  - Drug-drug interactions greater, esp with NS3 PI containing regimens
  - TDF regimens appears safe with LDV/SOF, SOF/VEL
- Switch of ARVs prior to DAA therapy - likely safe and effective- ☑️ stable
- Early treatment of acute HCV is successful
- Reinfection can occur
- HCV cure improves survival (liver, AIDS, all cause), renal dz and diabetes
Lower Mortality after SVR in HIV HCV

Overall Mortality

Liver-related Death

5 y follow-up: SVR associated with
Significant decrease in diabetes mellitus
(sHR 0.57; 95% CI 0.35 - 0.93; P = .024)
Decline in chronic renal failure
(pHR 0.43; 95% CI 0.17 - 1.09; P = .075)

Lower AIDS-defining conditions: P = .003
Lower non-liver-related deaths: P = .002
Lower non-liver-related, non-AIDS-related deaths: P = .002

Predictors of HCC post HCV SVR

33,005 VA patients; 10,827 SVR
100 new HCC cases

Incidence rate of
• No SVR 1.32% per year
• SVR to IFN-based Rx 0.33% per year

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis at SVR</td>
<td>6.69 (4.3-10.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age &gt;65</td>
<td>4.51 (2.0-10.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Age 55-64 y</td>
<td>2.04 (1.3-3.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hispanic vs Caucasian</td>
<td>2.3 (1.1-4.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>DM</td>
<td>1.80 (1.2-2.9)</td>
<td>0.005</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.68 (1.08-2.60)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Post-HCV cure follow-up depend on pre Rx Fibrosis Stage

Assess Pre-treatment Fibrosis Stage

**PRE**
- Low F0-1
  - No further monitoring needed; release back to PCP
- Intermediate F2
  - Regress
- Advanced F3-4
  - Progress

**POST**
- No further monitoring needed; release back to PCP
- Monitor for progression to advanced fibrosis
- Long-term follow-up surveillance for HCC varies

---

**HCV: Incident Infection**

- HCV incidence is still increasing in French HIV-infected MSM. Cote Liver International 2016

**Treatment as prevention**

- Declining HCV incidence in Dutch HIV+ MSM after unrestricted access to HCV therapy. deKempa et al. Clin Inf Dis, 2018

---

**HCV: Reinfection and spontaneous clearance**

- HCV Ab is not protective
- Reinfection can occur
  - Germany: GECCO 9
  - 9/02/100py in MSM; 1.14/100py in PWID
  - Madrid: 5.93 per 100 patient-years in MSM
  - Canada: 3.1 per 100 patient-years active PWID
  - Spontaneous clearance after acute HCV is lower in PLWH

- SC: 11.9% (409/364)
- PV: 88.1% (88/100)

SVR: 75.6% (245/324); Reinfections: 17% (51/300)
Concomitant Liver Disease

Prospective Longitudinal cohort
- N=275, HIV/HCV and HCV
- >95% with liver bx prior to treatment
- After SVR abnormal LE in ~12% overall, 20% in PLWH
- Risk factors for LE elevation
  - HIV (ARV toxicity)
  - Steatosis
  - ETOH
  - Statin use
  - Severe fibrosis/cirrhosis

HCV Summary in PLWH
- Many benefits of HCV cure: liver and non-liver- systemic inflammation
- Those with F3/4 pre-treatment need HCC monitoring post-SVR
- Imaging and alfa fetoprotein q 6months
- Need to stage fibrosis pre-treatment to optimally monitor post-cure
- Concurrent alcohol or fatty liver places patients at risk for future cirrhosis
  - Monitor for fibrosis progression in these patients
- Counsel healthy liver practices for all- alcohol, drugs, diet, lifestyle, MS
- Monitor for reinfection in at-risk patients
  - Discuss reinfection risk with patient

NAFLD in the general population and high risk groups

NAFL: non alcoholic fatty liver
- Fat
- Steatohepatitis: NASH
- Fat
- Inflammation
- +/- Fibrosis
- Cirrhosis
- HCC
**Risk Factors**

**Metabolic Syndrome**
- Obesity/central adiposity
- Insulin resistance
- Hypertriglyceridemia
- Hypertension

NAFLD is the hepatic manifestation of the metabolic syndrome

Emerging associations:
- Hispanic ethnicity
- Hereditary/genetic (PNPLA3)
- Polycystic ovary syndrome (PCOS)
- HIV
- Sleep apnea
- Hypothyroidism

---

**Primary NAFLD vs HIV-associated NAFLD**

<table>
<thead>
<tr>
<th></th>
<th>Primary NAFLD</th>
<th>HIV-associated NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD Prevalence</td>
<td>~30%, varies by study</td>
<td>35%, HIV not independent risk factor</td>
</tr>
<tr>
<td>NAFLD Risk Factors</td>
<td>Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, hereditary/genetic</td>
<td>Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, hereditary/genetic</td>
</tr>
<tr>
<td>Ethnicity/Other</td>
<td>NAFLD at lower BMI “lean NASH”</td>
<td>HIV-specific older NRTI’s, “D-drugs”, early generation PI’s, lipodystrophy</td>
</tr>
<tr>
<td>NAFLD Prevalence</td>
<td>25-10% of NAFLD patients with liver biopsy</td>
<td>42% of NAFLD patients with liver biopsy</td>
</tr>
<tr>
<td>NASH Progression</td>
<td>NAFLD: stage 0-4</td>
<td>HIV: stage 0-4</td>
</tr>
<tr>
<td>Long-term outcomes</td>
<td>Increased CVD risk, increased liver-related and all-cause mortality</td>
<td>Emerging evidence of independent NASH risk, lower deaths as long-term outcomes</td>
</tr>
</tbody>
</table>

Determine liver fibrosis: FIB-4 (AST, ALT, age, platelets); Nash Fibrosis score (age, BMI, hyperglycemia, platelets, albumin, AST/ALT) *Stanley Lancet HIV 2019

Determine inflammation: liver biopsy; abnormal ALT (47% had NASH, Lemoine JAIDS 2019)

---

**Management options**

- **Lifestyle Change**
  - Diet
  - Exercise
  - Bariatric surgery

- **Hepatitis C Virus (HCV)**

- **Treat Metabolic Syndrome**
  - Hypertension
  - Dyslipidemia
  - T2DM

- **Chemoprevention**
  - Vitamin E (not DMF)
  - Pioglitazone (weight gain)
  - Trials include: Tesamorelin (GHRH), FXR agonists (OCA), CCR2/5 antagonists (cenicriviroc), PPAR FGF19 and GLP-1 agonists

**CAD** 1st cause of death in NAFLD; 25% major CV events have NAFLD

---

Summary of NAFLD in PLWH

- NAFLD is an umbrella term that includes NAFL and steatohepatitis (NASH)
- NAFLD is common in PLWH
- NASH (inflammation +/- fibrosis) – higher progression to cirrhosis
- Biopsy is needed to diagnose NASH
- NASH is higher in PLWH
- Steatogenic and fibrotic effects of HIV/ART likely impact the natural history
- PLWH at higher risk for “lean” NAFLD (45% in one series)
- NAFLD Prevalence is likely to increase with aging HIV+ population
- Main risk factors are metabolic, genetic/hereditary
- Leading cause of death in NAFLD: CAD
- NAFLD is an important contributor to HCC incidence and need for liver transplant
- Management hinges on weight loss, exercise, avoiding added carbohydrates, metabolic syndrome control

Hepatocellular carcinoma in PLWH

- Increasing prevalence of HCC with longer life span
  - Viral hepatitis, ETOH and NAFLD most common cause of cirrhosis
  - Treatment of viral hepatitis decreases fibrosis/cirrhosis and risk of HCC
  - But HCC can occur after HCV cure
  - HCC occurs in younger PLWH with likely worse survival
  - Essential to diagnose cirrhosis - Fibroscan, APRI, FIB-4, imaging if PHTN
  - Screen all HBV patients (HCC can occur without F3-4) and all cirrhotics
  - Screening and early diagnosis critical for optimal therapy
  - Access to therapies includes locoregional therapy and liver transplant

Liver Disease in PLWH

- There is a lot of liver disease in HIV persons
  - HCV can be treated and can recur
  - HBV: new drugs in pipeline
  - NAFLD major new disease requiring diagnosis and management of metabolic syndrome
- While viral hepatitis, alcohol and NAFLD are most common, abnormal LFTs should be evaluated as in HIV negative persons
- Less hepatotoxicity with newer ART
- With longer life span
  - Increasing morbidity and mortality from liver disease
  - Increased HCC - so need to determine amount of fibrosis