Fundamentals in the Care of People with Hepatitis B and C Co-Infection

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Learning Objectives
Upon completion of this presentation, learners should be better able to:

• Review the epidemiology of viral hepatitis and HIV co-infection
• Define management concerns with HCV co-infection
• Define management concerns with HBV co-infection
Faculty and Planning Committee Disclosures

Please consult your program book.

Off-Label Disclosure

The following off-label/investigational uses will be discussed in this presentation:

- All-oral therapy in HIV-HCV co-infected patients
HBV, HCV and HIV

- Substantial morbidity world wide
- HBV infection 370 million chronic infections
- HCV infection 130 million
- HIV infection 40 million
  - 2-4 Million with HBV
  - 4-5 Million with HCV
- Share common routes of transmission,
  - Differ in efficiency during exposures and in geographic prevalence

J Hepatol. 2006; 44(1 Suppl):S6-9 (ISSN: 0168-8278)
HBV CO-INFECTION
What percentage of HIV infected individuals show evidence of past or active HBV infection?

A. <10%
B. 10-25%
C. 25-50%
D. 50-70%
E. >70%
Prevalence

• 70-90% of HIV-infected in US evidence of past or active infection
  – age at time of infection and mode of acquisition
  – HIV-infected persons are half as likely to spontaneously clear HBV.

Am J Gastroenterol. 2000 May;95(5):1316-22
Which of the following is true regarding HIV infected individuals co-infected with hepatitis B?

A. Both viruses are always suppressed by ART therapy
B. HBV increases the virulence of HIV
C. HIV increases the risk of end stage liver disease secondary to HBV
D. The viral load of HBV is low as only one virus can be dominant.
Impact of HIV on the Course of HBV Infection

- Less symptomatic acute infection
  - Lower spontaneous clearance
- Higher levels of HBV DNA
- Lower rates of HBeAg clearance
- Increased risk of cirrhosis and ESLD
  - Liver-related mortality 2-3 times higher in HIV/HBV-coinfected (14% vs 6%)

Impact of HBV on the Course of HIV Disease

• Recent data have not found HBV coinfection to have a substantial impact on immunologic or HIV virologic responses to ART or on the development of AIDS-defining illness or HIV-related death.

Diagnosis of HBV in HIV Infection

- HIV-infected individuals should be screened for HBV coinfection with HBsAg
- If HBsAg is negative, HBsAb, HBcAb should be assessed
  - Vaccinate if negative
- HBsAg positive: assess HBeAg, HBeAb, HBV DNA
Adverse Outcomes
Relationship to HBV DNA Levels

Incidence of Cirrhosis

- <300: 0.35%
- ~1,000: 0.45%
- ~10,000: 0.75%
- ~100,000: 1.81%
- >1,000,000: 2.78%

Incidence of HCC

- <300: 0.10%
- ~1,000: 0.11%
- ~10,000: 0.27%
- ~100,000: 0.94%
- >1,000,000: 1.15%

1. Iloeje UH et al. Gastroenterology 2006;130:678-686.
## Definitions of Disease

<table>
<thead>
<tr>
<th></th>
<th>Immune Tolerant</th>
<th>HBeAg (+) CHB</th>
<th>Inactive HBsAg Carrier</th>
<th>HBeAg (-) CHB (Precore Mutant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HBeAg</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
<td>↑</td>
<td>Normal</td>
<td>↑</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>&gt;20,000 IU/mL</td>
<td>&gt;20,000 IU/mL</td>
<td>&lt;200 IU/mL</td>
<td>&gt;2,000 IU/mL</td>
</tr>
<tr>
<td>Histology</td>
<td>Normal/Mild</td>
<td>Active</td>
<td>Normal</td>
<td>Active</td>
</tr>
</tbody>
</table>

Adapted from Hoofnagle JH et al. Hepatology. 2007;45:1056-1075
Therapy of HBV in HIV-Coinfected Individuals

• Goal: Suppress HBV viral replication and minimize ongoing hepatic damage.
• Loss of sAg and seroconversion to sAb are uncommon
  – indefinite treatment typical
Chronic HBV Treatment: Simplified Flow Chart

HBeAg Positive
- HBV DNA >20 000 IU/mL

HBeAg Negative
- HBV DNA >2000 IU/mL

Normal ALT:
- Man < 30 IU/mL
- Woman < 20 IU/mL

Elevated ALT:
- Monitor
- Liver Biopsy

Abnormal Histology:
- Treat

Indications for treatment of HBV in HIV infection

• All HIV/HBV-coinfected patients with abnormal ALT or HBV DNA >2,000 IU/mL.

• BUT, many experts recommend treatment of HBV for all HIV-coinfected patients with HBV replication
  – HBV DNA <2000 IU/mL and normal ALT -liver biopsy may be considered IF not on HIV therapy

Therapy for Hepatitis B

Timeline based on FDA Approval in the United States

1992
Interferon alfa

1998
Lamivudine (LAM)
“The New Era” ORAL Therapy

2002
Adefovir (ADV)

2005
Entecavir (ETV)
Pegylated IFN-α

2006
Telbivudine (LDT)

2008
Tenofovir (TDF)
Treatment of HBV in the setting of ART

• Most HIV treatment contains HBV-active agents
  – lamivudine [3TC], emtricitabine [FTC], tenofovir [TDF]
• Most HBV treat contains HIV-active agents
  – lamivudine, tenofovir, telbivudine, entecavir (ETV)
• If either disease has indication for treatment – both ART (regardless CD4 count), and 1st line HBV treatment should be started
  – Prevent partial treatment and RAVs
  – Consider addition of ETV if TDF contraindicated
  – ADV and INF are only options if not treating HIV
Long Term Monitoring

- On treatment: HBV DNA, ALT at 3-6 month intervals
  - Extended TDF-based HBV treatment will fully suppress HBV replication in majority
  - TDF resistance despite viremia not documented
- Do not interrupt HIV and HBV therapy,
  - Can be associated with HBV viral rebound and hepatic decompensation
- HCC screening at 6 month intervals

HCV CO-INFECTION
What is the reported rate of HCV eradication using all-oral therapy in HIV-HCV co-infected individuals?

A. <50%
B. 50-60%
C. 60-70%
D. 70-80%
E. >80%
SVR is Associated with Reduced Mortality Among HCV-infected Persons

- 530 adults in Europe prospectively followed for median 8.4 years after HCV treatment
- 192 (36%) achieved SVR


Adapted from D:A:D Study Group. AIDS 2010, 24: 1537-1548

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Pre-treatment Evaluation Should Include:

• Evaluate for limitations to therapy
  – There are few absolute contraindications to HCV therapy
  – Adherence is essential
• Smoking and alcohol cessation counseling
• HCV viral load, Genotype, renal function
• Assess degree of fibrosis
Treat Now or Wait—Two Major Issues to Consider

1. Relative urgency of treatment (ie, risk of progression)

2. Probability of achieving SVR
Progression is Probably Not Linear: Importance of Duration and Aging


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Patients meeting “highest” or “high” priority criteria for HCV Treatment in the CHeCS

<table>
<thead>
<tr>
<th>Hierarchy of care</th>
<th>A (n=2,084)</th>
<th>B (n=929)</th>
<th>C (n=3,188)</th>
<th>D (n=2,303)</th>
<th>All sites (N=8,504)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highest priority</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F3 or higher by biopsy or FIB4 score ≥2.5</td>
<td>35.3%</td>
<td>40.5%</td>
<td>38.2%</td>
<td>20.4%</td>
<td>32.9%</td>
</tr>
<tr>
<td>&lt;F3 with chronic kidney disease (ICD-9 codes)</td>
<td>33.1%</td>
<td>37.6%</td>
<td>33.5%</td>
<td>19.2%</td>
<td>30.0%</td>
</tr>
<tr>
<td><strong>High priority</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F2 by biopsy or 1.6&lt;FIB4 score &lt;2.5</td>
<td>36.3%</td>
<td>31.2%</td>
<td>29.3%</td>
<td>20.8%</td>
<td>28.9%</td>
</tr>
<tr>
<td>&lt;F2 with HIV co-infection</td>
<td>29.0%</td>
<td>23.9%</td>
<td>22.9%</td>
<td>16.2%</td>
<td>22.7%</td>
</tr>
<tr>
<td>&lt;F2 with HBV co-infection</td>
<td>0.3%</td>
<td>0.4%</td>
<td>1.4%</td>
<td>0.3%</td>
<td>0.7%</td>
</tr>
<tr>
<td>&lt;F2 with NASH (ICD-9 codes)</td>
<td>0.2%</td>
<td>0%</td>
<td>0.2%</td>
<td>0.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>&lt;F2 with diabetes (ICD-9 codes)</td>
<td>0.3%</td>
<td>0.9%</td>
<td>0.3%</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Not meeting “highest” or “high” priority criteria</td>
<td>28.4%</td>
<td>28.3%</td>
<td>32.5%</td>
<td>58.8%</td>
<td>38.2%</td>
</tr>
</tbody>
</table>

Xu F, et al. AASLD 2014, Boston. #LB-29

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**Milestones in Therapy of HCV: Overall SVR Rates**

### Average SVR Rates from Clinical Trials

<table>
<thead>
<tr>
<th>Year</th>
<th>SVR Rate</th>
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<tbody>
<tr>
<td>1991</td>
<td>6%</td>
</tr>
<tr>
<td>1999</td>
<td>16%</td>
</tr>
<tr>
<td>2002</td>
<td>34%</td>
</tr>
<tr>
<td>2004</td>
<td>42%</td>
</tr>
<tr>
<td>2006</td>
<td>39%</td>
</tr>
<tr>
<td>2009</td>
<td>42-46%</td>
</tr>
<tr>
<td>2010</td>
<td>54-56%</td>
</tr>
<tr>
<td>2012</td>
<td>68%*</td>
</tr>
<tr>
<td>2014</td>
<td>99%</td>
</tr>
</tbody>
</table>

Paritaprevir/ritonavir/ombitasvir + dasabuvir + RBV: SAPPHIRE-I

Genotype 1, treatment-naïve, non-cirrhotic, 12 weeks, n=473

Overall 96

G1a 95

G1b 98


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Paritaprevir/ritonavir/ombitasvir + dasabuvir + RBV: SAPHIRE-II

Genotype 1, treatment-experienced, non-cirrhotic, 12 weeks, n=394

 Overall  G1a  G1b
SVR12 % 96  96  97

286/297 166/173 119/123


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TURQUOISE-II: Cirrhosis; Naïve or Treatment Experienced G1

Arm A: 12-week regimen

Arm B: 24-week regimen


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ION-1: Non-cirrhotic vs cirrhotic patients

<table>
<thead>
<tr>
<th>Regimen</th>
<th>12 weeks</th>
<th>24 weeks</th>
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</thead>
<tbody>
<tr>
<td>LDV/SOF</td>
<td>99/180 32/34</td>
<td>97/184 33/34</td>
</tr>
<tr>
<td>LDV/SOF+RBV</td>
<td>98/184 31/33</td>
<td>99/181 36/36</td>
</tr>
</tbody>
</table>

LDV/SOF = Ledipasvir/Sofosbuvir
LDV/SOF+RBV = Ledipasvir/Sofosbuvir plus Ribavirin

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ION-2: Sofosbuvir + ledipasvir ± RBV
Genotype 1, treatment-experienced:
Cirrhosis in 20%


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Interferon-Free Treatment
HCV-HIV Co-infection

• Growing data that HIV Co-Infection is no longer a special population
Drug-Drug Interactions Must Be Discussed

DAAs have many potential drug interactions
Co-administered medications may inhibit or induce various metabolic pathways
Solutions may be found for virtually all potential drug-drug interactions
  – Review package inserts for interaction lists
  – Reconcile patient medication list
  – Patient needs to communicate new meds started by other health care providers
  – Other resource: www.hep-druginteractions.org

PI (acting as inhibitor) may ↑AUC of drug
Drug acting as inducer may ↓AUC of PI
AUC=area under the curve
3D + RBV for 12 vs 24 weeks: Virologic Response in GT1 Treatment-Naïve or Treatment-Experienced HCV/HIV Coinfection (TURQUOISE-I: Ongoing)

- RVR (Week 4): 100% 100% 31/32 32/32
- EOTR (Week 12 or 24): 96.8% 96.9% 30/31 31/32
- SVR4: 93.5% 96.9% 29/31 31/32
- SVR12: 93.5% 29/31

ION-4: LDV/SOF for 12 Wks in HIV/HCV-Coinfected Pts

- Virologically suppressed HIV/HCV
- HCV GT 1 or 4 (N = 335)
- ART regimens:
  - TDF/FTC/EFV (n = 160)
  - TDF/FTC + RAL (n = 146)
  - TDF/FTC/RPV (n = 29)
- 20% with compensated cirrhosis
- Treatment-experienced pts:
  - 29% failed HCV PI therapy
  - 13% failed SOF + RBV

ALLY-2: SOF + DCV in HIV/HCV-Coinfected Pts

- Phase III open-label study in coinfectected pts with HCV GT 1-6
  - Non GT1 < 20% in each cohort; compensated cirrhosis < 50% overall; HIV-1 RNA < 50 c/mL and CD4+ ≥ 100 in pts on ART; CD4 ≥ 350 in pts not on ART
  - ART allowed: PI/RTV, NRTIs, NNRTIs, INSTIs, MVC, ENF

Treatment-naive pts (N = 151)

SOF 400 mg + DCV 30/60/90* mg QD (n = 101)

Pts followed to Wk 36

Treatment-experienced pts (N = 52)

SOF 400 mg + DCV 30/60/90* mg QD (n = 50)

*Standard dose of 60 mg adjusted for ART: 30 mg with RTV; 90 mg with NNRTIs except RPV.

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ALLY-2: High Levels of SVR12 With SOF/DCV in All Pt Subgroups

- In 12-wk groups analyzed by GT, 100% with SVR12 except GT1a
- GT1a naive: 96%; Exp’d: 97%

- Similar SVR12 rates in pts with or without baseline NS5A RAVs
- 12 pts with relapse,
  - 10 in 8-wk arm
  - 1/10 relapses in 8-wk arm had emergent NS5A RAVs
- No NS5B RAVs at BL or time of failure
- No discontinuation of therapy due to AEs

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Summary

- SVR decreases liver and all-cause mortality
- HIV/HCV co-infection increases risk for hepatic decompensation
- SVR rates for HIV/HCV are comparable to mono-infection
- Highly effective all-oral therapies are available