Considerations for the management of Hepatitis C in patients with HIV co-infection

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Objectives

- Define the drug therapy options available for the treatment of Hepatitis C Virus
- Identify pertinent drug-drug interactions regarding the management of HCV/HIV co-infection
- Describe the monitoring needed when managing treatment regimens for patients with HCV/HIV co-infection

Background Information

- Basic mechanisms of infection:
  - Human immunodeficiency virus (HIV)
  - Hepatitis C virus (HCV)
- Population statistics for HIV, HCV, and HIV/HCV coinfection
- Effects of HIV/HCV co-infection on the liver
HIV Incidence

- Therapy is recommended for ALL HIV-infected patients
- In patients who choose to remain untreated
  - CD4 counts should be monitored every 3-6 months to assess urgency of treatment and need for OI prophylaxis
  - Drug resistance testing is recommended prior to initial therapy and in virologic failure: HIV RNA levels >1000 copies/mL

Question 1

In an HIV/HCV co-infected patient, at which CD4 count would you consider delaying HCV treatment?

A. 150 cells/mm³
B. 250 cells/mm³
C. 350 cells/mm³
D. 450 cells/mm³
Hepatitis C Statistics

- How common is acute Hepatitis C in the United States?
  - In 2009, there were an estimated 16,000 acute Hepatitis C virus infections reported in the United States.

- How common is chronic Hepatitis C in the United States?
  - An estimated 3.2 million persons in the United States have chronic Hepatitis C virus infection. Most people do not know they are infected because they don’t look or feel sick.

- Worldwide estimates are up to 80 million people suspected to be infected with Hepatitis C

- How likely is it that acute Hepatitis C will become chronic?
  - Approximately 75%–85% of people who become infected with Hepatitis C virus develop chronic infection.

- How common is HIV/HCV co-infection?
  - 50%–90% of HIV-infected persons who use injection drugs are also infected with the Hepatitis C virus.

http://www.cdc.gov/hepatitis/C/cFAQ.htm#statistics


Do ARV therapies cause liver disease?

COINS Study

- Retrospective multicenter cohort study
- 26 hospitals in Spain, 2000-2006
- HCV/Treatment naïve HIV co-infection
- 3 cohorts based on ARV regimen to determine predictors of grade 3 or 4 ALT elevations and of grade 4 total bilirubin elevations
- Exposure to ARV regimen for at least 1 week
- Lab values at baseline, within first 3 months, and every 4-6 months afterward
- Patients receiving HCV treatment during follow-up period were included

COINS Study

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>NVP (n=126)</th>
<th>EFV (n=323)</th>
<th>PI/r (n=296)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>96 (76%)</td>
<td>251 (78%)</td>
<td>221 (75%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>41 (37-46)</td>
<td>42 (36-46)</td>
<td>41 (37-45)</td>
</tr>
<tr>
<td>HCV GT 1</td>
<td>50 (40%)</td>
<td>141 (38%)</td>
<td>108 (30%)</td>
</tr>
<tr>
<td>ALT, SU/mL</td>
<td>42 (39-43)</td>
<td>53 (35-82)</td>
<td>49 (30-72)</td>
</tr>
<tr>
<td>AST, SU/mL</td>
<td>38 (28-54)</td>
<td>48 (32-81)</td>
<td>48 (32-70)</td>
</tr>
<tr>
<td>T.Bili, mg/dL</td>
<td>0.6 (0.4-0.8)</td>
<td>0.5 (0.4-0.8)</td>
<td>0.5 (0.4-0.7)</td>
</tr>
<tr>
<td>Significant liver fibrosis</td>
<td>81 (77%)</td>
<td>29 (9%)</td>
<td>57 (14%)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>5 (4%)</td>
<td>9 (3%)</td>
<td>41 (9%)</td>
</tr>
<tr>
<td>Nucleos(t)ide analogs - ZDV+3TC</td>
<td>56 (45%)</td>
<td>108 (33%)</td>
<td>109 (37%)</td>
</tr>
</tbody>
</table>


Figure 2. Grade 3 or 4 ALT or AST elevations by treatment group during the follow-up.


COINS Study

Table 3. Predictors of grade 3 or 4 ALT (A) and grade 4 total bilirubin elevations (B)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Grade 3 or 4 ALT (A)</th>
<th>p</th>
<th>Grade 4 TB (B)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td>Male</td>
<td>1.0</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>1.0</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>≤50 years</td>
<td>0.594</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;50 years</td>
<td>1.0</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>Daily alcohol intake</td>
<td></td>
<td>&lt;20 g/day</td>
<td>1.0</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥20 g/day</td>
<td>1.0</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>Baseline ALT</td>
<td></td>
<td>&lt;50 IU/mL</td>
<td>1.0</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥50 IU/mL</td>
<td>1.0</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count</td>
<td></td>
<td>&lt;200 cells/µL</td>
<td>1.0</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥200 cells/µL</td>
<td>1.0</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>Antiretroviral regimen</td>
<td></td>
<td>EFV</td>
<td>1.0</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PI/r</td>
<td>1.0</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
<td>Yes</td>
<td>1.0</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>1.0</td>
<td>0.017</td>
<td></td>
</tr>
</tbody>
</table>

COINS Study

ARV regimens including EFV, NVP, or PI/r are generally safe for initial treatment in HIV/HCV co-infection

EFV patients tended to have less ALT elevations compared to PI/r regimens

EFV patients tended to have less discontinuations related to hepatotoxicity compared to NVP regimens

No analysis on patients receiving HCV therapy

HIV Anti-retroviral Therapy

HIV-related immunodeficiency and a direct interaction between HIV and hepatic stellate and Kupffer cells have been implicated

ART may attenuate liver disease progression by preserving or restoring immune function and reducing HIV-related immune activation and inflammation

HCV treatment outcomes typically improved when HIV replication is controlled or CD4 counts increase

Combined treatment of HIV and HCV can be complicated by large pill burden, drug interaction, and overlapping toxicities

Does HCV/HIV Co-Infection effect Liver Disease?

HIV/HCV co-infection associated with higher rates compared to HCV mono-infection:

- Accelerated hepatic fibrosis

- Liver decompensation

- Death

- Liver disease leading cause of non-AIDS-related mortality among HIV-patients

- Co-infection increases the urgency of HIV therapy initiation

- Co-infection associated with poor CD4 count response


CD4 Counts

- In patients with co-infection and CD4 counts greater than 500, clinicians may defer ART until after HCV treatment is completed.
- In patients with co-infection and CD4 counts less than 200 cells/mm³, ART should be initiated and HCV therapy may be delayed until the patient is stable on HIV treatment.


Question 1

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Does HCV Treatment Reduce Liver Disease in HCV/HIV Co-Infection?

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Timeline of Drug Therapy Options

- 1957 discovered antiviral properties of interferon
- 1991 FDA approves first alfa interferon (Schering’s Intron A) to treat hepatitis C
- 1992 blood test to detect hepatitis C virus
- 1996 FDA approves alfa interferon (Roche, now Genentech-Roferon A) to treat hepatitis C
- 1997 FDA approves consensus interferon (Amgen-now InterMune-Infergen) to treat hepatitis C
- 1998 FDA approves Rebetron (Schering’s Intron A plus ribavirin) for treatment of HCV

Franciscus A. A brief history of hepatitis C. HCSP. May 2014;11, 1-7.
Timeline of Drug Therapy Options

- 2001 Peg-Intron approved (Schering’s pegylated interferon alpha-2b)
- 2002 Pegasys approved (Genentech’s pegylated interferon alpha-2a)
- 2007 Drugs in development (telaprevir) and HCV Rapid Test (HCV anti-body test) by OraSure
- 2011 Boceprevir (Victrelis) and Telaprevir (Incivek) approved to be used as triple therapy with pegylated interferon and ribavirin

Franciscus A. A brief history of hepatitis C. HCPJ May 2014;11, 1-3.

Timeline of Drug Therapy Options

- 2012 Direct acting antiviral medications (DAAs) in phase 3 clinical trials
- 2012 HCV testing recommended by CDC in all baby boomers (born between 1945 and 1965)
- 2013 FDA approves Olysio (simeprevir) and Sovaldi (sofosbuvir)
- 2014 FDA approved Interferon-free regimens:
  - VIEKIRA (ombitasvir, paritaprevir, ritonavir, dasabuvir) with and without ribavirin
  - Harvoni (ledipasvir, sofosbuvir) with and without ribavirin

Franciscus A. A brief history of hepatitis C. HCPJ May 2014;11, 1-3.

Benefits of SVR

- Treatment with peg/ribavirin in prior non-responders with HCV/HIV co-infection
  - SVR in 14/42
    - 0 hepatic decompensation or death
    - Trend toward increased CD4 counts
    - Treatment failure in 28/42
    - 8 hepatic decompensation or death
  - Efficacy of peg/ribavirin for SVR in HCV/HIV co-infection
    - 27-44% after 48 weeks of therapy
    - With response guided therapy and weight based ribavirin
    - Best SVR rate reported 49.6%

Question 2

Which HCV medication regimen would cause concern in an HIV/HCV co-infected patient not on stable antiretroviral therapy?

A. Harvoni
B. Olysio PLUS pegylated interferon PLUS weight based ribavirin
C. Sovaldi PLUS Olysio
D. VIEKIRA PAK PLUS weight based ribavirin

Question 3

What monitoring parameter should be completed routinely in a patient taking Harvoni for HCV and on a tenofovir (TDF) containing antiretroviral regimen?

A. CBC
B. Echocardiogram
C. Liver function tests
D. Renal parameters
Simeprevir

- Olysio (simeprevir)
- HCV NS3/4A Protease Inhibitor
- Substrate of CYP3A4 and \( p \)-glycoprotein enzymes
- Inhibits drug transporter OATP1B1/3
- ART drug interactions:
  - Efavirenz, etravirine, nevirapine, All HIV PIs, cobicistat, elvitegravir/cobicistat/tenofovir/emtricitabine

http://www.drugs.com/olysio.html


Simeprevir Interactions

<table>
<thead>
<tr>
<th>HIV Treatment</th>
<th>Mechanism</th>
<th>Result of Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>Mixed inducer/inhibitor of CYP3A</td>
<td>Reduced simeprevir AUC</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Induces CYP3A</td>
<td>Reduced concentration of simeprevir (expected)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Mixed inducer/inhibitor of CYP3A</td>
<td>Reduced concentration of simeprevir (expected)</td>
</tr>
<tr>
<td>All HIV PIs</td>
<td></td>
<td>Increased simeprevir AUC</td>
</tr>
<tr>
<td>Cobicistat</td>
<td>CYP3A inhibitor</td>
<td>Increased simeprevir (expected)</td>
</tr>
<tr>
<td>Elvitegravir/cobicistat /tenofovir/emtricitabine</td>
<td>EVG – CYP3A substrate Cobi – CYP3A inhibitor TDF – non-CYP hydrolysis FTC – non-CYP oxidation/conjugation</td>
<td>Increased simeprevir (expected)</td>
</tr>
</tbody>
</table>


Sofosbuvir

- Sovaldi (sofosbuvir)
- HCV NS5B nucleotide polymerase inhibitor
- Substrate for \( p \)-glycoprotein
- Avoid \( p \)-gp inducers, tipranavir


Ledipasvir/Sofosbuvir

- Harvoni (ledipasvir, sofosbuvir)
- Ledipasvir – HCV NS5A inhibitor
- Sofosbuvir – HCV NS5B/polymerase inhibitor
- Both are substrates for p-glycoprotein
- Avoid tipranavir - p-glycoprotein inducer
- Tenofovir containing regimens -> increased tenofovir exposure -> increased risk of tenofovir associated renal injury

-the-first-oncedaily-single-tablet-regimen-for-the-treatment-of-genotype-1-chronic-hepatitis-c


Ombitasvir, Paritaprevir/ Ritonavir PLUS Dasabuvir

- VIEKIRA PAK (ombitasvir, paritaprevir, ritonavir, dasabuvir)
- Ombitasvir – NS5A inhibitor, substrate for CYP3A and p-glycoprotein, inhibits CYP2C8 and UGT1A1
- Paritaprevir – protease inhibitor, substrate for CYP3A4, p-glycoprotein and OATP1B1/3
- Ritonavir – potent CYP450 inhibitor, hepatotoxicity in patients with cirrhosis
- Dasabuvir – NS5B/polymerase inhibitor, oxidative pathway -> liver conjugation ->biliary excretion

http://www.nrg.org/articles/8t-approved-obinutuzumab-herceptin-treatment-4882308802
http://www.hepatitis.uw.edu/page/treatment/drugs/3d


VIEKIRA Interactions

- Tenofovir reduces paritaprevir exposure by 32%
- Tenofovir increases paritaprevir by 24%
- Co-administration of VIEKIRA with Raltegravir has no effect, but raltegravir exposure increases by 150%
- Ritonavir increases paritaprevir exposure by 30%
- Ritonavir exposure increases more than 150% when co-administered with VIEKIRA – concerns for QT prolongation
- Efavirenz exposure increases more than 200% when co-administered with VIEKIRA
- Elvitegravir/cobicistat is contraindicated with VIEKIRA given cobicistat strong inhibitory effect on CYP349 enzymes
- ALL HIV PI’s should not be boosted with ritonavir in a patient treated with VIEKIRA because VIEKIRA contains 100mg of ritonavir

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- D. Renal parameters

Take Away Points

- Both HIV and HCV can cause/worsen liver fibrosis
- Treatment of HCV in HIV/HCV co-infection is a necessary with many considerations:
  - Drug-drug interactions
  - Toxicity/efficacy
  - Increased pill burden
- May require change in HIV anti-retroviral regimen
- Need to consider long half life of some HCV therapies
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