Clinical cases: HIV/HCV coinfection

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Case #1
General considerations about antiviral therapy

Presented at the 6th International Workshop on HIV & Hepatitis Co-infection,
31 May – 2 June 2010, Tel Aviv, Israel
CASE # 1

• 43 year-old, male patient
• Former IDU
• No prior history of relevant diseases
• Hospitalized because of a community-acquired pneumonia
• During hospitalization, the patient is found to be HIV and HCV (+)
• CD4 cell count 380/μL and HIV-RNA 135,000 copies/μL
• HLA B5701 (-)
QUESTION 1

Would you initiate any treatment in this patient?

1. Begin HAART
2. Delay HAART, since CD4 cells are >350/μL
3. Consider beginning HCV treatment after determining HCV genotype and viral load
4. Answers 1 and 3 are correct
5. Answers 2 and 3 are correct
WHEN TO START HAART?

- Start therapy when CD4 <350/μL or AIDS-defining illnesses
- 350-500 CD4/μL
  - A/B-II (DHHS)
  - Pregnancy
  - Higher HIV-RNA viral loads
  - HCV coinfection
  - HBV treatment
  - HIV-associated nephropathy or other specific organ disease
- >500 CD4/μL
  - DHHS guidelines B/C-III
  - EACS guidelines recommend to generally defer

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QUESTION 2

• What would you start with?
  1. Avoid Nevirapine due to hepatotoxicity risk
  2. Liver toxicity may be increased with some RTV-boosted PI regimens
  3. Any NRTI backbone will be equally effective in this patient
NEVIRAPINE AND LIVER TOXICITY

- Risk factors
  - Male patients with baseline CD4 >400
  - Female patients with baseline CD4 >250
  - Baseline ALT >2.5x ULN
  - Positive HCV serology
  - Positive HBV serology
Severe hepatotoxicity-free survival over 1 year. NVP vs EFV

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Severe hepatotoxicity-free survival over 1 year according to HCV infection status

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Incidence of severe liver toxicity during initial PI-containing HAART


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Hepatotoxicity of Antiretroviral Drugs Is Reduced after Successful Treatment of Chronic Hepatitis C in HIV-Infected Patients

![Graph showing cumulative incidence of hepatic events](image)

Sustained HCV Clearance

- No
- Yes

Log Rank: 14.01 ($P < .001$)

Follow-Up, months

Cumulative Incidence of Hepatic Events, %

No. of Patients

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### WHAT TO START WITH?

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **Abacavir + lamivudine (ABC/3TC)** | • Virologic response noninferior to ZDV/3TC  
  • Better CD4 T-cell count response than with ZDV/3TC  
  • Once-daily dosing  
  • Coformulation  
  • No food effect  
  • No cumulative TAM-mediated resistance | • Potential for abacavir hypersensitivity reaction (HSR) in patients with HLA-B*5701  
  • Potential for increased cardiovascular events, especially in patients with cardiovascular risk factors  
  • Inferior virologic responses when compared with TDF/FTC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study; however, this was not seen in the HEAT study. |
| **Tenofovir/ emtricitabine (or lamivudine) (TDF/FTC or TDF + 3TC)** | • Better virologic responses than with ZDV/3TC  
  • Better virologic responses than with ABC/3TC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study; however, this was not seen in the HEAT study.  
  • Once-daily dosing  
  • No food effect  
  • Coformulated (TDF/FTC) and (EFV/TDF/FTC)  
  • No cumulative TAM-mediated resistance | • Potential for renal impairment  
  • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials  
  • Potential for decrease in bone mineral density |
| **Zidovudine/ lamivudine (ZDV/3TC)** | • Coformulated (ZDV/3TC and ZDV/3TC/ABC)  
  • No food effect (although better tolerated with food)  
  • Preferred 2 NRTI in pregnant women | • Bone marrow suppression, especially anemia and neutropenia  
  • Gastrointestinal intolerance, headache  
  • Mitochondrial toxicity, including lipoatrophy, lactic acidosis, hepatic steatosis  
  • Inferior to TDF/FTC in combination with EFV  
  • Diminished CD4 T-cell responses compared with ABC/3TC |

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**DHHS Guidelines, December 1st, 2009**
WHAT TO START WITH?

DHHS preferred regimens
- TDF+FTC+EFV (AI)
- TDF+FTC+ATV/r (AI)
- TDF+FTC+ DRV/r QD (AI)
- TDF+FTC+ RAL (AI)

EACS preferred regimens
- NVP
- EFV
- ATV/r
- DRV/r
- LPV/r
- SQV/r

All of them in combination with either TDF+FTC or ABC+3TC

DHHS Guidelines, December 1st, 2009
EACS Guidelines, November 2009
CASE STUDY

• The patient began HAART with TDF+FTC+EFV
• Good tolerance and adherence
• After 6 months of therapy, HIV viral load was undetectable and CD4 cells rose up to 520 cells/μL
CASE STUDY

• The patient was infected with HCV genotype 4
• His HCV-RNA level was 750,000 copies/mL
• ALT remained elevated
• Autoimmune disorders, hemochromatosis, and thyroid diseases were discounted
• Abdominal ultrasound showed no signs of liver cirrhosis or portal hypertension
• A psychiatric assessment was undertaken to identify any prior serious behavioural or emotional disorders
• He was advised to stop consuming alcohol
• The patient declined a liver biopsy

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QUESTION 3

Should the patient receive antiviral treatment under these circumstances?

1. No, since no liver biopsy has been performed and therefore there is no information of liver fibrosis stage
2. Yes. As far as it is a non-1 genotype, treatment should last for 6 months
3. Yes. High doses of Ribavirin (1000-1200 mg/day) must be used and treatment should last for 48 weeks

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Response to interferon-based therapies in HIV-infected patients with chronic hepatitis C due to genotype 4

Vincent Soriano¹*, Marina Núñez¹, Matilde Sánchez-Conde¹, Pablo Barreiro¹, Javier García-Samaniego², Luz Martín-Carbonero¹, Miriam Romero² and Juan González-Lahoz¹

Figure 1. Sustained virological response according to HCV genotype and HCV treatment modality in 390 HIV/HCV co-infected patients

[Diagram showing the sustained virological response for different genotypes and treatment modalities.]
LIVER FIBROSIS ASSESSMENT

HCV Ab+ / HCV-RNA+

Genotype
- 2, 3
- 1, 4

Viral load*
- Low
- High

Liver fibrosis

Non-invasive tools
- FibroScan
- Serum fibromarkers

Agreement
Disagreement

Liver biopsy

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TRANSIENT ELASTOMETRY

Diagnostic accuracy of TE in comparison with liver biopsy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fibrosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSM cutoff value, kPa</td>
<td>≥9.3</td>
<td>≥12.3</td>
</tr>
<tr>
<td>AUC-ROC, % (95% CI)</td>
<td>0.81 (0.75–0.86)</td>
<td>0.81 (0.74–0.87)</td>
</tr>
<tr>
<td>Sensitivity, % (95% CI)</td>
<td>85.9 (75.6–93.0)</td>
<td>75.0 (60.4–86.4)</td>
</tr>
<tr>
<td>Specificity, % (95% CI)</td>
<td>75.2 (66.5–82.6)</td>
<td>86.1 (79.4–91.3)</td>
</tr>
<tr>
<td>PPV, % (95% CI)</td>
<td>67.0 (56.4–76.5)</td>
<td>64.3 (50.4–76.6)</td>
</tr>
<tr>
<td>NPV, % (95% CI)</td>
<td>90.1 (82.5–95.1)</td>
<td>91.2 (85.1–95.4)</td>
</tr>
<tr>
<td>Percentage of cases that were correctly classified</td>
<td>79.2</td>
<td>83.3</td>
</tr>
</tbody>
</table>

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SERUM BIOMARKERS

- **Fibrotest**
  - $\alpha^2$-macroglobulin, GGTP, apolipoprotein A1, haptoglobin, total bilirubin, age and gender
- **Forns index**
  - age, platelet count, cholesterol, GGTP
- **AST to Platelet Ratio (APRI)**
- **Hepascore**
  - bilirubin, GGTP, hyaluronate, $\alpha^2$-macroglobulin, age, sex
- **Fibrometer**
  - platelet count, prothrombin index, AST, $\alpha^2$-macroglobulin, hyaluronate, urea, age
- **SHASTA**
  - Hyaluronate, AST, albumin
- **FIB-4**
  - Age, AST, ALT, platelet count

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SERUM BIOMARKERS

Sánchez-Conde M et al. J Viral Hepat 2010 Apr 1;17(4):280-6

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CURRENT THERAPY ALGORITHM

HCV-RNA neg

G1/4

G2/3

24 weeks therapy *

HCV-RNA pos

< 2 log drop in HCV-RNA

Stop

> 2 log drop in HCV-RNA

HCV-RNA neg

HCV-RNA pos

G1/4

G2/3

48 weeks therapy

72 weeks therapy

24 weeks therapy

< 2 log drop in HCV-RNA

72 weeks therapy

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*In patients with baseline low viral load and minimal liver fibrosis

CASE STUDY

- At week 12, HCV viral load was still detectable, but had decreased >2 log
- Transaminases remained slightly elevated
- CD4 cell count decreased to 220/μL
QUESTION 4

Should HCV therapy be discontinued?

1. Yes, because HCV-RNA was still detectable
2. Yes, because his transaminase levels had not normalized
3. Yes, because the CD4 count had dropped considerably
4. No, Treatment should be continued and re-checked at week 24 of therapy
CURRENT THERAPY ALGORITHM

HCV-RNA neg

HCV-RNA pos

> 2 log drop in HCV-RNA

< 2 log drop in HCV-RNA

G2/3

G1/4

24 weeks therapy *

48 weeks therapy

72 weeks therapy

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*In patients with baseline low viral load and minimal liver fibrosis

CASE STUDY

- At week 24 of HCV therapy, the patient was HCV-RNA negative
- The patient completed 48 weeks of treatment
- Six months after completing treatment (week 72) the patient still had undetectable HCV-RNA and his aminotransferase levels had normalized

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WHAT CAN WE EXPECT?

Liver-related complications and deaths (%)

SVR, n=77

NR, n=274

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Case #2
Retreatment. The role of IL-28b

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CASE #2

- 43 year-old, male patient
- Former IDU
- Diagnosed with HIV infection at age 24 in the context of acute hepatitis
  - CDC A2 (225 CD4)
  - IgM anti-HBc, HBsAg, HBeAg +
  - Coinfection with HDV
  - HBsAg- 4 months later
  - HBV-DNA undetectable ever since
  - HCV (+)

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CASE #2

• Began ARV with AZT (93)
  • Switch to ddI due to my tochondrial myopathy (95)
  • 3TC added-on (96)
  • Good adherence, immune restoration and undetectable HIV-RNA

• HAART initiated in 1999
  • IDV/r+3TC+ddI
  • Good adherence.
  • Undetectable HIV-RNA

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CASE #2

• 2003
  • HIV-RNA increased to 730 copies/μL
  • A resistance test was carried out
  • M184V, 41L, 215Y
  • Resistance to AZT, 3TC and FTC
  • Switch to TDF+ABC+ LPV/r
    – HIV-RNA <50 copies
    – Good tolerance and adherence

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CASE #2

• 2008
  • Worsening of renal function
  • Decrease in ionic tubular resorption
  • Appearance of NRTI-associated neuropathy
  • NRTI- sparing regimen
    – LPV/r+RAL
  • Improvement in kidney function

• 2009
  • Switch to DRV/r+RAL
  • Undetectable HIV-RNA and CD4 >500

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CASE #2

• HCV
  – 1996
  • Liver biopsy carried out
    – Cirrhosis
  • HCV-RNA 17x10⁶ copies/mL
  • Genotype 1a
  • 48-week course with standard IFNα-2b
    – 3 MU 3x week
  • At the end of therapy HCV-RNA 26x10⁶ copies/mL
  • The patient remained stable, with no decompensations

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CASE #2

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QUESTION 1

• In 2001, PegInterferon α-2b became available
• Would you initiate therapy in this patient?
  1. No, as far as standard IFN therapy failed
  2. Yes, but just in case therapy adherence was not good enough
  3. Yes. Standard IFN monotherapy is a suboptimal regimen, and PegIFN+RBV can be more effective
<table>
<thead>
<tr>
<th>Category</th>
<th>Recommended intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suboptimal prior treatment schedules: interferon (monotherapy or with ribavirin); low ribavirin doses; short length of therapy Limiting toxicities and poor adherence</td>
<td>Retreatment using combination therapy with peginterferon plus weight-based ribavirin doses Optimal support (psychiatric, pharmacists, use of hematopoietic growth factors) Maintenance therapy in patients with advanced liver fibrosis; wait until new antiviral drugs come to the market in the rest</td>
</tr>
<tr>
<td>Virological failure</td>
<td></td>
</tr>
</tbody>
</table>
CASE STUDY

• The patient began a 72-week course of PegIFN α-2b (100 mcg/w)+ RBV (1000 mg/d)
  • At week 4, HCV-RNA was still detectable
  • At week 12, HCV-RNA had decreased >2 log
  • At week 24, HCV-RNA was undetectable
• Throughout the last 24 weeks of therapy the patient reported irregular adherence
• Though at end of therapy HCV-RNA was still undetectable, 6 months later HCV-RNA was 9x10^6 copies/mL
CASE STUDY

• The patient remained stable, with mildly elevated liver enzymes
• FS was performed (05)
  • 10.1 kPa (F3)
• No decompensations of liver disease appeared
QUESTION 2

• What now?

1. Wait for new therapies
2. Try another course due to insufficient adherence
CASE STUDY

• A course of PegIFN α-2a+RBV was suggested to the patient
• Length extended to 48 weeks
• RBV doses were readjusted to 1200 mg/d

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CASE STUDY

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CASE STUDY

Liver stiffness evolution (kPa)

- Therapy beginning: 10.7 (F3)
- End of therapy: 7.7 (F2)
- 6 mo. after therapy finish: 6.8 (F1)
- 8.9 (F2)
- 7.4 (F2)

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Sustained virological response

End of therapy

PRESCO

No. | Total  | G1   | G2/3  | G4   |
---|--------|------|-------|------|
    | 389    | 191  | 152   | 46   |

Núñez M, et al. 57th Annual Meeting AASLD. Abstract #365

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Núñez M, et al. 57th Annual Meeting AASLD. Abstract #365

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CASE STUDY

- HCV-RNA was still detectable at week 4
- Undetectable ever since
- The patient achieved SVR with liver enzymes normalization and liver stiffness decrease
- IL-28 polymorphism analysis was carried out
  - Genotype CC
STUDY POPULATION

HIV-HCV coinfected cohort
(n=650) *

Completion of HCV therapy & validated outcomes

SVR
(n=90)

NR
(n=74)

Spontaneous HCV clearance
(n=24)

SVR defined as undetectable serum HCV-RNA six months after completion of HCV therapy.

Patients with poor drug compliance and/or who discontinued therapy due to side effects were excluded from the NR group.
SVR rates according to the number of protective factors

- Low serum HCV-RNA
- HCV genotype 3
- Lack of advanced liver fibrosis (Metavir F0-F2)
- rs12979860 CC genotype

<table>
<thead>
<tr>
<th>No. of protective factors</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (n=164)</td>
<td>12%</td>
<td>23%</td>
<td>75%</td>
<td>88%</td>
<td>100%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HCV-1 and -4 genotype patients (n=113)</td>
<td>12%</td>
<td>22%</td>
<td>68%</td>
<td>100%</td>
<td>NA</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HCV-3 genotype patients (n=51)</td>
<td>50%</td>
<td>84%</td>
<td>82%</td>
<td>100%</td>
<td>NA</td>
<td>0.372</td>
</tr>
</tbody>
</table>

NA, Not applicable
Factors related with higher SVR rates

<table>
<thead>
<tr>
<th>Patient</th>
<th>Virus</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasians</td>
<td>Genotypes 2-3</td>
<td>PegIFN dosing</td>
</tr>
<tr>
<td>Younger ages</td>
<td>Low HCV viral load</td>
<td>Weight-adjusted RBV dose</td>
</tr>
<tr>
<td>Lower fibrosis stage</td>
<td>Rapid virological response</td>
<td>Good adherence</td>
</tr>
<tr>
<td>Normal BMI</td>
<td></td>
<td>No prior use of AZT or ddI</td>
</tr>
<tr>
<td>No insuline resistance</td>
<td></td>
<td>Use of hematopietic growth factors when needed</td>
</tr>
<tr>
<td>Absence of steatosis</td>
<td></td>
<td></td>
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<tr>
<td>High CD4 cell count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protective IL28 genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No substance abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No psychiatric disorders</td>
<td></td>
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</tbody>
</table>

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