Treatment of Hepatitis C in HIV-Coinfected Patients

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Madrid, Spain
Estimated no. of persons infected with HIV and hepatitis viruses worldwide (in millions)

- HCV: 175
- HIV: 35
- HCV-HIV: 7
- HCV-HBV: 15
- HCV-HBV-HIV: 0.5
- HIV-HBV: 3
- HIV: 35
- HBV: 350

Puoti et al. Sem Liver Dis 2012
### Benefit of antiretrovirals

<table>
<thead>
<tr>
<th>ARV (HIV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral replication</td>
</tr>
<tr>
<td>Major clinical benefit</td>
</tr>
<tr>
<td>Drug-related toxicity</td>
</tr>
<tr>
<td>Chronic inflammation &amp; persistent</td>
</tr>
<tr>
<td>immune activation (premature ageing)</td>
</tr>
<tr>
<td>Transmission</td>
</tr>
</tbody>
</table>

Soriano et al. AVR 2012; 97: 36-40.
REVEAL-HCV

- 23,820 adults followed for a mean of 16.2 years
- 1095 HCV Ab+ (4%)
- 69% of HCV Ab+ were HCV-RNA pos
- 2394 deaths during the study period

Adjusted hazard ratio

HCV Ab-pos vs HCV Ab-neg

All causes death 1.9
Liver-related 12.5
Liver cancer
Cirrhosis 5.4
Extrahepatic 1.4
Cancers* 1.3
Cardiovascular 1.5
Kidney 2.8

Adjusted hazard ratio

*esophagus, prostate & thyroid

Different effect of antivirals

<table>
<thead>
<tr>
<th></th>
<th>ARV (HIV)</th>
<th>DAA (HCV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral replication</td>
<td>Suppression without clearance</td>
<td>eradication</td>
</tr>
<tr>
<td>Major clinical benefit</td>
<td>Reversal of immune deficiency</td>
<td>Reversion of liver fibrosis</td>
</tr>
<tr>
<td>Drug-related toxicity</td>
<td>Long-lasting, cumulative</td>
<td>Short-term, reversible</td>
</tr>
<tr>
<td>Chronic inflammation &amp; persistent immune activation (premature ageing)</td>
<td>amelioration</td>
<td>elimination</td>
</tr>
<tr>
<td>Transmission</td>
<td>reduction</td>
<td>elimination</td>
</tr>
</tbody>
</table>

Soriano et al. AVR 2012; 97: 36-40.
Reasons to treat hep C in HIV

1. Faster hepatic disease progression.
2. Increased liver toxicity of ARVs
3. Enhanced metabolic abnormalities and cardiovascular risk
4. Reduce transmission
# A New Era for Hepatitis C—New Diagnostics Tools and New Weapons

Vicente Soriano*

Department of Infectious Diseases, Hospital Carlos III, Calle Sinesio Delgado 10, Madrid 28029, Spain

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• IL28B alleles</td>
<td>• Protease inhibitors</td>
</tr>
<tr>
<td>• Non-invasive liver fibrosis tools</td>
<td>• Polymerase inhibitors</td>
</tr>
<tr>
<td>• Viral load</td>
<td>• NS5A inhibitors</td>
</tr>
<tr>
<td>• HCV geno/subtyping</td>
<td>• Interferon lambda</td>
</tr>
<tr>
<td>• Drug resistance</td>
<td></td>
</tr>
</tbody>
</table>
New & Old Predictors of HCV treatment response

**Old**
- Genotype
- Viral load
- Fibrosis
- RVR
- Adherence
- Anemia

**New**
- IL28B
- Resistance polymorphisms
- HCV-1 subtypes
Association of a single nucleotide polymorphism near the interleukin-28B gene with response to hepatitis C therapy in HIV/hepatitis C virus-coinfected patients

Norma I. Rallón, Susanna Naggie, José M. Benito, José Medrano, Clara Restrepo, David Goldstein, Kevin V. Shianna, Eugenia Vispo, Alex Thompson, John McHutchison and Vincent Soriano

AIDS 2010

SVR

<table>
<thead>
<tr>
<th></th>
<th>CC 75</th>
<th>CT/TT 89</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>75%</td>
<td>38%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CC 34</th>
<th>CT/TT 61</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV-1</td>
<td>65%</td>
<td>30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CC 35</th>
<th>CT/TT 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV-3</td>
<td>86%</td>
<td>81%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CC 6</th>
<th>CT/TT 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV-4</td>
<td>67%</td>
<td>25%</td>
</tr>
</tbody>
</table>

p<0.0001, p=0.001, p=0.087

AIDS 2010
Modeling the Probability of Sustained Virological Response to Therapy with Pegylated Interferon plus Ribavirin in Patients Coinfected with Hepatitis C Virus and HIV

Prometheus index

- HCV genotype
- Fibrosis stage (KPa)
- Serum HCV-RNA
- IL28B SNPs

http://www.fundacionies/prometheusindex.php
Prometheus Index

Prediction of Sustained Virological Response (SVR) after treatment of Hepatitis C with Pegylated Interferon plus weight adjusted Ribavirin

Challenges and opportunities for hepatitis C drug development in HIV–hepatitis C virus-co-infected patients

* AIDS 2011, 25:2197–2208*

Vincent Soriano\(^a\), Kenneth E. Sherman\(^b\), Juergen Rockstroh\(^c\), Douglas Dieterich\(^d\), David Back\(^e\), Mark Sulkowski\(^f\) and Marion Peters\(^g\)

- More elevated HCV load. More virological failures?
- Faster selection of drug resistance?
- Drug-drug interactions
- Overlapping toxicities – rash & anemia
- Drug compliance with polymedication
- Additional cost
HCV kinetics

- HCV-RNA (IU/mL)
- HIV
- DAA
- pegIFNα + RBV
- Virion release blocking
- Loss of infected hepatocytes

Time scale:
- Days
- Weeks
# Interactions between DAA & ARVs

<table>
<thead>
<tr>
<th></th>
<th>Telaprevir</th>
<th>Co-medication</th>
<th>Boceprevir</th>
<th>Co-medication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tenofovir</strong></td>
<td>≈</td>
<td>↑30%</td>
<td>↑8%</td>
<td>↑8%</td>
</tr>
<tr>
<td><strong>Efavirenz</strong></td>
<td>↓26% (tid)</td>
<td>↓7% (tid)</td>
<td>↓40%</td>
<td>↑20%</td>
</tr>
<tr>
<td><strong>Atazanavir/r</strong></td>
<td>↓20%</td>
<td>↑17%</td>
<td>↓5%</td>
<td>↓49%</td>
</tr>
<tr>
<td><strong>Darunavir/r</strong></td>
<td>↓35%</td>
<td>↓40%</td>
<td>↓32%</td>
<td>↓59%</td>
</tr>
<tr>
<td><strong>Fosamprenavir/r</strong></td>
<td>↓32%</td>
<td>↓47%</td>
<td>↓30%</td>
<td>↓50%</td>
</tr>
<tr>
<td><strong>Lopinavir/r</strong></td>
<td>↓54%</td>
<td>↑6%</td>
<td>↓45%</td>
<td>↓43%</td>
</tr>
<tr>
<td><strong>Ritonavir (low dose)</strong></td>
<td>↓24%</td>
<td>--</td>
<td>↓19%</td>
<td>--</td>
</tr>
<tr>
<td><strong>Raltegravir</strong></td>
<td>≈</td>
<td>≈</td>
<td>≈</td>
<td>≈</td>
</tr>
</tbody>
</table>
Provisional Guidance on the Use of Hepatitis C Virus Protease Inhibitors for Treatment of Hepatitis C in HIV-Infected Persons

David L. Thomas,¹ John G. Bartlett,¹ Marion G. Peters,² Kenneth E. Sherman,³ Mark S. Sulkowski,¹ and Paul A. Pham¹

¹Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland; ²Department of Medicine, University of California, San Francisco School of Medicine; and ³Department of Medicine, University of Cincinnati School of Medicine, Ohio

BOCEPREVIR Naive

HCV RNA

Undetectable $< 100$ IU/mL

Early response: stop at Wk 28; f/u 24 wks

BOC + PegIFN + RBV

Wks

Detectable $< 100$ IU/mL

Slow response: extend triple therapy to Wk 36; PR to Wk 48; f/u 24 wks

BOC + PegIFN + RBV

PegIFN + RBV

Stop all treatment if HCV RNA $\geq 100$ IU/mL

Use quantitative assay to determine if HCV RNA $< 100$ IU/mL at Wk 12

Stop all treatment if HCV RNA detectable

Use an assay with LLOQ of 10-15 IU/mL to determine if "target not detected" at Wk 24

*Poorly IFN responsive patients (patients who do not achieve a 1 log reduction in HCV RNA by Week 4 of therapy) should be considered for 4 weeks of pegIFN/RBV followed by 44 weeks of BOC + pegIFN/RBV; cirrhotic patients should receive 4 weeks of pegIFN/RBV followed by 44 weeks of BOC + pegIFN/RBV.

$^1$A quantitative assay with an LLOQ of $< 25$ IU/mL and an LLOD of approximately 10-15 IU/mL must be used.
BOCEPREVIR
Pre-treated

- RGT recommended only for previous relapsers and previous partial responders
- Previous null responders should receive the full 48-week regimen

HCV RNA

- *Undetectable* < 100 IU/mL
- *Undetectable*

**Early response:** stop at Wk 36; f/u 24 wks

PegIFN + RBV

BOC + PegIFN + RBV

Wks

0 4 8 12 24 28 36 48

HCV RNA

- *Detectable*< 100 IU/mL
- *Undetectable*

**Slow response:** PR to Wk 48; f/u 24 wks

PegIFN + RBV

BOC + PegIFN + RBV

Wks

0 4 8 12 24 28 36 48

*Poorly IFN responsive patients (patients who do not achieve a 1 log reduction in HCV RNA by Week 4 of therapy) should be considered for 4 weeks of pegIFN/RBV followed by 44 weeks of BOC + pegIFN/RBV; cirrhotic patients should receive 4 weeks of pegIFN/RBV followed by 44 weeks of BOC + pegIFN/RBV.

1*A quantitative assay with an LLOQ of < 25 IU/mL and an LLOD of approximately 10-15 IU/mL must be used.*
TELAPREVIR
Naive & Pre-treated

- RGT not recommended for previous partial^ or null responders; these patients should receive the full 48-week regimen

*Cirrhotic treatment-naive patients may benefit from a full 48 weeks of treatment.

HCV RNA²

Undetectable

TVR + PegIFN + RBV

Undetectable

PegIFN + RBV

eRVR: stop at Wk 24, f/u 24 wks

Undetectable

HCV RNA³

Detectable
(but ≤ 1000 IU/mL)

TVR + PegIFN + RBV

Undetectable or detectable (but ≤ 1000 IU/mL)

PegIFN + RBV

No eRVR: extend pegIFN + RBV to Wk 48; f/u 24 wks

Undetectable

Wks

0 4 12 24 48

Use quantitative assay to determine if HCV RNA ≥ or > 1000 IU/mL at Wks 4 and 12

Use an assay with LLOD of 10-15 IU/mL to determine if "target not detected" at Wk 24

Stop all treatment if HCV RNA > 1000 IU/mL

Stop all treatment if HCV RNA > 1000 IU/mL
HIV-HCV co-infection facing HCV protease inhibitor licensing: implications for clinicians

Management of newly diagnosed HIV-HCV coinfected genotype-1 patients.

Patrick Ingiliz\textsuperscript{1} and Jürgen K. Rockstroh\textsuperscript{2}

\textbf{Consider}

- low HCV viral load, IL28B CC genotype, absence of insulin resistance and high CD4 count.

\textbf{F0F1}
- Individual decision
  - Individual decision/triple therapy
  - Defer

\textbf{F2F3}
- Triple therapy
- Triple therapy

\textbf{F4}
- Triple therapy
- Triple therapy

\textbf{*monitor fibrosis stage annually, preferably with two established methods. Treat with triple therapy, if rapid progression.}

*Defer*
G1 naïve

Enfermos con fibrosis < F2

Genotipo CC de la IL28B
P-IFN + RBV

Genotipo TT o TC de la IL28B
TRIPLE TERAPIA (P-IFN + RBV + BOC o TVP)

Enfermos con fibrosis F3 ó F4 en biopsia ó Fibroscan >9,5 Kilopascales

EL TRATAMIENTO CON TRIPLE TERAPIA NO ESTÁ RECOMENDADO

RVR

Cv < 400.000
24 Semanas

Cv ≥ 400.000
48 Semanas

NO RVR
48 Semanas
G1 pre-treated

Enfermos RECIDIVANTES al tratamiento con P-IFN + RBV (RELAPSEERS)

Enfermos NO RESPONDedores CON RESPUESTA PARCIAL a un tratamiento previo con P-IFN + RBV

Enfermos con RESPUESTA NULA a un tratamiento previo con P-IFN + RBV

F0-F1

≥ F2

TRIPLE TERAPIA (P-IFN + RBV + BOC o TVP)

ESPERAR NUEVOS TRATAMIENTOS

TRIPLE TERAPIA (P-IFN + RBV + BOC o TVP)

ESPERAR NUEVOS TRATAMIENTOS

P-IFN + RBV (lead-in 4 sem)

↓ > 1 log10 RNA-VHC sem 4

NO ↓ > 1 log10 RNA-VHC sem 4

SUSPENDER TODOS LOS TRATAMIENTOS

Respuesta a tratamientos Previos DESCONOCIDA
Criterios y recomendaciones generales para el tratamiento con boceprevir y telaprevir de la hepatitis crónica C en pacientes infectados por el VIH,

20 de marzo de 2012

**CRITERIOS VHC**

1. Infección por VHC genotipo 1, independientemente de que el paciente haya recibido o no tratamiento previo para el VHC
2. Fibrosis F3 y F4 confirmada por biopsia hepática o rigidez hepática medida por Fibroscan ≥9.5 Kilopascales
3. Hepatopatía compensada (Child-Pugh grado A)
4. Concentración de hemoglobina >11 g/dl en mujeres y >12 g/dl en hombres

**CRITERIOS VIH**

5. Pacientes con tratamiento antirretroviral
   - Linfocitos CD4+ totales en sangre periférica >1000/ml o porcentaje de linfocitos CD4+ >12%
   - Carga viral plasmática de VIH <1000 copias/ml

**Length of therapy: always 48 weeks**
Telaprevir in HIV/HCV coinfected patients

- 60 HIV/HCV coinfected patients with G1, naive to interferon.
- No ARV in 13. Of the rest, 24 on efavirenz and 23 on ATV/r
- Three patients on T/P/R discontinued earlier due to AEs.
- Rash in 13 (34%) on telaprevir.
- Relapses in 1/32 (3%) patients on telaprevir and 2/13 (15%) on P/R

Dieterich et al. CROI 2012; abstract 46.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>No ART</th>
<th>Efavirenz</th>
<th>Atazanavir/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/P/R</td>
<td>38</td>
<td>7</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>74%</td>
<td>71%</td>
<td>69%</td>
<td>80%</td>
</tr>
<tr>
<td>P/R</td>
<td>22</td>
<td>6</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>45%</td>
<td>33%</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Dieterich et al. CROI 2012; abstract 46.
Boceprevir in HIV/HCV coinfected patients

- 98 HIV/HCV coinfected patients with G1, naive to interferon were randomized (2:1) to triple therapy vs standard of care (peginterferon plus ribavirin).
- Two thirds were HCV subtype 1a.

Mallolas et al. EASL 2012
SVR$_{12}$ with Telaprevir and Boceprevir in HIV/HCV coinfected patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Triple therapy</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVR/P/R</td>
<td>74%</td>
<td>45%</td>
</tr>
<tr>
<td>BOC/P/R</td>
<td>62%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Δ 29% for TVR/P/R, Δ 35% for BOC/P/R
Hepatitis C virus (HCV) treatment uptake and changes in the prevalence of HCV genotypes in HIV/HCV-coinfected patients

J. Medrano,1 S. Resino,2 E. Vispo,1 A. Madejón,1 P. Labarga,1 P. Tuma,1 L. Martín-Carbonero,1 P. Barreiro,1 S. Rodríguez-Novoa,3 I. Jiménez-Nacher3 and V. Soriano1

1Department of Infectious Diseases & CIBERehd, Hospital Carlos III, Madrid, Spain; 2Research Unit, Instituto de Salud Carlos III, Majadahonda, Spain; and 3Pharmacy Unit, Hospital Carlos III, Madrid, Spain

Journal of Viral Hepatitis, 2011, 18, 325–330

Dynamic cohort

1/1/2000

31/12/2008

403

268

58

Deaths

130

Lost-to-follow-up

270

Treated

116

Cured

367
Predicted effect of direct acting antivirals in the current HIV–HCV–coinfected population in Spain

Eva Poveda¹, Eugenia Vispo¹, Pablo Barreiro¹, Carmen de Mendoza¹, Pablo Labarga¹, José Vicente Fernández-Montero¹, Luz Martin-Carbonero¹, Vincent Soriano¹*

¹Department of Infectious Diseases, Hospital Carlos III, Madrid, Spain

Antivir Ther 2012; 17: 571-5.

IFN experience

- Yes: 41%
- No: 59%

HCV genotype

- G1a: 39%
- G4: 20%
- G3: 11%
- G1b: 22%
- Others: 8%

Advanced liver fibrosis

- Yes: 53%
- No: 47%

IL28B

- CC: 30%
- CT/TT: 70%

424 HIV/HCV–coinfected patients in 2011
## Main challenges for DAA in special HIV/HCV populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Caveat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver transplantation</td>
<td>Drug-drug interactions; rejection</td>
</tr>
<tr>
<td>Advanced liver disease (cirrhosis)</td>
<td>Impaired DAA metabolism; enhanced toxicity</td>
</tr>
<tr>
<td>Prior IFNα null responders</td>
<td>Lower response; increased risk of selecting HCV drug resistance</td>
</tr>
<tr>
<td>IFNα and/or RBV intolerant</td>
<td>Wait for IFN and/or RBV sparing combinations</td>
</tr>
<tr>
<td>Non-1 HCV genotypes</td>
<td>Poor or null activity</td>
</tr>
<tr>
<td>Hemodyalisis</td>
<td>No data</td>
</tr>
<tr>
<td>Children</td>
<td>Dose adjustments</td>
</tr>
<tr>
<td>Acute hepatitis C</td>
<td>No data; added value?</td>
</tr>
<tr>
<td>Inherited hematological disorders: thalassemia, hemophilia</td>
<td>Enhanced toxicities: anemia, bleeding</td>
</tr>
<tr>
<td>Socially dysfunctional groups (i.e., homeless, illegal immigrants)</td>
<td>Difficult-to-reach and keep on satisfactory drug adherence</td>
</tr>
<tr>
<td>Intravenous drug users</td>
<td>Concerns about drug adherence and transmission of drug-resistant HCV mutants</td>
</tr>
</tbody>
</table>
Ongoing phase II/III trials in HIV

- Telaprevir
- Boceprevir
- Simeprevir (formerly TMC-435)
- Faldaprevir (formerly BI-1335)
- Daclatasvir
- ABT-450, -267, 333
- Sofosbuvir
Sofosbuvir in HIV

- Phase 1 trial
- 19 patients on stable HAART (VL <50 & CD4 >350)
- Coinfected with HCV genotypes 1 or 2/3
- SOF 400 mg QD for 1 week
- Median HCV-RNA drop:
  - At 24 h: >1.5 log
  - Maximal: >4 log
- No differences according to HIV or HCV genotypes.
- Well tolerated.
- No effect on HIV-RNA nor CD4 counts.
- Phase II PHOTON studies ready to start

Rodriguez-Torres et al. ICAAC 2012, H-1921a
Acknowledgments

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Jose Miguel Benito
Clara Restrepo
Mariola Lopez
Zulema Plaza