Hepatitis C Virus Infection in Children with and without HIV TREATMENT

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AOU Meyer, Firenze
Hepatitis C
Disclosure

- nothing to disclose
Hepatitis C
Outline

- clinical background

- treatment: the present and the future
Hepatitis C in Children

Natural history of the infection

- 504 children with hepatitis C
- follow up: 10 years

% clearance: 7.5

92% persistent infection

1.8% cirrhosis

Bortolotti F, Gastroenterology 2008
HCV/HIV Coinfected Adults

Main data

- accelerated hepatic fibrosis progression
- higher rates of liver failure and death
- hepatocellular carcinoma at younger ages than those with HCV monoinfection

EASL Guideline, J Hepatol 2015
HCV/HIV Coinfection and Liver Disease
Paediatric data

HCV treatment in children and young adults with HIV/HCV co-infection in Europe

Turkova A, J Virus Erad 2015

HIV /HCV co-infection in 229 children and young adults: results from a European cohort collaboration

Thorne C for EPPICC, ESID 2014
Hepatitis C in HCV/HIV Coinfection
Paediatric data

- HIV coinfection
  - increases the risk of HCV vertical transmission
  - reduces the rate of spontaneous clearance of HCV
  - is associated with higher HCV viraemia and ALT levels
  - worsens the natural history of hepatitis C

HCV/HIV Coinfection and Liver Disease
Paediatric data

Transient elastography

- 7.3-9.5 kP: 20%
- 13%
- >9.5 kP
- <7.2 kP: 67%

n 95

Turkova A, J Virus Erad 2015
Chronic hepatitis C in children

The drugs

- **peg-IFN-α-2b** (1.5 µg/Kg/week) (>3 yrs)
  (approved FDA Dec 2008; EMA Dec 2009)

- **peg-IFN-α-2a** (100 µg/m²/week) (>5 yrs)
  (approved FDA Dec 2009, EMA Mar 2013)

- **ribavirin** 15 mg/Kg/day (max 1.2 g) (>3 yrs)
Paediatric Data PEG-IFN + RIBA

**monoinfection**

SVR%

coinfection

Druyts E, Clin Infect Dis 2013

Turkova A, J Virus Erad 2015
PEG-IFN + RIBA

HCV/HIV coinfected children

- median duration of treatment, independently of genotype: 47 weeks (range 8-82)

- SVR24 was very low (12%) in children with advanced liver fibrosis
# Direct Acting Antiviral Agents (DAAs)

<table>
<thead>
<tr>
<th>Category</th>
<th>Resistance profile</th>
<th>Pangenotypic efficacy</th>
<th>Antiviral potency</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3/4A protease inhibitors (PI)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1st-generation PI</td>
<td>Red</td>
<td>Red</td>
<td>Green</td>
<td>Red</td>
</tr>
<tr>
<td>2nd-generation PI</td>
<td>Yellow</td>
<td></td>
<td>Green</td>
<td>Green</td>
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<tr>
<td>NS5A inhibitors</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>Nucleoside NS5B polymerase inhibitors</td>
<td>Green</td>
<td></td>
<td>Green</td>
<td></td>
</tr>
<tr>
<td>Non-nucleoside NS5B polymerase inhibitors</td>
<td>Red</td>
<td>Yellow</td>
<td>Red</td>
<td>Yellow</td>
</tr>
</tbody>
</table>

Modified from Lange C, EMBO Mol Med 2014;
**Direct Acting Antiviral Agents (DAAs)**

<table>
<thead>
<tr>
<th>Direct Acting Antiviral Agents (DAAs)</th>
<th>Main Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3/4A protease inhibitors (xxx-previr)</td>
<td>boceprevir, telaprevir, paritaprevir, simeprevir, asunaprevir, grazoprevir</td>
</tr>
<tr>
<td>NS5A inhibitors (xxx-asvir)</td>
<td>daclatasvir, ledipasvir, ombitasvir, elbasvir, GS-5816</td>
</tr>
<tr>
<td>Nucleoside NS5B polymerase inhibitors (xxx-buvir)</td>
<td>sofosbuvir, VX-135, IDX 24437, ACH 3422</td>
</tr>
<tr>
<td>Non-nucleoside NS5B polymerase inhibitors (xxx-buvir)</td>
<td>dasabuvir, beclabuvir</td>
</tr>
</tbody>
</table>
How Many Drugs To Treat HCV?

- Nucleoside NS5B polymerase inhibitors
- Non-nucleoside NS5B polymerase inhibitors
- NS3/4A protease inhibitors
- NS5A inhibitors

Choose one combination:

- Nucleoside NS5B polymerase inhibitors + Non-nucleoside NS5B polymerase inhibitors
- NS3/4A protease inhibitors + NS5A inhibitors
- NS3/4A protease inhibitors + NS5A inhibitors
- NS3/4A protease inhibitors + NS5A inhibitors
Sofosbuvir\textsuperscript{(nNS5B)} + ledipasvir\textsuperscript{(NS5A)} (FDC) ± RBV

Treatment-naïve, HCV G1 non-cirrhotic patients

SVR12, %

<table>
<thead>
<tr>
<th></th>
<th>8 weeks</th>
<th>12 weeks</th>
</tr>
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<tbody>
<tr>
<td>+ RBV</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>ION 3</td>
<td>93</td>
<td>216</td>
</tr>
</tbody>
</table>

Sofosbuvir (400 mg QD), ledipasvir (90 mg QD), RBV weight-based.

Sofosbuvir\textsubscript{(nNS5B)} + ledipasvir\textsubscript{(NS5A)} (FDC) ± RBV in HIV/HCV coinfection

GT1

- patients receiving ART therapy
- HIV RNA values < 50 copies/mL
- CD4 T-lymphocyte > 100 cells/µL
- untreated with CD4 > 500 cells/µL

Sofosbuvir (400 mg QD), ledipasvir (90 mg QD), RBV weight-based.

Naggie S, CROI 2015
Paritaprevir/r(PI) + ombitasvir(NS5A) (FDC) + dasabuvir(nnNS5B) ± RBV

HCV G1 non-cirrhotic patients, treated for 12 weeks

Treatment-naïve

<table>
<thead>
<tr>
<th></th>
<th>PEARL-III</th>
<th>PEARL-IV</th>
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<tbody>
<tr>
<td>G1b</td>
<td>99/209/210</td>
<td>97/100/185</td>
</tr>
<tr>
<td>G1a</td>
<td>99/207/209</td>
<td>90/205/100</td>
</tr>
</tbody>
</table>

SVR12, %

Paritaprevir/ritonavir/Aombitasvir (150/100/25 mg QD), Dasabuvir (250 mg BID), RBV weight-based

Paritaprevir/r<sub>(PI)</sub> + ombitasvir<sub>(NS5A) (FDC)</sub> + dasabuvir<sub>(nnNS5B)</sub> ± RBV in HIV/HCV coinfection

TURQUOISE-I

5 patients did not achieve SVR

- 1 withdrew consent
- 2 HCV reinfection
- 1 virologic relapse
- 1 breakthrough

Paritaprevir/ritonavir/Aombitasvir (150/100/25 mg QD), Dasabuvir (250 mg BID), RBV weight-based

Sulkowski MS, JAMA 2015
Sofosbuvir(nNS5B) + ribavirin

SVR12, %

- Treatment-naïve
  - FISSION (1): 97% (68/70)
  - VALENCE (2): 97% (31/32)
- Treatment-naïve, IFN-inelegible
  - POSITRON (3): 93% (101/109)

Sofosbuvir (400 mg QD), RBV weight-based.

Sofosbuvir\textsuperscript{(nNS5B)} + ribavirin

**SVR12, %**

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<thead>
<tr>
<th>Treatment-naïve</th>
<th>Treatment-naïve, IFN-inelegible</th>
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</thead>
<tbody>
<tr>
<td>FISSION (1)</td>
<td>POSITRON (2)</td>
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<tr>
<td>56</td>
<td>61</td>
</tr>
<tr>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>102/183</td>
<td>98/105</td>
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</tbody>
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Sofosbuvir (400 mg QD), RBV weight-based.

Sofosbuvir (nNS5B) + ribavirin

**Treatment-naïve Egyptian patients**
- 12 weeks: 84%
- 24 weeks: 92%

**Treatment-experienced Egyptian patients**
- 12 weeks: 70%
- 24 weeks: 89%

Sofosbuvir (400 mg QD), RBV weight-based (1,000-1,200 mg)

Esamt GE, AASLD 2014, abstract 959
Sofosbuvir(nNS5B) + ribavirin in HIV/HCV coinfection

GT 1, 3, 4 24wks
GT 2 12 wks

Sofosbuvir (400 mg QD), RBV 1000--1200 mg.

Molina JM, Lancet 2015
WARNINGS

- **DILI # ART**
- **drug-drug interaction**
  - ledipasvir increases tenofovir levels
  - ritonavir needs to be adjusted (or held) when administered with ritonavir-boosted anti-HCV medications
  - simeprevir NOT be used with efavirenz, etravirine, nevirapine, cobicistat, or any HIV protease inhibitor

[aidsinfo.nih.gov](http://aidsinfo.nih.gov) / [hep-druginteractions.org](http://hep-druginteractions.org), last accessed yesterday
<table>
<thead>
<tr>
<th>Drug-drug interactions between HCV DAAs and HIV antiretrovirals.</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td><strong>NRTIs</strong></td>
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<tr>
<td>Abacavir</td>
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<tr>
<td>Didanosine</td>
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<tr>
<td>Emtricitabine</td>
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<tr>
<td>Lamivudine</td>
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<td>Stavudine</td>
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<tr>
<td>Tenofovir</td>
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<tr>
<td>Zidovudine</td>
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<tr>
<td><strong>NNRTIs</strong></td>
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<tr>
<td>Efavirenz</td>
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<tr>
<td>Etravirine</td>
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<td>Nevirapine</td>
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<td>Rilpivirine</td>
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<tr>
<td><strong>Protease inhibitors</strong></td>
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<tr>
<td>Atazanavir/ritonavir</td>
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<tr>
<td>Darunavir/ritonavir/daranavir/cobicistat</td>
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<tr>
<td>Fosamprenavir</td>
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<td>Lopinavir</td>
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<td>Saquinavir</td>
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<tr>
<td><strong>Entry/Integrate inhibitors</strong></td>
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<tr>
<td>Dolutegravir</td>
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<tr>
<td>Elvitegravir/cobicistat</td>
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<tr>
<td>Maraviroc</td>
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<tr>
<td>Raltegravir</td>
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EASL Guideline, J Hepatol 2015
**Hepatitis C in Mono and Coinfected Children**

**Conclusions**

- hepatitis C in coinfected children could be a severe disease
- new anti-HCV drugs will change the paradigm of treatment in mono- and coinfected children
- HCV/HIC coinfected patients are no longer a difficult to treat population
Acknowledgments

Paediatric and Liver Unit
Massimo Resti
Elisa Bartolini

Immunology Lab
Chiara Azzari
Maria Moriondo
Giusi Mangone

PENTA-Hep
Carlo Giaquinto
Claire Thorne
Anna Turkova ............