XHC-HCV/HBV,HIV co-infections

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Α.Π.Θ, Α’ Παθ. Κλινική ,ΠΓΝΘ ΑΧΕΠΑ
• Ασθενείς με HCV και HIV συλλοίμωξη
HIV-infected persons engaged in selected stages of the continuum of HIV care
Cohen et al., JAMA 2012;307:247-250

Approximately 8% of HIV-infected persons also have chronic HBV infection
Initiation of ART in HIV-positive Persons with Chronic Infection without prior ART Exposure
EACS 2015

<table>
<thead>
<tr>
<th>Symptomatic HIV disease (CDC B or C conditions, incl. tuberculosis)</th>
<th>Asymptomatic HIV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CD4 count</td>
<td>Current CD4 count</td>
</tr>
<tr>
<td></td>
<td>&lt; 350</td>
</tr>
<tr>
<td></td>
<td>≥ 350</td>
</tr>
<tr>
<td>SR</td>
<td>SR</td>
</tr>
<tr>
<td></td>
<td>R</td>
</tr>
</tbody>
</table>

**SR** = Strongly Recommended  
**R** = Recommended
# Initial Combination Regimen for ART-naive Adult HIV-positive Persons  
EACS 2015

## A) Recommended regimens (one of the following to be selected)*;**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 NRTIs + INSTI</td>
<td></td>
</tr>
<tr>
<td><strong>ABC/3TC/DTG</strong>(i, ii)</td>
<td><strong>ABC/3TC/DTG</strong> 600/300/50 mg, 1 tablet qd</td>
</tr>
<tr>
<td><strong>TDF/FTC</strong>(iii, iv) + <strong>DTG</strong></td>
<td><strong>TDF/FTC</strong> 300**(vii)**/200 mg, 1 tablet qd + <strong>DTG</strong> 50 mg, 1 tablet qd</td>
</tr>
<tr>
<td><strong>TDF/FTC/EVG/c</strong>(iii, iv, v)</td>
<td><strong>TDF/FTC/EVG/c</strong> 300**(vii)**/200/150/150 mg, 1 tablet qd</td>
</tr>
<tr>
<td><strong>TDF/FTC</strong>(iii, iv) + <strong>RAL</strong></td>
<td><strong>TDF/FTC</strong> 300**(vii)**/200 mg, 1 tablet qd + <strong>RAL</strong> 400 mg, 1 tablet bid</td>
</tr>
</tbody>
</table>

| 2 NRTIs + NNRTI | |
| **TDF/FTC/RPV**(iii) | **TDF/FTC/RPV** 300**(vii)**/200/25 mg, 1 tablet qd |

| 2 NRTIs + PI/r | |
| **TDF/FTC**(iii, iv) + **DRV/r** | **TDF/FTC** 300**(vii)**/200 mg, 1 tablet qd + **DRV** 800 mg, 1 tablet qd + **RTV** 100 mg, 1 tablet qd |
Incidence of Acute HCV-HIV in EuroSIDA

Interaction between transmission group and year $p$-value=0.044
Number of events in each risk group (MSM=95, IDU=16, OTH including hetero=39)

Rockstroh, JIAS 2012
Mortality Related to Chronic Hepatitis C in France

Estimated annual number of deaths associated with
HCV 3618
HBV 1507

Mean age at death (years)

- HCV mono-infection: 70 years
- HCV and excessive alcohol consumption: 58 years
- HCV and HIV co-infection: 39 years

Marcellin et al; J Hepatol. 2008
HIV/HCV coinfection patients

• Due to shared routes of viral transmission, *coinfection with both HCV* and the human immunodeficiency virus (*HIV*) range from around

• **10–30%** in men who have sex with men (*MSM*)

• up to **80–90%** in intravenous (*i.v.*) drug users

• *Two types of HIV/HCV coinfected patients* can be distinguished:

  A) those infected for decades who have often severe fibrosis and several comorbidities vs.

  B) those recently infected with HCV
Etiology of liver disease in the HIV-infected patient

SHERMAN K ET AL HEPATOLOGY 2015
Chemokine (C-C motif) receptor 5 and cysteine-X-cysteine receptor 4

**HIV** isolates can infect primary human hepatic Stellate cells (**HSCs**)

**HIV** causes a productive noncytopathic *infection of Kupffer* cells (**LPS hyperresponse**)
HIV infects multiple cells in the liver

- **In vitro** (cell lines and primary cells)
  - Hepatocytes (HC)
  - Kupffer cells (KC)
  - Stellate cells (HSC)
  - Endothelial cells (LSEC)

- **In vivo**
  - Hepatocytes
  - Kupffer cells

HIV infection increases stellate cell activation

**Profibrogenic effects of inflammasome activation:** are the result of **direct HSC activation** by DAMPs or indirect DAMP-induced **Kupffer cell activation** with **subsequent IL-1β and IL-18-mediated** HSC activation?
Gp120 + CXCR4 (and CCR5) mediate stellate cell activation

LX-2 cell line; changes in collagen confirmed in primary HSCs

Hong et al., Plos One 2012; e33659
Does HIV persist in the liver in patients on cART?

HIV in liver accounts for 9% of total HIV in RT-SHIV infected macaques on cART

Luciw et al., Strategies toward an HIV Cure, Washington DC, Nov 2012
Microbial translocation associated with liver disease in HIV-HCV

HIV → Intestinal villous effacement and CD4+ depletion → Microbial Translocation

HCV → HCV-infected Liver → AIDS → Immune Activation

LPS → Stellate cells
Kupffer cells → Cirrhosis → fibrosis

Είσοδος του HCV στο ηπατοκύτταρο
HCV life cycle

1. Binding and internalisation
2. Release and uncoating
3. IRES mediated translation
4. Polyprotein processing
5. Membraneous web formation
6. Replication
7. Assembly and release

3D Structures of Membrane-Associated HCV Proteins  Paul D et al, Cell Host & Microbe 2014
Immune response to HCV infection/HIV

Rosen HR NEJM 2011

Intra-hepatic T cells were less capable of IFNγ production

CD4 level-dependent reduced HCV-specific lymphoproliferative responses

Impaired HCV-specific responses were more pronounced in HIV/HCV coinfected patients

Impairment in HCV-specific IFN-γ responses in acute infection (NK)
Anti-viral CD8 T cell immunity during chronic viral infection in the liver

Wong YC et al, J Hepatol 2015;63:1005-1014
Antigen level in the liver influences the outcome of CD8 T cell responses against hepatic antigens

HCV-specific CD8+ T cells seem to return promptly after DAA therapy-induced viral clearance
CD4 T cells in providing help to CD8 T cells recognizing hepatocyte-expressed antigens

- **CD4 T cells in providing help to CD8 T cells** recognizing hepatocyte-expressed antigens antigen-specific CD4 T cell intrahepatic retention and activation is dependent upon TCR affinity

- If **high affinity naive CD4 T cells** can be activated in the liver in parallel to CD8 T cells, they could potentially provide help to CD8 T cells in this organ

- In addition to the liver, hepatocyte-expressed antigens were also presented in secondary lymphoid organs by professional **APCs**, and led to the parallel activation of CD4 T cells in this compartment

- **CD4 T cell help** could thus potentially be provided in both liver and lymphoid tissues

- **Low affinity CD8 T cells** may require more help from CD4 T cells than high affinity T cells to induce a functional response within the liver
Factors influencing liver fibrosis progression  
Wong YC et al, J Hepatol 2015;63:1005-1014

Methodological issues with most of these studies

- HIV related factors
  - Duration of HIV viremia
  - Presence of immune activation
  - Low CD4 cell counts
  - Hepatotoxic cART

- HCV related factors
  - HCV genotype
  - Duration of infection

- Host related factors
  - Steatosis
  - Male gender
  - Age at acquiring infection
  - Lifestyle (alcohol/smoking)

Increased liver fibrosis progression may be abrogated by improved control of HIV with safer, less hepatotoxic cART and with commencement of HIV therapy at an earlier stage and higher CD4 count.
Incidence of HCC

- A recent large cohort study in 189,332 HCV mono-infected (included between 1995–2010) and 8563 HIV/HCV coinfected (included between 1985–2010) patients showed a higher incidence of HCC in the latter group.

- HCC prevalence was significantly higher among coinfected patients diagnosed with HIV in the pre-cART compared to early cART and late cART eras (43.0% vs. 37.3% and 19.7%).
Treatment of HCV in HIV-Coinfected Persons

SHERMAN K ET AL HEPATOLOGY 2015;62:1871-82

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Patients</th>
<th>Study</th>
<th>Medications</th>
<th>Duration (weeks)</th>
<th>n</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 4*</td>
<td>TN</td>
<td>ION-4</td>
<td>LDV/SOF</td>
<td>12</td>
<td>335</td>
<td>96</td>
</tr>
<tr>
<td>1</td>
<td>TN</td>
<td>National Institutes of Health</td>
<td>LDV/SOF</td>
<td>12</td>
<td>50</td>
<td>98</td>
</tr>
<tr>
<td>1</td>
<td>TN + TE</td>
<td>TURQUOISE-1</td>
<td>OPrD RBV</td>
<td>12</td>
<td>31</td>
<td>94</td>
</tr>
<tr>
<td>1</td>
<td>TN + TE</td>
<td>TURQUOISE-1</td>
<td>OPrD RBV</td>
<td>24</td>
<td>32</td>
<td>91</td>
</tr>
<tr>
<td>1</td>
<td>TN</td>
<td>ALLY-2</td>
<td>DCV/SOF</td>
<td>12</td>
<td>83</td>
<td>96</td>
</tr>
<tr>
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<td>ALLY-2</td>
<td>DCV/SOF</td>
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<td>41</td>
<td>76</td>
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<tr>
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<td>TE</td>
<td>ALLY-2</td>
<td>DCV/SOF</td>
<td>12</td>
<td>44</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>TN</td>
<td>PHOTON 1+2</td>
<td>SOF + RBV</td>
<td>12</td>
<td>45</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>TE</td>
<td>PHOTON 1+2</td>
<td>SOF + RBV</td>
<td>24</td>
<td>42</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>TN</td>
<td>PHOTON 1+2</td>
<td>SOF + RBV</td>
<td>12</td>
<td>57</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>TN</td>
<td>PHOTON 1+2</td>
<td>SOF + RBV</td>
<td>24</td>
<td>57</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>TE</td>
<td>PHOTON 1+2</td>
<td>SOF + RBV</td>
<td>24</td>
<td>66</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>TN + TE</td>
<td>ALLY-2</td>
<td>DCV/SOF</td>
<td>12</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>TN</td>
<td>PHOTON 1+2</td>
<td>SOF + RBV</td>
<td>24</td>
<td>31</td>
<td>84</td>
</tr>
</tbody>
</table>
Newest DAAs in HIV/HCV coinfection

Arends JE et al, J Hepatol 2015;63:1254-62

Depicted studies are:

**SOF/LDV** – ION-4 and ION-1;
**3D+RBV** – Turquoise-1 and PEARL-III and PEARL-IV;
**GZR/EBR** – C-EDGE COINFECTION and C-EDGE
Management of Persons with Chronic HCV/HIV Co-infection  EACS 2015

• **Metavir fibrosis score:** F0=no fibrosis; F1= portal fibrosis, no septae; F2=portal fibrosis, few septae, F3=bridging fibrosis, F4=cirrhosis.

• **FibroScan ®:** F0-F1 < 7.1 KPa; F2 7-10 KPa; F3/F4 > 10 Kpa

**Treatment must be considered independently from liver fibrosis** in persons with low CD4 count (<200 cells/μL), ongoing HIV replication, HBV co-infection, debilitating fatigue, extrahepatic manifestations, high risk of HCV transmission (IVDU, prisoners, MSM with high risk behavior, fertile women who want to be pregnant)
### HCV Treatment Options in HCV/HIV Co-infected Persons  EACS 2015

<table>
<thead>
<tr>
<th>HCV GT</th>
<th>Treatment regimen</th>
<th>Treatment duration &amp; ribavirin usage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-cirrhotic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compensated cirrhotic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decompensated cirrhlic CTP class B/C</td>
</tr>
<tr>
<td>1 &amp; 4</td>
<td>SOF + SMP + RBV</td>
<td>12 weeks without RBV</td>
</tr>
<tr>
<td></td>
<td>SOF/LDV + RBV</td>
<td>12 weeks without RBV</td>
</tr>
<tr>
<td></td>
<td>SOF + DCV + RBV</td>
<td>12 weeks without RBV</td>
</tr>
<tr>
<td></td>
<td>OBV/PTV/r + DSV</td>
<td>12 weeks in GT 1b</td>
</tr>
<tr>
<td></td>
<td>OBV/PTV/r + DSV + RBV</td>
<td>12 weeks in GT 1a</td>
</tr>
<tr>
<td></td>
<td>OBV/PTV/r + RBV</td>
<td>12 weeks in GT 4</td>
</tr>
<tr>
<td>2</td>
<td>SOF + DCV + RBV</td>
<td>12 weeks without RBV</td>
</tr>
<tr>
<td></td>
<td>SOF + RBV</td>
<td>12 weeks without RBV</td>
</tr>
<tr>
<td>3</td>
<td>SOF + PEG-IFN/RBV</td>
<td>Not recommended&lt;sup&gt;(iv)&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>SOF + RBV</td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF/LDV</td>
<td>12 weeks without RBV</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>In the absence of clinical data on DAAs in HCV GT 6 infection persons should be treated similarly to HCV GT 1 and 4 infection</td>
</tr>
</tbody>
</table>
IFN-containing Treatment of HCV in Persons with HCV/HIV Co-infection

<table>
<thead>
<tr>
<th>HCV GT</th>
<th>Treatment</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &amp; 4</td>
<td>SOF + PEG-IFN/RBV</td>
<td>12 weeks (possible extension up to 24 weeks in cirrhotics)</td>
</tr>
<tr>
<td></td>
<td>SMP* + PEG-IFN/RBV</td>
<td>24 weeks** (48 weeks in cirrhotics and treatment-experienced)</td>
</tr>
<tr>
<td></td>
<td>DCV + PEG-IFN/RBV***</td>
<td>24 weeks if RVR, 48 weeks if non-RVR</td>
</tr>
<tr>
<td>2</td>
<td>PEG-IFN/RBV</td>
<td>IFN-free treatment recommended. If SOF not available: PR 24 weeks if RVR, 48 weeks if non-RVR</td>
</tr>
<tr>
<td>3</td>
<td>SOF + PEG-IFN/RBV</td>
<td>12 weeks (possible extension up to 24 weeks in cirrhotics)</td>
</tr>
<tr>
<td>5 &amp; 6</td>
<td>In the absence of clinical data on DAAs in HCV GT 5 and 6 infection persons should be treated similar to HCV GT 1 and 4 infection</td>
<td></td>
</tr>
</tbody>
</table>

PEG-IFN/RBV: pegylated-interferon + ribavirin
RBV: ribavirin
SOF: sofosbuvir
SMP: simeprevir
DCV: daclatasvir

* SMP for 12 weeks only
** also in relapers
*** GT4 only, DCV for 24 weeks only
## Drug-drug Interactions between DAAs and ARVs

**EACS European AIDS Clinical Society 10/2015**

### Table 1: Interactions between HCV drugs and ARVs

<table>
<thead>
<tr>
<th>HCV drugs</th>
<th>ATV/r</th>
<th>DRV/c</th>
<th>DRV/r</th>
<th>LPV/r</th>
<th>EFV</th>
<th>ETV</th>
<th>NVP</th>
<th>RPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>boceprevir</td>
<td></td>
<td></td>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>daclatasvir</td>
<td>↑110%</td>
<td>↑</td>
<td>↑</td>
<td>↑15%</td>
<td>↓32%</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>ombitasvir/paritaprevir/r/dasabuvir</td>
<td>↑94%</td>
<td>↑</td>
<td>D</td>
<td>vii</td>
<td>↓</td>
<td>↓</td>
<td>E(vii)</td>
<td></td>
</tr>
<tr>
<td>ombitasvir/paritaprevir/r</td>
<td>↑(iv)</td>
<td>↑(vi)</td>
<td>↑(vi)</td>
<td>vii</td>
<td>↓</td>
<td>↓</td>
<td>E(vii)</td>
<td></td>
</tr>
<tr>
<td>simeprevir</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓81%</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>sofosbuvir/ledipasvir</td>
<td>↑8/113%</td>
<td>↑E(x)</td>
<td>↑34/39%</td>
<td>↓34%</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>sofosbuvir</td>
<td></td>
<td>↑</td>
<td>↑</td>
<td>↓6%</td>
<td>↓</td>
<td>↓</td>
<td>↑9%</td>
<td></td>
</tr>
<tr>
<td>telaprevir</td>
<td>↓20%E17%</td>
<td>↓D</td>
<td>↓35%</td>
<td>↓54%</td>
<td>↓26%</td>
<td>↓16%</td>
<td>↓</td>
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### Table 2: Interactions between DAAs and ARVs

<table>
<thead>
<tr>
<th>HCV drugs</th>
<th>MVC</th>
<th>DTG</th>
<th>EVG/c</th>
<th>RAL</th>
<th>ABC</th>
<th>FTC</th>
<th>3TC</th>
<th>TDF</th>
<th>ZDV</th>
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<tbody>
<tr>
<td>boceprevir</td>
<td>E</td>
<td></td>
<td>↓D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(i)</td>
</tr>
<tr>
<td>daclatasvir</td>
<td></td>
<td></td>
<td>↑(ii)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ombitasvir/paritaprevir/r/dasabuvir</td>
<td>E</td>
<td>E38%</td>
<td>↑</td>
<td>E134%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ombitasvir/paritaprevir/r</td>
<td>E</td>
<td></td>
<td>↑</td>
<td>E20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>simeprevir</td>
<td></td>
<td></td>
<td>↑</td>
<td>↓11%E8%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>sofosbuvir/ledipasvir</td>
<td>E?</td>
<td>↑36/78E(x)</td>
<td>D≈20%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>sofosbuvir</td>
<td></td>
<td></td>
<td>↑</td>
<td>5%D27%</td>
<td>↓6%</td>
<td>↓6%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>telaprevir</td>
<td>E</td>
<td>E25%</td>
<td>↑13%D16%</td>
<td>E31%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(i)</td>
</tr>
</tbody>
</table>

**Colour Legend:**
- **Red**: No clinically significant interaction expected; these drugs should not be co-administered.
- **Orange**: Potential interaction which may require a dosage adjustment or close monitoring.
HIV antiretroviral agent

- **ATV**, atazanavir
- **DRV**, darunavir
- **DTG**, dolutegravir
- **EFV**, efavirenz
- **ETR**, etravirine
- **EVG/cobi**, elvitegravir/cobicistat
- **LPV**, lopinavir
- **MVC**, maraviroc ; /r, ritonavir-boosted
- **RAL**, raltegravir
- **RPV**, rilpivirine
- **TPV**, tipranavir
Drug-drug Interactions between DAAs and ARVs
EACS 10/2015

i) Potential hematological toxicity

ii) Daclatasvir should be reduced to 30 mg qd with **ATV** (atazanavir )/r or **EVG/c** (elvitegravir/cobicistat). No dose reduction with unboosted ATV

iii) Daclatasvir should be increased to 90 mg qd (**EFV**, efavirenz)

iv) 3D use only with **unboosted ATV** and in persons without significant HIV PI mutations (**ATV** increased paritaprevir exposure due to CYP3A4 and OATP1B1/3 inhibition, not recommended without **dasabuvir**
Drug-drug Interactions between DAAs and ARVs
EACS 10/2015

• v) 3D co-administration decreased **DRV** (darunavir) trough concentration by approximately 50%. Although co-administration of **DRV** with **ombitasvir/paritaprevir/r + dasabuvir** is not recommended in the **US Prescribing Information**, the **European SPC advises** that **DRV** (dosed at 800 mg qd and administered at the same time as ombitasvir/paritaprevir/r + dasabuvir) can be used in the absence of extensive HIV PI resistance and should be taken without additional RTV

• vi) Increase in **paritepravir** exposure when co-administered with **DRV** 800 mg given with **Viekirax**
Drug-drug Interactions between DAAs and ARVs

EACS 10/2015

• vii) Severe tolerability issues 3D - (RPV, rilpivirine)

• viii) 3D not recommended unless benefit outweighs the risk due to potential for QT interval prolongation with higher concentrations of rilpivirine, co-administration should only be considered in persons without known QT prolongation and without other QT prolongation co-medications

• ix) SOF/LDV frequent monitoring of kidney function due to increase of TDF if contained in the regimen
DDI SOF and SOF/LDV

• **Least involved in drug-drug interactions** with combination antiretrovirals (cART)

• **SOF and SOF/LDV** can be used in combination with nonnucleoside reverse transcriptase inhibitors (NNRTIs), integrase inhibitors or **ritonavir-boosted HIV PIs** (excluding tipranavir)

• **Potential nephrotoxicity** when combining sofosbuvir/ledipasvir with tenofovir (increase in levels) [inhibition of the P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters by ledipasvir]
DDI paritaprevir/ritonavir, ombitasvir and dasabuvir (3D)

- Especially with **NNRTIs and HIV PIs**. These combinations are often not recommended for simultaneous use.

- The HIV PIs **darunavir** (only when once daily dosing is applicable and administered at the same time), and **atazanavir** can be given concomitantly **with the 3D** regimen, however,

- **Ritonavir** used in the HIV regimen **should be stopped** during HCV treatment because sufficient ritonavir is already co-formulated with paritaprevir.
Dual HCV Therapy in Persons with Chronic HCV/HIV Co-infection Not Eligible for Triple Therapy Including DAAs against HCV

Where no access to DAAs available or high chances of cure even with dual therapy (favourable IL28B GT, low HCV-RNA and no advanced fibrosis)
Use of Boceprevir, Telaprevir, Simeprevir or Sofosbuvir with PEG-IFN + RBV in Persons with HIV/HCV Co-infection

- **Boceprevir 800 mg tid + PEG-IFN + RBV**
  - If ≥ 100 IU/mL, stop all therapy
  - If detectable, stop all therapy

- **Telaprevir 750 mg tid + PEG-IFN + RBV**
  - If > 1000 IU/mL, stop all therapy
  - If detectable, stop PEG-IFN/RBV

- **Simeprevir 150 mg qd + PEG-IFN + RBV**
  - If > 25 IU/mL, stop all therapy

- **Sofosbuvir 400 mg qd + PEG-IFN + RBV**

Therapy should be stopped if there is a confirmed increase in HCV-RNA by 1*10 following a decline at any stage.

No stopping rules apply: Fixed duration of 12 weeks regardless of HCV-RNA decline.
Algorithm for Management of Acute HCV in Persons with HIV infection

- Initial presentation: Acute HCV
  - Week 4: Decay HCV-RNA
    - $< 2^{*log_{10}}$
      - Treatment with PEG-IFN + RBV
        - Week 4: HCV-RNA level
          - Positive
            - Treatment for 48 weeks, stop treatment if $< 2^{*log_{10}}$ decrease in HCV-RNA level at week 12
          - Negative
            - Stop treatment after 24 weeks
        - Negative
          - Week 12: HCV-RNA level
            - $\geq 2^{*log_{10}}$
              - Positive
                - Serial HCV-RNA measurements throughout week 48 to confirm resolution
              - Negative
HCV vs HIV/HCV coinfected patients

- **Higher** observed number of **HCV reinfections** in the latter group, either in i.v drug users or MSM

- As high as **7.8 and 15.2 per 100 patient years** of follow-up

- Unchanged sexual behaviours, as well as other risk behaviours in combination with the emergence of national and international networks of HIV positive men preferentially having unprotected sex with HIV positive men

- In-depth **quasispecies analysis** should be performed to reliably **distinguish between HCV relapse and reinfection**

- **Increasing DAA use** in combination **with high rates of HCV reinfection** has the potential to result in **accumulation of HCV DAA-resistant variants!**
Conclusion 1

- Despite significant advances in treatment of **hepatitis C virus**, treatment and management principles for liver disease **in HIV infected patients** remain challenging;
- *limited resources*,
- *fragmented health care*, and
- high levels of *injection drug use, alcohol use, and depression* remain relevant issues in the HIV-infected patient.
Conclusion 2

• Coinfected patients enrolled in DAA studies to date have comparable, if not equivalent, SVR rates to mono-infected patients treated with the same regimen.

• Therefore, the *HIV coinfection* patients appear to be *no longer a ‘hard to treat’ population*, and, as international organisations now suggest,

• *Should be treated in identical fashion as the mono-infected* patients.
• Ασθενείς με HCV και HBV συλλοίμωξη
HCV-HBV coinfection

- In HCV-HBV coinfection, the HBV DNA level is often low or undetectable, and **HCV is usually the main driver** of chronic hepatitis activity.
- Patients characterized for the replicative status of both HBV and HCV, and hepatitis delta virus infection should be sought.
- There is a potential **risk of HBV reactivation** during or after HCV clearance (60%).
- 30% of the dually infected patients cleared hepatitis B surface antigen within 5 years after the start of peginterferon-based therapy.
ΚΕ.ΕΛ.Π.ΝΟ., Δεκέμβριος 2015

• Οι ενδείξεις για τη θεραπεία του HCV σε ασθενείς με HCV και HBV συλλοίμωξη ή ακόμη και με τριπλή HCV, HBV και HDV συλλοίμωξη είναι σήμερα παρόμοιες με εκείνες των ασθενών με μόνον HCV λοίμωξη.

• Τα ίδια θεραπευτικά σχήματα, όπως περιγράφονται παραπάνω ανά γονότυπο, μπορούν να χρησιμοποιηθούν και σε ασθενείς με HCV και HBV συλλοίμωξη, αφού τα αναμενόμενα ποσοστά SVR είναι παρόμοια.
EASL 2015 HCV: Treatment should be prioritized

- Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis

- **Patients with HIV coinfection**

- **Patients with HBV coinfection**

- Clinical observatory studies suggest a higher risk of liver disease progression in patients with dual HCV/ HBV infection than in HBV or HCV monoinfected patients
DAA based therapy in patients with HCV/HBV

Liu CJ et al 2016

HCV RNA-positive & HBsAg-positive

- General chronic hepatitis C patients
- Patients not eligible for or tolerating Peg-IFN or RBV
- Liver transplant recipients
- Decompensated liver cirrhosis

DAA-based therapy

- Replace P+R
- Increase rate of HCV SVR when added onto P+R
- Treat HCV by IFN- or RBV-free regimens
- Treat HCV by IFN-free regimens
- Treat HCV by IFN-free regimens
HBV co-infection: Conclusions

- Patients should be treated with the same regimens, following the **same rules as HCV monoinfected** patients.

- **If HBV replicates** at significant levels before, during or after HCV clearance, **concurrent HBV nucleoside/nucleotide analogue therapy** is indicated (Simeprevir increases exposure to tenofovir)