Medical Education Workshops on HIV/AIDS
Updates of Hep C co-infection management in co-infected patients

Jürgen Rockstroh, Department of Medicine I, University Hospital Bonn, Bonn, Germany
Topics to cover

- Diagnosis of HCV
- Epidemiology
- HCV genotypes
- Goal of HCV therapy
- Natural history of liver disease in HIV coinfection
- Monitoring under HCV therapy
- Antiviral HCV therapy
- Drug drug interactions
- Real world experience
- HCV elimination
How to diagnose acute and chronic HCV?
EASL Recommendations on Treatment of Hepatitis C 2015

European Association for the Study of the Liver *

- Anti-HCV antibodies are the first-line diagnostic test for HCV infection (A1)
- In the case of suspected acute hepatitis C or in immunocompromised patients, HCV RNA testing should be part of the initial evaluation (A1)
- If anti-HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method (A1)
- Anti-HCV-positive, HCV RNA negative individuals should be retested for HCV RNA three months later to confirm true convalescence (A1)
Epidemiology of HCV
The global number of HCV infections (anti-HCV and viraemic)

Global prevalence of HIV/HCV co-infection

Burden of co-infection with HIV and HCV by region, 2013

- **Africa**: 2.8 million (IQR: 1.6–5.9 million)
- **Eastern Europe**: Estimate
- **South East Asia**: Estimate
- **North America**: Estimate
- **Latin America**: Estimate
- **Europe**: Estimate
- **Western Pacific**: Estimate
- **East Med**: Estimate

HCV, hepatitis C virus; IQR, inter-quartile ratio

Anti-HCV antibody prevalence in different EuroSIDA regions

- South: 28.8%
- West: 20.1%
- North: 17.3%
- East Central: 34.0%
- East: 57.7%
- Argentina: 20.6%

Peters L et al., BMC Infect Dis. 2014;14 Suppl 6:S13
Acute HCV among HIV+ MSM

What are HCV genotypes?
HCV Genotypes

HCV genetically diverse
Seven genotypes and many subtypes.

- Regional variations in genotype prevalence
- G1 most common worldwide (44%-48%%) ~50-60 million cases, most in East Asia
- G4 and G5 more prevalent in lower-income countries.

What is the goal of HCV therapy and what does SVR mean for further clinical endpoints?
What do we mean when we talk about ‘cure’ in HCV?

- Sustained virological response: Undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after treatment completion\(^1\)

- HCV is cured (does not relapse) in > 99% of patients who achieve SVR\(^1,2\)

Concordance between SVR4, SVR12, and SVR24 in Phase 3 ION Studies

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<td></td>
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- 99.6% positive predictive value
- 100% negative predictive value

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<td></td>
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<td>3</td>
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</tbody>
</table>

- 100% positive predictive value
- 100% negative predictive value

Bernstein, AASLD, 2014, Poster #1947
Sustained Virologic Response is associated with a reduction in liver-related mortality and HCC

Ten-year cumulative incidence of liver-related mortality or transplantation in HCV patients (n=530) was also calculated in the European/Canadian study within five large tertiary hospitals. All patients had received an interferon-based regimen between 1990 and 2003.

SVR reduces all-cause mortality

- IFN: interferon

Long-term follow-up study from 5 tertiary care hospitals in Europe and Canada of HCV patients with advanced fibrosis/cirrhosis (n=530) treated with an IFN-based regimen between 1990–2003

Cumulative Risk of Liver-Related Death after HCV therapy \( \{n=3500\} \) in HIV/HCV coinfected individuals

<table>
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<tr>
<th>Stratum</th>
<th>Obs</th>
<th>Events</th>
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<td>45</td>
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<tr>
<td>2</td>
<td>996</td>
<td>4</td>
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<tr>
<td>3</td>
<td>917</td>
<td>12</td>
</tr>
</tbody>
</table>

Logrank \( p=0.0001 \)

Peters L, et al. EACS 2015, abstract 550
Cumulative risk of all-cause mortality after HCV therapy (n=3500)

![Cumulative risk of all-cause mortality](image)

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Obs</th>
<th>Events</th>
</tr>
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<tbody>
<tr>
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<td>1587</td>
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<td>2</td>
<td>996</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>917</td>
<td>49</td>
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</tbody>
</table>

Logrank p=0.0019

- Non-responders
  - 1587 events
  - 1222 deaths
- Responders
  - 996 events
  - 646 deaths
- Unknown response
  - 917 events
  - 736 deaths

Peters L et al., EACS 2015
How is the course of HCV different in HIV-coinfection?
HCV co-infection in EuroSIDA

- EuroSIDA: prospective, European study of 18,295 HIV-1–infected patients at 105 centres across Europe, Israel and Argentina
- Prevalence of HCV seropositivity in EuroSIDA is 31% (4,044 patients), 74.2% of which were serum HCV RNA-positive

### Progression to liver-related death in HIV-positive population

<table>
<thead>
<tr>
<th>HCVAb serostatus:</th>
<th>Events (PYFU)</th>
<th>IRR (95% CI; p value)</th>
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</thead>
<tbody>
<tr>
<td>Negative</td>
<td>43 (66,653)</td>
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<tr>
<td>Positive</td>
<td>175 (26,494)</td>
<td>8.90 (5.60–14.14; p&lt;0.0001)</td>
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<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>Events (PYFU)</th>
<th>IRR (95% CI; p value)</th>
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<tr>
<td>GT 1</td>
<td>55 (8122)</td>
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<tr>
<td>GT 2</td>
<td>2 (554)</td>
<td>0.27 (0.07–1.13; p=0.073)</td>
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<tr>
<td>GT 3</td>
<td>28 (4503)</td>
<td>0.99 (0.62–1.59; p=0.98)</td>
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<tr>
<td>GT 4</td>
<td>9 (2188)</td>
<td>0.91 (0.44–1.89; p=0.80)</td>
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<table>
<thead>
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<th>HCV-RNA viremia</th>
<th>Events (PYFU)</th>
<th>IRR (95% CI; p value)</th>
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<td>HCVAb-</td>
<td>43 (66,653)</td>
<td>0.18 (0.10–0.32; p&lt;0.0001)</td>
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<tr>
<td>Ab+/RNA-</td>
<td>21 (4838)</td>
<td>1</td>
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<tr>
<td>Ab+/RNA+</td>
<td>86 (11,302)</td>
<td>2.11 (1.30–3.42; p=0.0025)</td>
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<tr>
<td>Ab+/unknown</td>
<td>68 (10,354)</td>
<td>1.42 (0.86–2.35; p=0.17)</td>
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Multivariate analysis adjusted for gender, exposure group, race, prior AIDS, region of Europe, CD4+ T-cell nadir, HCV treatment status at baseline, age, and baseline date. Starting cART, HBsAg status, diagnosis of a new AIDS-defining illness and CD4+ T-cell count were included as time-updated variables.

Adjusted incidence rate ratio (95% CI)

HCVAb, anti-HCV antibodies; PYFU, person years of follow-up; IRR, incidence rate ratio;
HIV/HCV co-infection burden: Accelerated disease progression and morbidity

• ➨ Prevalence, especially in some populations\textsuperscript{1–3}

• Compared with HCV mono-infected patients, patients co-infected with HIV display:
  • ➨ viraemia (2–8-fold greater)\textsuperscript{1,4}
  • ➨ infectivity increases risk of transmission from mother to child (20% vs 6%) and risk of sexual transmission (3% vs <1%)\textsuperscript{1,5}
  • ➩ likelihood of spontaneously clearing HCV\textsuperscript{1,4}
  • ➨ hepatic fibrosis (2–5-fold greater), cirrhosis, decompensation, hepatocellular carcinoma and liver-related mortality\textsuperscript{1,5}

What is the optimal treatment strategy in HIV/HCV co-infected patients?

- Treat HCV first?
- Treat HIV first?
- Treat HIV/HCV simultaneously?
First, antiretroviral therapy (ART) should be initiated in everyone living with HIV at any CD4 cell count.

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

**SR** = Strongly Recommended  
**R** = Recommended

- HBV requiring anF-HBV treatment  
- HBV not requiring anF-HBV treatment  
- HCV for which anF-HCV treatment is being considered or given  
- HCV for which anF-HCV treatment not feasible

EACS guidelines:

- Initiation of ART is always recommended if CD4 count < 350 cells/mm$^3$
- ART is always recommended if CD4 count < 350 cells/mm$^3$

Antiretroviral therapy reduces the rate of hepatic decompensation among HIV- and hepatitis C virus-coinfected veterans

**Objective:**

- To evaluate 10,090 HIV/HCV-co-infected males from the Veterans Aging Cohort Study Virtual Cohort, who had not initiated ART at entry, for incident hepatic decompensation between 1996 and 2010

**Results:**

- Initiation of ART significantly reduced the rate of hepatic decompensation by 28–41% on average

HCV Disease Progression Remains Faster in Coinfected Patients, Despite Effective ART

**HCV Disease Progression Remains Faster in Coinfected Patients, Despite Effective ART**

If HIV RNA <1000 copies/mL: +65% excess risk
If HIV RNA >1000 copies/mL: +82% excess risk

If CD4 < 200/mm²: +203% excess risk
If CD4 > 200/mm²: 56–63% excess risk

**ART,** antiretroviral therapy; **HCV,** hepatitis C virus; **HIV,** human immunodeficiency virus.

Quantitative HCV-RNA monitoring before and under therapy
Hepatitis C Viral Load Monitoring with Ledipasvir/Sofosbuvir

Patients with HCV RNA ≥LLOQ or TD <LLOQ at W4 and EOT

- The majority of patients with HCV RNA ≥LLOQ or HCV RNA TD <LLOQ at week 4 achieved SVR12 (NPV <13%)
- 5 patients on SYNERGY and 7 patients on ERADICATE had HCV RNA TD <LLOQ at EOT by the Abbott assay
- All 12 patients achieved SVR12
- By the Roche assay, all patients had HCV RNA TND <LLOQ at EOT

Whom to treat?
EASL HCV guidelines 2015

- All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV should be considered for therapy (A1)

- Treatment should be prioritized for patients with significant fibrosis or cirrhosis (METAVIR score F3 to F4) (A1)

- Patients with decompensated cirrhosis (Child-Pugh B and C) should be urgently treated with an IFN-free regimen (A1)

- Treatment should be prioritized regardless of the fibrosis stage in patients with HIV or HBV coinfection, patients in the pre- or post-liver transplant setting, patients with clinically significant extra-hepatic manifestations (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non–Hodgkin B cell lymphoma), and patients with debilitating fatigue (A1)

- Treatment should be prioritized regardless of the fibrosis stage for individuals at risk of transmitting HCV, including active injection drug users, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, haemodialysis patients, and incarcerated individuals (B1)

- Treatment is justified in patients with moderate fibrosis (METAVIR score F2) (A2)

- In patients with no or mild disease (METAVIR score F0–F1) and none of the above-mentioned extra-hepatic manifestations, the indication for and timing of therapy can be individualized (B1)

- Treatment is not recommended in patients with limited life expectancy due to non-liver-related comorbidities (B1)
Summary of Recommendations for When and in Whom to Initiate HCV Therapy

Goal of Treatment

- The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response.
  Rating: Class I, Level A

Recommendations for When and in Whom to Initiate Treatment

- Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.
  Rating: Class I, Level A

Recommendations for Pretreatment Assessment

- Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection, to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening). (see HCV Testing and Linkage to Care [11])
  Rating: Class I, Level A
How has HCV therapy changed?
Milestones in the treatment of HCV Genotype 1 infection

1988/89 – Discovery HCV-Virus

Direct-Acting Antivirals (DAA)

Interferon

Ribavirin

1991

1998

2001

2011

2014

2015

SVR (%)

0

100

1991

1998

42

39

55

70+

80+

95+

IFN 6 Mo.

IFN 12 Mo.

IFN/RBV IFN/RBV

PegIFN 12 Mo.

PegIFN/RBV 12 Mo.

PegIFN/RBV+ TVR/BOC

SOF+ Peg/ RBV

IFN frei DAAs ±RBV

6

16

34

42

39

55

70+

80+

95+

HCV DAAs

5' UTR - Core - E1 - E2 - p7 - NS2 - NS3 - NS4B - NS5A - NS5B - 3' UTR

- Protease
- Polymerase

Ribavirin
NS3 Protease Inhibitors
Telaprevir
Boceprevir
Simeprevir
Asunaprevir
Veruprevir
Grazoprevir

NS5A Replication Complex Inhibitors
Daclatasvir
Ledipasvir
Ombitasvir
Elbasvir
GS-5816

NS5B NUC Inhibitors
Sofosbuvir
VX-135
IDX21437
ACH-3422

NS5B Non-NUC Inhibitors
Dasabuvir
Beclabuvir

-previr
-asvir
-buvir
Improved SVR12/24 rates over time in HCV GT 1 patients co-infected with HIV

3D, ABT-450/ritonavir/ombitasvir; BOC, boceprevir; DAA, direct-acting antiviral agent; P/R, pegylated interferon/ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir

IN THE DAA ERA HIV+ PATIENTS WILL ACHIEVE SIMILAR SVR RATES

Dieterich D et al. CROI 2014; P#24;
Rodriguez-Torres M et al. IDWeek 2013; P#714;
Sulkowski M et al. AIDS 2014; P#104 LB;
Wyles D et al. IAS 2015
Drug-drug Interactions between DAAs 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>
<th>MVC</th>
<th>DTG</th>
<th>EVG/c</th>
<th>RAL</th>
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<td>bocaprevir</td>
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<td>32%D44%</td>
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<td>↓E</td>
<td>6%E35%</td>
<td>E</td>
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<td>↑</td>
<td>↑40%</td>
<td>↑15%</td>
<td>↓32%(iv)</td>
<td>↓</td>
<td>↓</td>
<td>←</td>
<td>←</td>
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<td>D(vi)</td>
<td>↑vii</td>
<td>↓E?</td>
<td>↓E?</td>
<td>E(h)</td>
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<td>↑(vi)</td>
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<td>↓E?</td>
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<td>↑36/78E(ox)</td>
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</tbody>
</table>

**Legend**

- ↑ potential elevated exposure of DAA
- ↓ potential decreased exposure of DAA
- no significant effect
- D potential decreased exposure of ARV
- E potential elevated exposure of ARV

Numbers refer to decreased/increased AUC of DAAs and ARVs as observed in drug interactions studies. Sofosbuvir/ledipasvir: first/second numbers refer to changes AUC sofosbuvir/ledipasvir.

**Colour legend**

- no clinically significant interaction expected.
- these drugs should not be co-administered.
- potential interaction which may require a dosage adjustment or close monitoring.

Note: the symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org.

- Potential hematological toxicity
- Daclatasvir should be reduced to 30 mg qd with ATV/r or EVG/c.
  No dose reduction with unboosted ATV
- Daclatasvir should be increased to 90 mg qd
- 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)
- Co-administration is not recommended due to decreased DRV/c trough by 50% when DRV administered 800 mg or 600 mg bid (second dose given with additional RTV)
- Increase in pantepravir exposure when co-administered with DRV 800 mg given with Viokirax
- Severe tolerability issues
- Not recommended unless benefit outweighs the risk due to potential for QT interval prolongation with higher concentrations of ritipivirine, co-administration should only be considered in persons without known QT prolongation and without other QT prolongation co-medications
- Frequent monitoring of kidney function due to increase of TDF if contained in the regimen
## Drug Interactions Between Select ARTs and HCV Therapies - *EACS*¹ (1 of 3)

<table>
<thead>
<tr>
<th></th>
<th>BOC</th>
<th>DCV</th>
<th>LED/SOF</th>
<th>OBV/PTV/r</th>
<th>OBV/PTV/r +DSV</th>
<th>SMV</th>
<th>SOF</th>
<th>TVR</th>
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<td>E134%</td>
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<td>↓5% D27%</td>
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<td>↑36/78 E</td>
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<td></td>
<td></td>
<td>↓6%</td>
</tr>
<tr>
<td>Lamivudine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>↑10% E10%</td>
<td>E</td>
<td></td>
<td>↓14% E18%</td>
<td>↓6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

↓ = potential decreased exposure of DAA; ↑ = potential increased exposure of DAA; D = potential decreased exposure of ARV; E = potential elevated exposure of ARV.

# Drug Interactions Between Select ARTs and HCV Therapies - EACS¹ (2 of 3)

## NNRTIs

<table>
<thead>
<tr>
<th></th>
<th>BOC</th>
<th>DCV</th>
<th>LED/SOF</th>
<th>OBV/PTV/r</th>
<th>OBV/PTV/r +DSV</th>
<th>SMV</th>
<th>SOF</th>
<th>TVR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efavirenz</strong></td>
<td><img src="image" alt="↓19%" /></td>
<td><img src="image" alt="↓32%" /></td>
<td><img src="image" alt="↓-/34%" /></td>
<td><img src="image" alt="Severe*" /></td>
<td><img src="image" alt="Severe*" /></td>
<td><img src="image" alt="↓71%" /></td>
<td><img src="image" alt="↓6%" /></td>
<td><img src="image" alt="↓26%" /></td>
</tr>
<tr>
<td><strong>Etravirine</strong></td>
<td><img src="image" alt="↑10%" /></td>
<td><img src="image" alt="↓E?" /></td>
<td><img src="image" alt="↓E?" /></td>
<td><img src="image" alt="↓E?" /></td>
<td><img src="image" alt="↓" /></td>
<td><img src="image" alt="↓E?" /></td>
<td><img src="image" alt="↓E?" /></td>
<td><img src="image" alt="↓?" /></td>
</tr>
<tr>
<td><strong>Nevirapine</strong></td>
<td><img src="image" alt="↓E" /></td>
<td><img src="image" alt="↓" /></td>
<td><img src="image" alt="↓E?" /></td>
<td><img src="image" alt="↓E?" /></td>
<td><img src="image" alt="↓" /></td>
<td><img src="image" alt="↓E?" /></td>
<td><img src="image" alt="↓E?" /></td>
<td><img src="image" alt="↓?" /></td>
</tr>
<tr>
<td><strong>Rilpivirine</strong></td>
<td><img src="image" alt="↓6%" /></td>
<td><img src="image" alt="E" /></td>
<td><img src="image" alt="E?" /></td>
<td><img src="image" alt="E" /></td>
<td><img src="image" alt="E" /></td>
<td><img src="image" alt="↑6%" /></td>
<td><img src="image" alt="↑9%" /></td>
<td><img src="image" alt="↓5%" /></td>
</tr>
</tbody>
</table>

## Entry Inhibitor

<p>| | | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maraviroc</strong></td>
<td><img src="image" alt="E" /></td>
<td><img src="image" alt="E?" /></td>
<td><img src="image" alt="E" /></td>
<td><img src="image" alt="E" /></td>
<td><img src="image" alt="E" /></td>
<td><img src="image" alt="E" /></td>
<td><img src="image" alt="E" /></td>
<td><img src="image" alt="E" /></td>
</tr>
</tbody>
</table>

↓ = potential decreased exposure of DAA; ↑ = potential increased exposure of DAA; D = potential decreased exposure of ARV; E = potential elevated exposure of ARV.

ART = antiretroviral therapy; BOC = boceprevir; DCV = daclatasvir; LED = ledipasvir; OBV/PTV/r + DSV = ombitasvir/paritaprevir/ritonavir + dasabuvir; SMV = simeprevir; SOF = sofosbuvir; TVR = telaprevir; Peg IFN = pegylated interferon; RBV = ribavirin.

Drug Interactions Between Select ARTs and HCV Therapies - EACS\(^1\) (3 of 3)

- ART = antiretroviral therapy; BOC = boceprevir; DCV = daclatasvir; LED = ledipasvir; OBV/PTV/r + DSV = ombitasvir/paritaprevir/ritonavir + dasabuvir; SMV = simeprevir; SOF = sofosbuvir; TVR = telaprevir; Peg IFN = pegylated interferon; RBV = ribavirin.

### Protease Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>BOC</th>
<th>DCV</th>
<th>LED/SOF</th>
<th>OBV/PTV/r</th>
<th>OBV/PTV/r + DSV</th>
<th>SMV</th>
<th>SOF</th>
<th>TVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/ritonavir</td>
<td>D35%</td>
<td>↑110%</td>
<td>↑8/113%</td>
<td>↑94%</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓20% E17%</td>
</tr>
<tr>
<td>Darunavir/cobicistat</td>
<td>↓D</td>
<td>↑</td>
<td>↑E</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓D</td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td>↓32% D44%</td>
<td>↑40%</td>
<td>↑34/39%</td>
<td>D</td>
<td>↑</td>
<td>↑</td>
<td>↑34%</td>
<td>↓35% D40%</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>↓45% D34%</td>
<td>↑15%</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓54%</td>
<td></td>
</tr>
</tbody>
</table>

\(\downarrow\) = potential decreased exposure of DAA; \(\uparrow\) = potential increased exposure of DAA; D = potential decreased exposure of ARV; E = potential elevated exposure of ARV.

Ledipasvir/sofosbuvir for 12 Weeks in Patients Coinfected with HCV and HIV-1: ION-4

Study Design:
GT1 and 4 with HIV/HCV co-infection*

LDV/SOF (N=335)

Study Design:
GT1 and 4 with HIV/HCV co-infection

Efficacy Results:
GT1 and 4 with HIV/HCV co-infection

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Naive</th>
<th>Exp</th>
<th>No cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12 (%)</td>
<td>96</td>
<td>95</td>
<td>97</td>
<td>96</td>
<td>94</td>
</tr>
<tr>
<td>n</td>
<td>321</td>
<td>142</td>
<td>179</td>
<td>258</td>
<td>63</td>
</tr>
<tr>
<td>N</td>
<td>335</td>
<td>150</td>
<td>185</td>
<td>268</td>
<td>67</td>
</tr>
</tbody>
</table>

Real Life DAA Data from Germany: GECCO Cohort

- 1346 patients from 9 centres: 21% HIV/HCV co-infected, 29% F4 fibrosis/cirrhosis

- Good response rates also in Tx experienced, F4, diabetics, co-infected

- 8 weeks of SOF/LDV very effective – even in “problematic” patients

ALLY-2: DCV+SOF in HIV/HCV Coinfection

New DAAs, in all four classes, are now approved

<table>
<thead>
<tr>
<th></th>
<th>Treatment duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOC</td>
<td>+ PEG-IFN + RBV</td>
</tr>
<tr>
<td>TVR</td>
<td>+ PEG-IFN + RBV</td>
</tr>
<tr>
<td>OMV</td>
<td>+ PEG-IFN + RBV</td>
</tr>
<tr>
<td>SOF</td>
<td>+ PEG-IFN + RBV</td>
</tr>
<tr>
<td>SOF</td>
<td>+ RBV</td>
</tr>
<tr>
<td>SOF</td>
<td>± RBV</td>
</tr>
<tr>
<td>SOF</td>
<td>± RBV</td>
</tr>
<tr>
<td>SOF</td>
<td>± RBV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Treatment duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOC</td>
<td>28–48</td>
</tr>
<tr>
<td>TVR</td>
<td>12–48</td>
</tr>
<tr>
<td>OMV</td>
<td>12–24</td>
</tr>
<tr>
<td>SOF</td>
<td>12</td>
</tr>
<tr>
<td>SOF</td>
<td>24</td>
</tr>
<tr>
<td>SOF</td>
<td>12–24</td>
</tr>
<tr>
<td>SOF</td>
<td>12–24</td>
</tr>
<tr>
<td>SOF</td>
<td>8–24</td>
</tr>
</tbody>
</table>

1. Merck, Sharp & Dohme Ltd. VICTRELIS▼ (boceprevir), SmPC July 2011; 2. Janssen Cilag International. INCIVO▼ (telaprevir), SmPC, September 2011; 3. AbbVie Ltd. VIEKIRAX▼ (ombitasvir/paritaprevir/ritonavir), SmPC, January 2015; 4. AbbVie Ltd. EXVIERA▼ (dasabuvir), SmPC, January 2015; 5. Gilead Sciences Europe Ltd. SOVALDI▼ (sofosbuvir), SmPC, March 2015; 6. Janssen Cilag International. OLYSIO▼ (simeprevir), SmPC, May 2014; 7. Bristol-Myers Squibb Pharma. Daklinza▼ (daclatasvir), SmPC, August 2014; 8. Gilead Sciences Europe Ltd. HARVONI▼ (ledipasvir/sofosbuvir), SmPC, November 2014

## Treatment Options 2015/2016

### IFN-free regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>GT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + RBV</td>
<td>2, 3</td>
</tr>
<tr>
<td>Sofosbuvir/Ledipasvir (± RBV)</td>
<td>1, 4, 5, 6</td>
</tr>
<tr>
<td>Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir (± RBV)</td>
<td>1</td>
</tr>
<tr>
<td>Sofosbuvir + Simeprevir (± RBV)</td>
<td>1, 4</td>
</tr>
<tr>
<td>Sofosbuvir + Daclatasvir (± RBV)</td>
<td>All</td>
</tr>
<tr>
<td>Ombitasvir/Paritaprevir/Ritonavir (± RBV)</td>
<td>4</td>
</tr>
</tbody>
</table>

### IFN-containing regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>GT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PegIFNα + RBV + sofosbuvir</td>
<td>All</td>
</tr>
<tr>
<td>PegIFNα + RBV + simeprevir</td>
<td>1, 4</td>
</tr>
</tbody>
</table>


(J-M Pawlotsky, ILC2015, Vienna, Austria, April 24, 2015. EASL Recommendations on Treatment of Hepatitis C 2015)
Characteristics that Inform Treatment Option Selection

- Prior treatment experience
- HCV genotype/subtype
- Severity of liver disease
- Drug-drug interactions
- PK profile of treatment
- Patient comorbidities

(J-M Pawlotsky, ILC2015, Vienna, Austria, April 24, 2015.
EASL Recommendations on Treatment of Hepatitis C 2015)
Real world experience
SVR12 by genotype and regime from the English EAP study

Interesting data on the NHS England Early Access Program (EAP) was presented at EASL which provided 12 weeks of therapy with SOF, with or without RBV and an NSSA inhibitor (provided by Gilead or BMS) to a cohort of ~500 patients with decompensated cirrhosis. In this first analysis, data from 467 HCV patients (235 with GT 1 infection, 189 with GT 3 infection) was presented.

Real Life DAA Data from France

- 215 HIV HCV co-infected patients from the ANRS HEPAVIH cohort
- 67% cirrhotics, 71% Tx experienced

No influence of cirrhosis or pre-treatment upon SVR

How can we change the HCV epidemic?
Risk of Late Relapse or Re-Infection with Hepatitis C After Sustained Virological Response: Meta-Analysis of 66 Studies in 11,071 Patients

Five-Year Rate (95% CI) of Recurrence Post-SVR, by Risk Group

- **Low Risk**
  - 43 studies
  - \( N = 9,419 \)
  - Avg. FU = 4.1 ± 2.1 y

- **High Risk (IDUs/prisoners)**
  - 16 studies
  - \( N = 819 \)
  - Avg. FU = 2.9 ± 1.6 y

- **HIV/HCV Co-Infected**
  - 7 studies
  - \( N = 833 \)
  - Avg. FU = 3.1 ± 1.2 years

- **Low Risk**
  - 5-yr recurrence rate post SVR, %
    - 1.1% (95% CI 0.9–1.4%)

- **High Risk**
  - 5-yr recurrence rate post SVR, %
    - 13.2% (95% CI 9.9–17.2%)

- **HIV/HCV Co-Infected**
  - 5-yr recurrence rate post SVR, %
    - 21.7% (95% CI 18.3–25.5%)

Increasing SVR and treatment reduces liver-related mortality
Summary

• 80 Million people are HCV viremic worldwide

• Individuals with HCV can now be ‘cured’ due to highly effective and well-tolerated DAA-based HCV treatment regimens

• Cure of HCV impacts not only liver disease outcome but also overall mortality

• Elimination of HCV in this population is theoretically possible

• To turn possibility into reality we need to overcome barriers and maximise initiatives already in place to prevent onward transmission and re-infection