THE THERAPEUTIC REVOLUTION THAT TRANSFORMED CHRONIC HEPATITIS C TO A CURABLE DISEASE

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DISCLOSURES

- Research grants: Roche, Bristol-Myers Squibb
- Lectures: Bristol-Myers Squibb, MSD, Gilead, Abbvie
- Advisory board: Abbvie, Gilead
- Education: Gilead
HEPATITIS C virus

- RNA virus, Flaviviridae family, hepacivirus
- RNA genome single strand, 9,600 bases
- 6 genotypes, at least 67 subtypes
- 1989 isolation for first time
- 2013 study completion of virus life cycle
HCV Infection: Worldwide Prevalence

HCV Infection: Worldwide Genotype Distribution

HEPATITIS C GLOBAL EPIDEMIOLOGY

✓ **In 2015**
✓ 71 million people with chronic HCV, 1% prevalence
✓ 1.75 million new HCV infections, 23.7 / 100 000 incidence
✓ 2.3 million HCV/HIV, 5.6 million PWID
✓ 20% of people infected are diagnosed, 7% of whom are treated
✓ 40% cirrhosis
✓ 399 000 people die each year from HCV (cirrhosis 65%, hepatocellular carcinoma 34%)
✓ No vaccine available

Towards the Elimination of Hepatitis B and C by 2030. The draft WHO Global Hepatitis Strategy, 2016–2021 and global elimination targets
• http://www.who.int/hepatitis/news-events/07_towards-elimination-Dr-Gottfried-Hirnschall.pdf
DISTRIBUTION OF HCV IN THE EU

Viremic prevalence
0.64%

Total viremic pool
3,238,000

New yearly infections
57,900
(plus ~30,000 from immigration)

Prevalence (viraemic)
- 0.0-0.55%
- 0.56-0.75%
- 0.76-1.3%
- 1.4-2.95%

Total infected
- 7,000,000
- 250,000
- 25,000

# Prevalence of HCV in Greece

<table>
<thead>
<tr>
<th>Group</th>
<th>HCV+ Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV drug users</td>
<td>45-60%</td>
</tr>
<tr>
<td>MSM</td>
<td>2-3%</td>
</tr>
<tr>
<td>General population</td>
<td>1-2%</td>
</tr>
<tr>
<td>Blood donors</td>
<td>0.16%</td>
</tr>
<tr>
<td>Immigrants</td>
<td>5-7%</td>
</tr>
</tbody>
</table>

## Table

<table>
<thead>
<tr>
<th>Group</th>
<th>Anti-HCV(+), %</th>
<th>Anti-HCV(+), Ar. (~9 M inhabitants)</th>
<th>Χρόνια HCV, Ar. (~80% incidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hprolipsis ¹</td>
<td>0.83</td>
<td>74,700</td>
<td>59,760</td>
</tr>
<tr>
<td>Εκτίμηση διορθ. για ηλικία</td>
<td></td>
<td>92,700</td>
<td>74,200</td>
</tr>
<tr>
<td>Με ομάδες υψηλού</td>
<td>1.03</td>
<td>(67,500 – 129,600)</td>
<td>(54,000-104,000)</td>
</tr>
<tr>
<td>κινδύνου</td>
<td>(95% CI: 0.75-1.44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Τηλεφωνική έρευνα ²</td>
<td>1.79</td>
<td>161,100</td>
<td>128,800</td>
</tr>
<tr>
<td>Εκτίμηση διορθ. για ηλικία</td>
<td></td>
<td>168,000</td>
<td>134,400</td>
</tr>
<tr>
<td>Με ομάδες υψηλού</td>
<td>1.87</td>
<td>(94,200-241,000)</td>
<td>(75,400-192,800)</td>
</tr>
<tr>
<td>κινδύνου</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NATURAL HISTORY OF HEPATITIS C

- Acute hepatitis
- Chronic hepatitis (80%)
  - Viral clearance (20%)
- Chronic Hepatitis
  - Stable disease (80%)
- Cirrhosis (20%)
  - Decompensated cirrhosis (~20%)
  - HCC (1–4%/y)

≥30 years
- Women, young patients

Rate of progression
- Normal
- FAST
- SLOW

≥20 years
- Alcohol, HIV coinfection, HBV coinfection

Impact of HCV: What Happens If We Do Nothing?

- Change in the number of HCV-related liver transplants, decompensated cirrhosis cases, and HCC cases over time

Impact of HCV: What Happens If We Do Nothing?

REVEAL HCV: Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (1991-2008) in a prospective Taiwanese cohort. Anti-HCV seronegative (n=18,541); anti-HCV seropositive (n=1095; detectable HCV RNA: 69.4%). Average follow-up: 16.2 years. Among extrahepatic causes of death, 68.5% and 69.3% were noncancer deaths for HCV seronegative and seropositive, respectively.

*P<.001 for comparison among all 3 groups and P<.001 for HCV RNA detectable vs undetectable.

HCV life cycle, DAAs* targets


*DAAs: Direct Acting Antivirals
Approved DAAs From Multiple Classes: Basis of 2017 Combination HCV Regimens

Structural Domain

5’UTR

Core E1 E2 P7 NS2 NS3 4A NS4B NS5A NS5B 3’UTR

Nonstructural Domain

Protease

Ribavirin (RBV)

NS3 Protease Inhibitors

Grazoprevir (GZR)
Paritaprevir/Ritonavir (PTV/RTV)
Simeprevir (SMV)
Voxilaprevir (VOX)*
Glecaprevir (GLE)*

Daclatasvir (DCV)
Elbasvir (EBR)
Ledipasvir (LDV)
Ombitasvir (OBV)
Velpatasvir (VEL)
Pibrentasvir (PIB)*

Polymerase

NS5A Replication Complex Inhibitors

NS5B NUC Inhibitors

Sofosbuvir (SOF)

NS5B Non-NUC Inhibitors

Dasabuvir (DSV)
GOAL OF THERAPY

- The goal of therapy is to cure HCV infection to prevent:
  - hepatic cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, severe extrahepatic manifestations and death

- The endpoint of therapy is to achieve SVR
  Sustained Virological Response

- SVR_{24} / SVR_{12} defined as the absence of detectable HCV RNA in the serum, six or three months after completion of therapy with a sensitive assay (LOD <15 IU/ml)

SVR = CURE!!!
Rate of SVR achievement in chronic HCV infection
From IFN to DAAs

*In patients with HCV genotype 1; ** In treatment-naïve patients
DAA, direct-acting antiviral; IFN, interferon; RBV, ribavirin, STR, single tablet regimen

*In patients with HCV genotype 1; ** In treatment-naïve patients
Benefits of Achieving SVR

Cure

Decreased transmission\textsuperscript{[1]}

Improved clinical outcomes\textsuperscript{[1,2]}

Hepatic

\downarrow Cirrhosis
\downarrow Decompensation
\downarrow HCC
\downarrow Transplantation

Extrahepatic

\downarrow All-cause mortality
Improved QoL
Malignancy
Diabetes
CVD
Renal
Neurocognitive

SVR reduces mortality of all causes

Long term FUP of patients (n=230) with severe fibrosis/cirrhosis treated with IFN between 1990–2003

Effect of SVR on the Risk of Clinical Outcomes

Meta-analysis of data on survival from 34,563 patients with HCV on the effect of SVR on the risk of liver transplant, HCC, death, and re-infection

SVR was associated with:
- 62–84% reductions in the risk of all-cause mortality
- 90% reduction in the risk of liver transplantation
- 68–79% reductions in the risk of HCC

Simmons B, Clin Infect Dis 2015
Effect of SVR on the Risk of Extrahepatic Clinical Outcomes

Cumulative incidence of type 2 diabetes in chronic hepatitis C: SVR vs non-SVR

- **Age >50 years**
- **Cirrhosis**
- **Pre-diabetes**

Curing HCV reduces the risk of developing diabetes by ~2/3

**ARASE et al, Hepatology 2009;49:739-744**

Antiviral therapy reduces the renal and cardiovascular complications in 9572 chronic hepatitis C patients with diabetes

- Taiwan National Health Insurance Research Database:
  - 1411 HCV treated vs. 1411 HCV untreated vs. 5644 uninfected, matched by propensity scores
  - (demographic factors, comorbidities, diabetes therapy)

**Cumulative incidence of ESRD**

- [Graph showing incidence with and without antiviral therapy]

**Cumulative incidence of acute coronary events**

- [Graph showing incidence with and without antiviral therapy]

**Cumulative incidence of Ischemic stroke**

- [Graph showing incidence with and without antiviral therapy]

**HR 0.16, 95% CI 0.07 – 0.33**

**HR 0.64, 95% CI 0.39 – 1.06**

**HR 0.53, 95% CI 0.30 – 0.93**

*Multivariate comorbidity-adjusted HR in treated vs. untreated cohort

**HSU et al, Hepatology 2014;59:1293-302**
Principles of HCV Therapy

Nucleotide analogue

Protease inhibitor

NS5A inhibitor

Non-nucleoside inhibitor

Adapted from Pawlotsky J, EASL Recommendations on treatment of hepatitis C 2016
SEVERAL DAAs COMBINATIONS

Different patients

- Different genotypes
- Naïve patients
- Retreated patients
- Discontinuation
- Adverse events with previous therapies
- Failures with PIs, NS5As
- Cirrhotics
DAAs APPROVAL in Greece in 2018

1. At least moderate fibrosis or cirrhosis: Liver Stiffness > 7 kPa

2. Independent of fibrosis stage

- HCV/HIV co-infection
- Chronic hemolytic syndromes (thalassemia major, sickle cell disease etc)
- Hemophilia and other disorders of hemostasis
- End stage Renal Failure (with or without dialysis)
- Transplanted or in the waiting list (bone marrow, solid organs)
- Severe extra-hepatic manifestation of HCV infection (Mixed Cryoglobulinemia type II and B-NHL, ITP, AAA)
- Autoimmune and autoinflammatory diseases

**APPROVED THERAPEUTIC OPTIONS FOR CHRONIC HCV IN GREECE IN 2017-2018**

<table>
<thead>
<tr>
<th>Naïve no cirrhosis</th>
<th>Naïve cirrhotic or tx exp without cirrhosis</th>
<th>Tx exp cirrhotics</th>
<th>Dec cirrhotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1a</td>
<td>SOF/LDV x8 eβδ.</td>
<td>PRV/r/OBV+DSV+RBV x12 eβδ.</td>
<td>SOF/VEL + RBV x12 eβδ.</td>
</tr>
<tr>
<td></td>
<td>GZR/EBR3 x12 eβδ.</td>
<td>GZR/EBR2 x12 eβδ.</td>
<td>SOF/VEL + RBV x12 eβδ.</td>
</tr>
<tr>
<td>GT1b</td>
<td>SOF/LDV x8 eRA</td>
<td>PRV/r/OBV+DSV x12 eβδ.</td>
<td>SOF/VEL + RBV x12 eβδ.</td>
</tr>
<tr>
<td></td>
<td>GZR/EBR x12 eβδ.</td>
<td>GZR/EBR x12 eβδ.</td>
<td>SOF/VEL + RBV x12 eβδ.</td>
</tr>
<tr>
<td>GT2</td>
<td>SOF + RBV x12 eβδ.</td>
<td>SOF/VEL x12 eβδ.</td>
<td>SOF/VEL + RBV x12 eβδ.</td>
</tr>
<tr>
<td></td>
<td>SOF/VEL x12 eβδ.</td>
<td>SOF/VEL + RBV x12 eβδ.</td>
<td>SOF/VEL + RBV x12 eβδ.</td>
</tr>
<tr>
<td>GT3</td>
<td>SOF/VEL x12 eβδ.</td>
<td>SOF/VEL x12 eβδ.</td>
<td>SOF/VEL + RBV x12 eβδ.</td>
</tr>
<tr>
<td>GT4</td>
<td>PRV/r/OBV + RBV x12 eβδ.</td>
<td>PRV/r/OBV + RBV x12 eβδ.</td>
<td>SOF/VEL + RBV x12 eβδ.</td>
</tr>
<tr>
<td></td>
<td>GZR/EBR x12 eβδ.</td>
<td>GZR/EBR3 x12 eβδ.</td>
<td>SOF/VEL + RBV x12 eβδ.</td>
</tr>
</tbody>
</table>

**Notes:**
- SOF: sofosbuvir (Sofvaldi™), SOF/LDV: sofosbuvir/ledipasvir (Harvoni™), PRV/r/OBV: paritaprevir/ritonavir/ombitasvir (Viekirax™), DSV: dasabuvir (Exviera™), SOF/VEL: sofosbuvir/velpatasvir (Eclusa™), GZR/EBR: grazoprevir/elbasvir (Zepatier™).
- eGFR: estimated glomerular filtration rate.
- eGFR <30 ml/min και GT1 ή GT4: PRV/r/OBV ή DSV x12 eβδ. ή GZR/EBR x12 eβδ. (βάσει του παραπάνω πίνακα)
- ΑΣΘΕΝΕΙΣ ΜΕ eGFR <30 ml/min και GT1 ή GT4: PRV/r/OBV ή DSV x12 eβδ. ή GZR/EBR x12 eβδ. (βάσει του παραπάνω πίνακα)
- ΑΣΘΕΝΕΙΣ ΠΟΥ ΑΠΕΤΥΧΗ ΣΕ ΣΧΗΜΑ ΜΕ DAA: ελεύθερη επιλογή σχήματος που μπορεί να περιλαμβάνει ακόμη και simprevir (Olysio™) ή daclatasvir (Daklinza™)

[https://www.eemh.gr/kateuthunthries-odhgies/newfarmaka2017_hcv.aspx](https://www.eemh.gr/kateuthunthries-odhgies/newfarmaka2017_hcv.aspx)
SOF/LDV Trials vs Real-World

ION-3 vs Real-world, Rx-naive. No cirrhosis, VL <6 M IU/mL

8 weeks duration

(Curry et al., EASL 2016)
8 weeks of OBV/PTV/r + DSV in Genotype 1b Treatment-Naïves

GARNET study
Genotype 1b
Treatment-naïve
No cirrhosis (F0-F3)
SVR: 13/15 F3 patients

(ABbvie, presented at the EASL/AASLD Special Conference on Hepatitis C)
Future approach: more simple treatment options
Dual combinations

<table>
<thead>
<tr>
<th></th>
<th>HCV-1</th>
<th>HCV-2</th>
<th>HCV-3</th>
<th>HCV-4</th>
<th>HCV-5,6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir+Ledipasvir</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sofosbuvir+Velpatasvir</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Grazoprevir+Elbasvir</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Glecaprevir+Pibrentasvir</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Adapted from Zeuzem S, EASL MONOTHEMATIC “Striving towards the elimination of HCV infection”, Berlin 2018
### Efficacy, safety and tolerability of dual antiviral combinations

<table>
<thead>
<tr>
<th></th>
<th>SVR</th>
<th>Side effects</th>
<th>Laboratory abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + Ledipasvir</td>
<td>&gt; 95%</td>
<td>headache, fatigue</td>
<td>amylase, CK</td>
</tr>
<tr>
<td>Sofosbuvir + Velpatasvir</td>
<td>&gt; 95%</td>
<td>headache, fatigue, sickness</td>
<td>amylase, CK</td>
</tr>
<tr>
<td>Grazoprevir + Elbasvir</td>
<td>&gt; 95%</td>
<td>Reduced appetite, sleeplessness, anxiety, depression, vertigo, headache, sickness, diarrhea, u.a., pruritus, arthralgia, asthenia, irritibility</td>
<td>bilirubin, ALT</td>
</tr>
<tr>
<td>Glecaprevir + Pibrentasvir</td>
<td>&gt; 95%</td>
<td>headache, diarrhea, sickness, fatigue</td>
<td>bilirubin, ALT</td>
</tr>
</tbody>
</table>

Adapted from Zeuzem S, EASL MONOTHEMATIC “Striving towards the elimination of HCV infection”, Berlin 2018
Characteristics of dual antiviral combinations

<table>
<thead>
<tr>
<th>Combination</th>
<th>Genotypic activity</th>
<th>CKD-4,5</th>
<th>decompensated cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + Ledipasvir</td>
<td>not GT-2 &amp; GT-3</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Sofosbuvir + Velpatasvir</td>
<td>pangenotypic</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Grazoprevir + Elbasvir</td>
<td>not GT-1 &amp; GT-4</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Glecaprevir + Pibrentasvir</td>
<td>pangenotypic</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

Adapted from Zeuzem S, EASL MONOTHEMATIC “Striving towards the elimination of HCV infection”, Berlin 2018
## Posology of dual antiviral combinations

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Dose per tablet</th>
<th>Number of tablets</th>
<th>Food effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + Ledipasvir</td>
<td>400 mg / 90 mg</td>
<td>1 tablet / day</td>
<td>with or without</td>
</tr>
<tr>
<td>Sofosbuvir + Velpatasvir</td>
<td>400 mg / 100 mg</td>
<td>1 tablet / day</td>
<td>with or without</td>
</tr>
<tr>
<td>Grazoprevir + Elbasvir</td>
<td>100 mg / 50 mg</td>
<td>1 tablet / day</td>
<td>with or without</td>
</tr>
<tr>
<td>Glecaprevir + Pibrentasvir</td>
<td>100 mg / 40 mg</td>
<td>3 tablets / day</td>
<td>with food</td>
</tr>
</tbody>
</table>

Adapted from Zeuzem S, EASL MONOTHEMATIC “Striving towards the elimination of HCV infection”, Berlin 2018
Sofosbuvir + Velpatasvir in G1-6

**Sofosbuvir + Velpatasvir**

ASTRAL-1 – Phase III, TN and TE (32%), Gt 1,2,4,5,6, 19% cirrhosis, 12 wks

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>Overall</th>
<th>No</th>
<th>Yes</th>
<th>Naive</th>
<th>Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=624</td>
<td>99%</td>
<td>N=501</td>
<td>99%</td>
<td>N=121</td>
<td>99%</td>
</tr>
</tbody>
</table>

**Sofosbuvir + Velpatasvir**

ASTRAL-2 – Phase III, TN and TE (14%), Gt 2, 14% cirrhosis, 12 weeks

<table>
<thead>
<tr>
<th>Treatment-experienced</th>
<th>No cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=100</td>
<td>99%</td>
<td>96%</td>
</tr>
<tr>
<td>N=100</td>
<td>100%</td>
<td>93%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-naive</th>
<th>No cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=15</td>
<td>100%</td>
<td>81%</td>
</tr>
<tr>
<td>N=15</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

(Feld et al., N Engl J Med 2015;373:2599-607)

(Foster et al., N Engl J Med 2015;373:2608-17)

**Sofosbuvir + Velpatasvir**

ASTRAL-3 – Phase III, TN and TE (26%), Gt 3, 30% cirrhosis, 12 weeks

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>Treatment-naive</th>
<th>No cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=163</td>
<td>98%</td>
<td>90%</td>
<td>93%</td>
</tr>
<tr>
<td>N=156</td>
<td>73%</td>
<td>71%</td>
<td>89%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>Treatment-experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=43</td>
<td>73%</td>
</tr>
<tr>
<td>N=45</td>
<td>71%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>Treatment-experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=34</td>
<td>89%</td>
</tr>
<tr>
<td>N=21</td>
<td>58%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>Treatment-experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=27</td>
<td></td>
</tr>
<tr>
<td>N=38</td>
<td></td>
</tr>
</tbody>
</table>

(Foster et al., N Engl J Med 2015;373:2599-607)

(Feld et al., N Engl J Med 2015;373:2608-17)

**Sofosbuvir + Velpatasvir**

ASTRAL-1 – Phase III, TN and TE (32%), Gt 4, 19% cirrhosis, 12 wks

<table>
<thead>
<tr>
<th>Treatment-experienced</th>
<th>No cirrhosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=116</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

(GT4)

(Feld et al., N Engl J Med 2015;373:2599-607)
Glecaprevir + Pibrentasvir in G1-6

**Glecaprevir/Pibrentasvir**

**ENDURANCE-1**: Phase III, GT1, non-cirrhotic, TN or TE, ±HIV, 8 vs 12 weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR12 rate (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1 8 weeks</td>
<td>99.0%</td>
<td>351</td>
</tr>
<tr>
<td>GT1 12 weeks</td>
<td>99.7%</td>
<td>352</td>
</tr>
</tbody>
</table>

(Kievam et al., AASLD 2016)

**Glecaprevir/Pibrentasvir**

**ENDURANCE-2**: Phase III, GT2, non-cirrhotic, TN or TE, 12 weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR12 rate (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT2 12 weeks</td>
<td>99%</td>
<td>196</td>
</tr>
</tbody>
</table>

(Kowdley et al., AASLD 2016)

**Glecaprevir/Pibrentasvir**

**SURVEYOR-II**: Phase II, Rx-naive, GT 3, ±cirrhosis, 8-12 weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR12 rate (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLE + PIB 8 weeks</td>
<td>97%</td>
<td>29</td>
</tr>
<tr>
<td>GLE + PIB 12 weeks</td>
<td>100%</td>
<td>23</td>
</tr>
<tr>
<td>GLE + PIB + RBV 12 weeks</td>
<td>100%</td>
<td>24</td>
</tr>
</tbody>
</table>

(Kiev et al., EASL 2016; Muz et al., EASL 2016)

**Glecaprevir/Pibrentasvir**

**ENDURANCE-4**: Phase III, GT4-5-6, non-cirrhotic, TN or TE, 12 weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR12 rate (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT4 12 weeks</td>
<td>99%</td>
<td>16</td>
</tr>
<tr>
<td>GT5 12 weeks</td>
<td>100%</td>
<td>26</td>
</tr>
<tr>
<td>GT8 12 weeks</td>
<td>100%</td>
<td>19</td>
</tr>
</tbody>
</table>

(Asselah et al., AASLD 2016)
Glecaprevir/Pibrentasvir
8 weeks in non-cirrhotics

SVR12 rate (%)

99%
N=351
ENDURANCE-1
GT1, TN/TE

95%
N=157
ENDURANCE-3
GT3, TN

100%
N=203
SURVEYOR-2
GT4, 5, 6, TN/TE

SOF/VEL/VOX for 12 weeks as a salvage regimen in NS5A inhibitor-experienced G1–6 patients

(i) Overall SVR12 (ITT)

(ii) SVR by genotype

(iii) SVR by cirrhosis

(iv) SVR by NS5A RASs

Bourlière M, et al., NEJM 2017
SAFETY OF DAAs

• DAAs are safe

• More common side effects:
  – headache, fatigue and nausea - mild, easily controlled

• More side effects in patients taking ribavirin - managing anemia

• A similar safety profile in patients with compensated cirrhosis
  – except for the more frequent occurrence of transient hyperbilirubinaemia in cirrhotic patients

• No treatment discontinuation (transient or permanent) due to side effects in patients not taking ribavirin.
Drug-Drug Interactions

www.hep-druginteractions.org
SUMMARY OF THERAPY

- Several DAAs combinations have been developed
- Clinical practice guidelines are frequently published and updated
- Treatment duration vary from 8-12 weeks
- Two pangenotypic regimens are available, SOF/VEL and GLE/PIB
- Access to therapy and selection of regimens depends on national programs
- Protease inhibitors are contraindicated for patients with decompensate cirrhosis
- SOF is not indicated in severe renal impairment (GFR<30 ml/min)
- Triple regimen SOF/VEL/VOX appropriate for patients with DAA failure
WHO Global Health Sector Strategy on Viral Hepatitis

- Vision: “A world where viral hepatitis transmission is stopped and everyone has access to safe, affordable and effective prevention, treatment and care”

- Goal: Eliminate viral hepatitis as a major public health threat by 2030

- Framework: Universal health coverage and continuity of services

Estimated global number of deaths due to viral hepatitis, HIV, malaria and TB, 2000-2015

What does elimination mean? Impact targets

90% reduction in new cases of chronic HBV and HCV infection

65% reduction in deaths from chronic HBV and HCV

From 6-10 million infections to 900,000 infections
From 1.4 million deaths to under 500,000 deaths

GLOBAL ELIMINATION STRATEGY: 2015 BASELINE  TOWARDS 2030 TARGETS

- HBV- Vaccination
- HBV- PMTCT
- Blood safety
- Injection safety
- Harm reduction
- HBV - Diagnosis
- HCV - Diagnosis
- HBV- Treatment
- HCV- Treatment

Coverage (%)

Σκοπός του Εθνικού Σχεδίου Δράσης για την Ηπατίτιδα C είναι η ανάδειξη της σπουδαιότητάς της ως πρόβλημα Δημόσιας Υγείας στη χώρα, η σημασία της έγκαιρης διάγνωσής της και της επιτήρησής της από τους αρμόδιους φορείς, προκειμένου να είναι εφικτή η βέλτιστη αντιμετώπισή της για την προστασία της Δημόσιας Υγείας.

Ως εκ τούτου, από το σκοπό του Σχεδίου είναι η σταδιακή διαχείριση και ο έλεγχος της νόσου και τελικώς η εξάλειψη της, όπως περιγράφεται από τη στρατηγική του ΠΟΥ μέχρι το έτος 2030.

CHRONIC HCV INFECTION IN GREECE

GENERAL POPULATION
- 70 000-128 000 Anti-HCV (+)

HIGH RISK POPULATION
- 14 000 Anti-HCV (+)
  - PWID, HIV (+), PRISONED

Recommendations for HCV Screening of General Population

SCREENING FOR HCV ALL PERSONS BORN BETWEEN 1945 AND 1980

SCREENING OF HIGH RISK POPULATION

Στόχοι
• Αύξηση των διαγνώσεων των ασθενών με HCV και διασύνδεση με θεραπεία
• Ένταξη του ελέγχου στην πρωτοβάθμια φροντίδα υγείας

Ενέργειες υλοποίησης (5 έτη)
• Σύσταση για εφάπαξ προσυμπτωματικό έλεγχο αντι-HCV σε όλα τα άτομα υψηλού κινδύνου και περιοδικός (ετήσιος) έλεγχος ατόμων σε συνεχή κίνδυνο HCV λοίμωξης
• Ενίσχυση προσυμπτωματικού ελέγχου σε XEN σε κέντρα υποκατάστασης/απεξάρτησης
• Ενίσχυση της παρέμβασης στο δρόμο (street work, κινητές μονάδες κ.α.) στους XEN
• Δωρεάν διάθεση ορολογικού ελέγχου σε Ρομά, αστέγους και μετανάστες από χώρες υψηλού επιπολασμού
• Οργάνωση και υλοποίηση προγραμμάτων προσυμπτωματικού ελέγχου στους έγκλειστους σε σωφρονιστικά ιδρύματα
• Εκπαίδευση των επαγγελματιών υγείας στην πρωτοβάθμια φροντίδα υγείας
• Επιβεβαιωτικός έλεγχος όσων δειγμάτων χαρακτηρίσθηκαν θετικά με μεθόδους ταχείας διάγνωσης
• Καταγραφή όλων των anti-HCV θετικών αποτελεσμάτων ... (ταυτοποίηση μέσω AMKA)

HIGH RISK POPULATION

- All people with transaminase elevations
- Former and active users of intravenous substances
- History of transfusion with blood or organ transplantation before 1992
- History of long term hemodialysis
- History of parenteral exposure to potentially contaminated medical or paramedical tools
- Sexual partners of people with hepatitis C
- People with multiple sexual partners
- Children of mothers with hepatitis C
- HIV-infected patients
- Patients with chronic HBV infection
- Enclosed in penitentiary institutions
- Immigrants from countries with a high prevalence of hepatitis C

Recommended Testing Sequence for Identifying Current HCV Infection

- **HCV antibody test**
  - Reactive: **HCV RNA test**
    - Detected: **Current HCV infection** → Provide care or link to care
    - Not detected: **No current HCV infection** → Additional testing as appropriate
  - Nonreactive: **Stop**

CONCLUSIONS

- Many years after the initial description of the virus and after intensive research into the genome and the life cycle of HCV...
- Revolution in the treatment of chronic hepatitis C...
  - New antiviral drugs, DAAs, interferon-free regimens
  - **High efficacy > 95%**
  - **Short treatment duration, 8-12 weeks**
- **Sustained virological response, SVR = CURE, SVR > 95%**
- High cost is the main obstacle to universal therapy, need for prioritization
- Real challenge is the screening, diagnosis, access to therapy and strategies for HCV elimination
- HCV infection control, eradication and elimination is expected in the future