The French and European Approach Towards Hepatitis C Virus Elimination

HEPDART 2017

USA

December 3rd, 2017

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Hepatology, Chief INSERM UMR 1149, Hôpital Beaujon, Clichy, France.
Disclosures

• Employee of Paris Public University Hospitals (AP-HP, Beaujon’s Hospital) and University of Paris

• Principal investigator for research grants: Funds paid to Hospital (AP-HP)

• Consultant, expert and speaker for: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp Dohme, Roche.

• Grants from: ANR, CNRS, INSERM, University of Paris, ANRS
The goal of this lecture will be to present the situation of HCV in Europe and in France.

Direct-acting antivirals with excellent efficacy and favourable safety, represent a unique opportunity to achieve HCV elimination.

We will discuss the European & French approach towards Hepatitis Programs and to identify models to achieve Elimination.
The French and European Approach Towards Hepatitis C Virus Elimination

1. Great Drugs (Direct-acting antivirals)
2. Epidemiology: Europe & France
3. HCV management: Europe & France
4. Remaining Challenges
5. Take home messages
Direct-acting antivirals: a Revolution

Asselah et al. Liver Int 2016; 36; S1:47-57.
Priorities for Direct-acting antivirals

- SVR > 95%
- Safety
- Tolerability

Priorities for Direct-acting antivirals

- SVR > 95%
- Safety
- Tolerability
- High barrier to resistance
- Short duration; Low pill burden
- Minimal drug–drug interactions
- Pan-genotypic
- Access/cost

SOF/VEL (Epclusa®) for 12 weeks is highly effective across all genotypes (ASTRAL-1, ASTRAL-2 and ASTRAL-3)

- 2% of patients experienced one or more SAE; no SAEs were considered study drug related
- 2 patients discontinued treatment due to AEs

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SVR12 (%)</th>
<th>12 weeks</th>
<th>Relapses</th>
<th>LTFU</th>
<th>D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>98</td>
<td>98</td>
<td>99</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>GT 1</td>
<td>1015/1035</td>
<td>323/328</td>
<td>237/238</td>
<td>264/277</td>
<td>116/116</td>
</tr>
<tr>
<td>GT 2</td>
<td>323/328</td>
<td>237/238</td>
<td>2 D/C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT 3</td>
<td>264/277</td>
<td></td>
<td>1 D/C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT 4</td>
<td>116/116</td>
<td></td>
<td>11 relapses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT 5</td>
<td>34/35</td>
<td></td>
<td>1 death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT 6</td>
<td>41/41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SOF/VEL (Epclusa®) for 12 weeks is highly effective in patients with advanced fibrosis and cirrhosis (ASTRAL 1, 2 & 3)

![Graph showing SVR rates for overall, advanced fibrosis, and cirrhosis.]

Glecaprevir/Pibrentasvir (Maviret) in Patients with HCV GT1, 2, 4-6 Infection with or without Compensated Cirrhosis

### MAVIRET for 8 Weeks in TN/TE NC Patients: ENDURANCE-1 and SURVEYOR-2

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>GT1</th>
<th>GT2</th>
<th>GT4</th>
<th>GT5</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>596</td>
<td>348</td>
<td>193</td>
<td>43</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>SVR12 (%)</td>
<td>98</td>
<td>99</td>
<td>98</td>
<td>93</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

### MAVIRET for 12 Weeks in TN/TE CC Patients: EXPEDITION-1

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>GT1</th>
<th>GT2</th>
<th>GT4</th>
<th>GT5</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>145</td>
<td>89</td>
<td>31</td>
<td>16</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>SVR12 (%)</td>
<td>99</td>
<td>99</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>GT1</th>
<th>GT2</th>
<th>GT4</th>
<th>GT5</th>
<th>GT6</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>146</td>
<td>90</td>
<td>31</td>
<td>16</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>SVR12 (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

### BT 1 1
Relapse 2 2 1 1
Non-VF* 7 2 2 3

All analyses are using the ITT population.

TN, treatment-naive; TE, treatment-experienced with IFN or pegIFN ± RBV, or SOF + RBV ± pegIFN; NC, non-cirrhotic; CC, compensated cirrhotic; ITT, intent-to-treat; BT, breakthrough; VF, virologic failure.

*Includes patients who discontinued due to adverse events, lost to follow-up, or withdrew.

Glecaprevir/Pibrentasvir (Maviret) in Patients with HCV GT3 Infection with or without Compensated Cirrhosis

**MAVIRET for 8 or 12 Weeks in TN NC Patients:**
- **ENDURANCE-3**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>VT (weeks)</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAVIRET</td>
<td>8 weeks</td>
<td>95</td>
</tr>
<tr>
<td>MAVIRET</td>
<td>12 weeks</td>
<td>95</td>
</tr>
<tr>
<td>DCV + SOF</td>
<td>12 weeks</td>
<td>97</td>
</tr>
</tbody>
</table>

**Breakthrough (BT)**
- MAVIRET 8 weeks: 1
- MAVIRET 12 weeks: 1
- DCV + SOF 12 weeks: 1

**Relapse**
- MAVIRET 8 weeks: 5
- MAVIRET 12 weeks: 3
- DCV + SOF 12 weeks: 1

**Non-VF**
- MAVIRET 8 weeks: 2
- MAVIRET 12 weeks: 7
- DCV + SOF 12 weeks: 3

**MAVIRET for 12 Weeks in TN CC Patients, or 16 Weeks in TE NC/CC Patients:**
- **SURVEYOR-2 Part 3**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>VT (weeks)</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TN CC</td>
<td>12 weeks</td>
<td>98</td>
</tr>
<tr>
<td>TE NC/CC</td>
<td>16 weeks</td>
<td>96</td>
</tr>
</tbody>
</table>

**Breakthrough (BT)**
- TN CC 12 weeks: 1
- TE NC/CC 16 weeks: 1

**Relapse**
- TN CC 12 weeks: 2
- TE NC/CC 16 weeks: 2

**Non-VF**
- TN CC 12 weeks: 1

All analyses are using the ITT population.

TN, treatment-naïve; TE, treatment-experienced with IFN or pegIFN ± RBV, or SOF + RBV ± pegIFN; BT, breakthrough; CC, compensated cirrhosis; NC, noncirrhotic; DCV, daclatasvir; ESRD, end-stage renal disease; SOF, sofosbuvir; TE, treatment experienced; TN, treatment naive; VF, virologic failure.

*Includes patients who discontinued due to adverse events, lost to follow-up, or withdrew.

Elbasvir/Grazoprevir (Zepatier): Efficacy in Different Patient Populations

Overall mFAS\textsuperscript{a} SVR12 rates from the Phase 3 clinical trial program

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>-</th>
<th>Stage 4-5 CKD</th>
<th>OAT/PWID ± HIV</th>
<th>IBLD ± HIV</th>
<th>HIV</th>
<th>± HIV</th>
<th>± HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypes</td>
<td>1,4,6</td>
<td>1</td>
<td>1,4,6</td>
<td>1,4</td>
<td>1,4,6</td>
<td>1,4,6</td>
<td>1,4,6</td>
</tr>
<tr>
<td>Treatment Experience</td>
<td>TN</td>
<td>TN/PR-PTF</td>
<td>TN/PR-PTF</td>
<td>TN</td>
<td>TN</td>
<td>PR-PTF</td>
<td>PR-PTF</td>
</tr>
</tbody>
</table>

\textsuperscript{a}mFAS excludes patients who failed for reasons unrelated to study medication.

EBR/GZR = elbasvir/grazoprevir; SVR12 = sustained virologic response 12 weeks after the cessation of treatment; CKD = chronic kidney disease; OAT = opioid agonist therapy; PWID = people who inject drugs; IBLD = inherited blood disorders; TN = treatment naive; HIV = human immunodeficiency virus; TE = treatment experienced; RBV = ribavirin; PR = peginterferon + ribavirin; PTF = prior-treatment failure; mFAS = modified full analysis set.

Tools for HCV screening

• **Enzyme immunoassays (EIAs)**
  – Anti-HCV antibodies
  – HCV core antigen

• **Point-of-care (POC) tests**
  – Rapid diagnostic tests (RDTs)
  – Molecular tests

• **Dried blood spot (DBS)**
The French and European Approach Towards Hepatitis C Virus Elimination

1 Great Drugs (Direct-acting antivirals)
2 Epidemiology : Europe & France
3 HCV management : Europe & France
4 Remaining Challenges
5 Take home messages
Estimated 70 Million Persons Living With HCV

Policies for HCV elimination

Total Viremic Infections by Country (2015)

Cascade of care in the EU, 2015
Virus Diversity: The prevalence of the 6 different HCV genotypes varies across countries in Europe.


GT: genotype
Patient’s Diversity, Prevalence of comorbidities
Patient’s Diversity, Prevalence of comorbidities
Alcohol: A Major Medical Need

How Many American Adults (18 & over) Drank in the Past Year

- Percentage who had at least one drink
- Percentage who have never drank -- lifetime abstainers
- Percentage of binge drinkers -- drinkers who consumed 4+/5+ (women/men) drinks within 2 hours at least once

Wave 1 NESARC, conducted by NIAAA’s Laboratory of Epidemiology and Biometry; accessed Feb 28, 2013 <http://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/drinking-statistics>
Alcohol Consumption in France

Litres d'alcool consommés par an, par habitant âgé de 15 ans et plus

- **20,1** (1980)
- **14** (2000)
- **11,6**
- **7**
- **2,5**
- **1,8**

Sources : OMS, groupe IDA, Insee
Worldwide: Diagnosis and treatment rates

Estimated chronic HCV prevalence, diagnosis rate and treatment rate in 2013

Note: size of bubble depicts viraemic HCV prevalence
Estimated chronic HCV prevalence, diagnosis rate and treatment rate in 2013

Note: size of bubble depicts viraemic HCV prevalence
Europe: Diagnosis and treatment rates (2015)
Europe: Diagnosis and treatment rates (2015)

### Number of patients with HCV infection in France: Estimation by risk group (2011)

<table>
<thead>
<tr>
<th>Sous-groupe</th>
<th>Effectif</th>
<th>Prévalence Ac anti-VHC</th>
<th>Prévalence ARN-VHC</th>
<th>Médiane Ac anti-VHC</th>
<th>IC 95% Ac anti-VHC</th>
<th>Médiane ARN VHC</th>
<th>IC 95% ARN VHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVDU</td>
<td>148 000</td>
<td>63.8</td>
<td>29.6</td>
<td>94 450</td>
<td>87 732-100 900</td>
<td>43 860</td>
<td>37 513-50 532</td>
</tr>
<tr>
<td>DU, non IV</td>
<td>132 000</td>
<td>4.9</td>
<td>2.2</td>
<td>6 325</td>
<td>3 573-10 155</td>
<td>2 935</td>
<td>1 632-4 797</td>
</tr>
<tr>
<td>Blood transfusion before ‘92</td>
<td>2 831 391</td>
<td>3.41</td>
<td>2.1</td>
<td>93 219</td>
<td>44 652-167 123</td>
<td>59 859</td>
<td>29 485-105 356</td>
</tr>
<tr>
<td>migrants</td>
<td>4 938 439</td>
<td>1.83</td>
<td>1.0</td>
<td>90 035</td>
<td>75 151-108 902</td>
<td>51 166</td>
<td>36 169-69 834</td>
</tr>
<tr>
<td>Rest of the population</td>
<td>38 114 942</td>
<td>0.15</td>
<td>0.09</td>
<td>58 718</td>
<td>39 587-83 579</td>
<td>33 210</td>
<td>20 443-51 455</td>
</tr>
<tr>
<td>Total population</td>
<td>46 164 772</td>
<td>0.75</td>
<td>0.42</td>
<td>344 503</td>
<td>287 373-423 549</td>
<td>192 737</td>
<td>150 935-246 055</td>
</tr>
</tbody>
</table>

* : données INSEE sur la population d’immigrés légaux

Focus on HCV infections in France in 2015

Adapted from Razavi H et al, Lancet Gastroenterol Hepatol 2017:2, 325-36

Viremia prevalence: 0.29% (0.14-0.34)

- New infections: 5,500
- 10% of the prevalence
- 90% SVR
- 74% Diagnosed
- 26% Non Diagnosed

Infections virémiques: 190,000
Total Diagnostiquées: 140,800
Nouvellement traitées: 19,400
Guéries: 17,500

Adapted from Razavi H et al, Lancet Gastroenterol Hepatol 2017:2, 325-36
Treatment of HCV infections in France
(≈ 20,000 in 2017)

Nb of Patients Treated per months (based on 12 weeks duration per patients)
Oct 2017 (Base GERS)
Great Drugs (Direct-acting antivirals)

Epidemiology: Europe & France

HCV management: Europe & France

Remaining Challenges

Take home messages
Different screening strategies (it should be synergistic)

- **Risk-based testing**
  - In populations at high risk of HCV
    - Prisons
    - People with injection drugs (PWID)
    - Men who have sex with men (MSM)
    - Migrant populations

- **Birth cohort testing**
  - In regions/countries where the majority of patients belong to a well-defined age group

- **Systematic one-time testing**
  - In countries with high endemicity and/or a goal of complete elimination
HCV candidates for Therapy

1. Treat F3/F4 patients
   Prevent mortality and morbidity

2. Treat high incidence
   Prevent new infections, contain the epidemic

3. Non-PWID screening and treatment
   Elimination

Public health threat

Burden of disease threat

High incidence population

Slow progression population

Advanced population

Risk of onward transmission

Risk of mortality and morbidity

F: fibrosis stage; PWID: people who inject drugs
Netherlands: National HCV/HIV treatment cascade
70% cured (n=939) / on treatment (n=49)

Boerekamps et al, Clin Infect Dis 2017 (in press)
Several countries have implemented broad HCV elimination programmes

Iceland

Aiming for elimination of domestic transmission of HCV by 2018

Major scale up of HCV testing and treating
- 56–70% of estimated total diagnosed so far

45 did not complete:
1 pregnancy,
1 discontinuation due to side-effects,
43 non-compliant

Gottfredsson M, et al. AASLD 2017. abstract #1135
France: Indications for therapy: Recent evolution

- **2014**
  - F3-F4 (Fibrosis stage) (by any evaluation)
  - Extra-hepatic manifestations
  - HIV/HCV coinfected patients

- **2015**
  - F2 (Fibrosis stage) («severe» F2)

- **June 2016**
  - Transplants
  - Genotype 3
  - At risk of contamination

- **January 2017**: Universal Treatment

**Individual Impact**
(collective Impact)

**Collective Impact**
(& individual)
• Universal access to DAAs

• Universal screening

• For all types of population including vulnerable ones

* Maladie hépatique compensée
HCV Epidemiology: Modelization in France

2,156 patients (63% with cirrhosis at baseline) were followed-up for a median of 18 months.

Outcome incidence rates over the first 24 months after initiating DAA therapy:

- **Hepatocellular Carcinoma (HCC)**: Incidence rates decreased by 43% after 12 months from initiation of therapy ($P=0.0256$)

- ** Decompensation of cirrhosis (DC)**: Incidence rates decreased by 77% after 6 months from initiation of therapy ($P=0.0004$)
ANRS CO22 HEPATHER: Outcomes in patients treated with DAAs

2,156 patients (63% with cirrhosis at baseline) were followed-up for a median of 18 months

Outcome incidence rates over the first 24 months after initiating DAA therapy*

HCC incidence rates decreased by 43% after 12 months from initiation of therapy (P=0.0256)

DC incidence rates decreased by 77% after 6 months from initiation of therapy (P=0.0004)

Major HCV-related outcomes decreased after DAA-based therapy

*SOF + RBV (n=283); SOF + PEG-IFN + RBV (n=228); SOF + DCV ± RBV (n=1048) or SOF + SMV ± RBV (n=597); †Number of events per period

Carrat F, et al. EASL 2016; Poster #LBP505
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3. HCV management: Europe & France
4. Remaining Challenges: Education, PWID, Migrants
5. Take home messages
Control viral hepatitis by 2030 (WHO)

- **90% reduction** in new cases of chronic hepatitis B and C
- **80%** of treatment-eligible people with chronic hepatitis B and C treated
- **65% reduction** in hepatitis B and C deaths

New cases of chronic hepatitis B and C

Treatment-eligible people with chronic hepatitis B and C treated

Hepatitis B and C deaths

---

2. WHO. SDG 3: Ensure healthy lives and promote wellbeing for all at all ages. Available at: http://www.who.int/sdg/targets/en/.

WHO: World Health Organization
ASCEND: Nonrandomized Phase IV Trial of HCV Treatment Outcomes by DAA Prescriber Type

- Pts (N = 600) from 13 urban, FQHCs in DC, all treated with LDV/SOF per FDA prescribing info; all providers given 3-hr training in AASLD/IDSA HCV guidance

Therapeutic Patient Education: a Multidisciplinary Team (Beaujon’s Model)

Boyé et al, Hepato-Gastro 2017
PWID face multiple challenges to accessing HCV treatment and care

Under-diagnosed¹

49% of HCV-infected PWID are undiagnosed in Europe

Poor linkage to care²


IFN: interferon
PWID face multiple challenges to accessing HCV treatment and care

Under-diagnosed

49% of HCV-infected PWID are undiagnosed in Europe

49% of HCV-infected PWID are undiagnosed in Europe

Poor linkage to care

Patient-related barriers

- Psychiatric co-morbidities
- Social difficulties
- Negative relationships with medical and social services
- Stigmatisation

Physician and system-related barriers

- Concerns over medication adherence and re-infection
- Lack of collaboration between drug and HCV services
- Distance of specialist HCV services

IFN-Free DAA Therapy: Opioid Substitution Therapy vs No Opioid Substitution Therapy

HCV re-infection rare

Re-infection rate in total population and among PWID (Canada)

<table>
<thead>
<tr>
<th>Incidence rate (/100 patients-year)</th>
<th>Population</th>
<th>PWID</th>
<th>Cure after treatment (SVR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Clearance</td>
<td>1.59</td>
<td>1.88</td>
<td>0.48</td>
</tr>
<tr>
<td>Cure after treatment (SVR)</td>
<td>0.48</td>
<td></td>
<td>1.14</td>
</tr>
</tbody>
</table>

Islam et al. AASLD 2016, A60
Integration of HCV screening in services used by PWID can improve testing rates

Clinics providing OST services may be an optimal facility for HCV testing

Multidisciplinary addiction facilities,\textsuperscript{1}
Amsterdam (n=497)

Specialised addiction outpatient clinics,\textsuperscript{2}
Switzerland (n=1782)

GP practice
Addiction clinic

HCV testing rate (%)

66% 78%

GP practices,\textsuperscript{3} Zürich (n=387 OST)

HCV testing rate (%)

91%


OST: opioid substitution therapy
Progress is needed to reduce HCV prevalence among migrants.

In high-income, low-HCV prevalence countries, a substantial proportion of HCV cases are among migrants.

- PWID
- MSM
- Blood transfusion pre-1992
- Others
- Migrants

The Netherlands

28,156 HCV cases

Barriers:
- Communication
- Poor linkage to care
- Stigma
- Transient

The need to take care of all Humans, No patient left behind

Asselah et al. Eliminating Hepatitis C within Low Income Countries – the need to cure Genotypes 4, 5, 6. Journal of Hepatology, 2018 in press

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Map key</th>
<th>Best estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td></td>
<td>31,0</td>
</tr>
<tr>
<td>America</td>
<td></td>
<td>6,4</td>
</tr>
<tr>
<td>Middle East</td>
<td></td>
<td>62,5</td>
</tr>
<tr>
<td>Europa</td>
<td></td>
<td>61,8</td>
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<tr>
<td>South Est Asia</td>
<td></td>
<td>14,8</td>
</tr>
<tr>
<td>West Pacific</td>
<td></td>
<td>6,0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>23,7</td>
</tr>
</tbody>
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Hutin J-F, Suisse, WHO, EASL 2017
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How to achieve HCV elimination

**PREVENTION**
- Harm reduction
- Infection control
- Blood safety

**TEST AND TREAT**
- HCV screening (universal)
- Linkage to care: Treat with optimal DAAs

**AWARENESS**
- Increase awareness
- Fights barriers & stigma
- Advocacy

Asselah, Marcellin & Schinazi. Liver Int 2018, in press.