Towards elimination of hepatitis C: myth or reality?

Massimo Colombo, MD
Center for Translational Research in Hepatology, Humanitas Hospital, Rozzano, Italy.
EASL International Liver Foundation, Geneva, Switzerland
# Financial Disclosures

## Advisory committees

<table>
<thead>
<tr>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck, Roche, Novartis, Bayer, BMS, Gilead Sciences, Tibotec, Vertex, Janssen Cilag, Achillion, Lundbeck, GSK, GenSpera, AbbVie, Alfa Wasserman, Intercept, Target HCC</td>
</tr>
</tbody>
</table>

## Speaking and teaching

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The Global Burden of Hepatitis C, 2015-2016

➢ > 69 million people chronically infected (± 1% of world population)

➢ The intersection with HIV: 2.3 million co-infected

➢ 1.75 million new infections every year

➢ 187,000 incident cases of liver cancer causing 150,000 related deaths

➢ Overall 350,000 deaths related to hepatitis C every year

## Net Change in Epidemic Size Between 2016 and 2017

<table>
<thead>
<tr>
<th>Region</th>
<th>HCV Epidemic 2016</th>
<th>New HCV infections</th>
<th>Number cured</th>
<th>HCV-related deaths</th>
<th>HCV Epidemic 2017</th>
<th>Net change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia and Pacific</td>
<td>29,564,900</td>
<td>574,330</td>
<td>456,552</td>
<td>179,810</td>
<td>29,502,868</td>
<td>-62,032</td>
</tr>
<tr>
<td>Central and Eastern Europe</td>
<td>6,507,700</td>
<td>322,800</td>
<td>26,110</td>
<td>15,505</td>
<td>6,788,885</td>
<td>+281,185</td>
</tr>
<tr>
<td>Latin and South America</td>
<td>3,477,400</td>
<td>27,537</td>
<td>47,859</td>
<td>21,496</td>
<td>3,435,582</td>
<td>-40,548</td>
</tr>
<tr>
<td>North Africa and Middle East</td>
<td>7,399,470</td>
<td>156,660</td>
<td>52,724</td>
<td>51,944</td>
<td>6,961,462</td>
<td>-438,008</td>
</tr>
<tr>
<td>North America</td>
<td>2,955,600</td>
<td>31,870</td>
<td>216,731</td>
<td>20,829</td>
<td>2,749,910</td>
<td>-205,690</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>5,069,000</td>
<td>130,800</td>
<td>3,805</td>
<td>21,540</td>
<td>5,174,455</td>
<td>+105,455</td>
</tr>
<tr>
<td>Western Europe</td>
<td>2,364,430</td>
<td>35,440</td>
<td>105,821</td>
<td>14,951</td>
<td>2,279,098</td>
<td>-85,332</td>
</tr>
<tr>
<td>91 country subtotal</td>
<td>57,338,500</td>
<td>1,279,437</td>
<td>1,399,602</td>
<td>326,075</td>
<td>56,892,260</td>
<td>-446,240</td>
</tr>
<tr>
<td>Missing countries</td>
<td>12,216,308</td>
<td>318,375</td>
<td>113,157</td>
<td>57,923</td>
<td>12,363,603</td>
<td>+147,295</td>
</tr>
<tr>
<td><strong>Global estimate</strong></td>
<td><strong>69,554,808</strong></td>
<td><strong>1,597,812</strong></td>
<td><strong>1,512,759</strong></td>
<td><strong>383,998</strong></td>
<td><strong>69,255,863</strong></td>
<td><strong>-298,945</strong></td>
</tr>
</tbody>
</table>

Eliminating Hepatitis by 2030. A Package of Interventions of High Impact

Elimination: reduction to zero of the incidence of a specified infection in a defined geographical area. Continued intervention measured needed. Example: poliomyelitis.

MMWR Supplements 1999; 48 (SU01); 23-27

1. Service coverage

2. Impact

4. Harm reduction
5. Testing and treatment

A. Incidence reduction
B. Mortality reduction

- 300 injection sets/PWID/year
- 90% diagnosed
- 80% eligible treated
- 90% treated
- 65% mortality reduction
### Criteria for Elimination of Hepatitis C

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global importance</strong></td>
<td>&gt;69 million chronically infected, 400 thousand deaths/yr</td>
</tr>
<tr>
<td><strong>Biologic feasibility</strong></td>
<td>Restricted to humans, does not propagate in the environment sensitive and specific diagnostic tests, parenteral risks.</td>
</tr>
<tr>
<td><strong>Technical feasibility</strong></td>
<td>Prevention with tests, precautions in HC settings, sterile equipments, user-friendly curative drugs.</td>
</tr>
<tr>
<td><strong>Global endorsement</strong></td>
<td>WHA, International Task force for Disease Eradication</td>
</tr>
</tbody>
</table>
What to Do to Achieve Hepatitis C Elimination

➢ Implement effective interventions to prevent transmission

➢ Expand testing and treatment access

➢ Simplify treatment and monitoring

➢ Develop, implement and evaluate elimination programs

➢ Build a coalition to assist elimination programs
## Global Elimination Strategy 2015 Baseline Towards 2030 Targets

<table>
<thead>
<tr>
<th>TARGET AREA</th>
<th>BASELINE 2015</th>
<th>2020 TARGETS</th>
<th>2030 TARGETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood safety</td>
<td>39 countries do not routinely test all blood donations for transfusion-transmissible infections</td>
<td>95% of donations screened in a quality-assured manner</td>
<td>100% of donations are screened in a quality-assured manner</td>
</tr>
<tr>
<td></td>
<td>89% of donations screened in a quality-assured manner&lt;sup&gt;12&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safe injections: percentage of</td>
<td>5%</td>
<td>50%</td>
<td>90%</td>
</tr>
<tr>
<td>injections administered with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>safety-engineered devices in and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>out of health facilities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harm reduction: number of sterile</td>
<td>20</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>needles and syringes provided per</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>person who injects drugs per year</td>
<td></td>
<td></td>
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</tbody>
</table>
The Contribution of Injecting Drugs to HCV Transmission: A Modelling Study

Global prevalence of HCV in PWID: 52.3% (8.2 mio)

Adequate access to opioid substitution therapy (OST) and syringe services programs (SSP) reduces HCV transmission risk by 74%.

In 2017, of 179 countries, only 93 and 86 countries reported having SSP and OST programs, respectively.

Lancet Glob Health 2017;5:e1208–e1220
Owing to the HCV epidemic among PWID, coverage of harm reduction (OST with NSP) needs to be increased to 40%. Only 1% of PWID live in countries with such high coverage.
Treatment as Prevention of HCV Transmission
MSM HIV/HCV Rotterdam

Acute hepatitis C

<table>
<thead>
<tr>
<th>Year</th>
<th>A-HCV n</th>
<th>PYFUn</th>
<th>Infection Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>93</td>
<td>8290</td>
<td>11.2/1000PYFU (95% CI 9-14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.1% per year</td>
</tr>
<tr>
<td>2016</td>
<td>49</td>
<td>8961</td>
<td>5.5/1000PYFU (95% CI 4-7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.55% per year</td>
</tr>
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IRR 0.49 (95% CI 0.34-0.69)
Jan-Dec 2014 11.2/1000
Jan-Jun 2016 6.9/1000
Jul-Dec 2016 4.0/1000
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<td>&lt;5% of chronic hepatitis infections diagnosed</td>
<td>30%</td>
<td>90%</td>
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<tr>
<td>Viral hepatitis B and C treatment</td>
<td>&lt;1% receiving treatment</td>
<td>5 million people will be receiving hepatitis B virus treatment</td>
<td>80% of eligible persons with chronic hepatitis B virus infection treated</td>
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<td></td>
<td></td>
<td>3 million people have received hepatitis C virus treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Both targets are cumulative by 2020)</td>
<td></td>
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### Map Showing the Percentage Treatment Rate by Country for HCV

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<td></td>
<td>(Both targets are cumulative by 2020)</td>
<td></td>
</tr>
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</table>

No reliable data in countries shaded in grey

The 2016 Hep-CORE Report on Hepatitis C Treatment in Europe

- Specialists restrictions for DAA prescriptions: 94%
- Treatment prescription by a GP: 5 - 15%
- Available HCV treatment in prisons: 32%
- Treatment of HCV in non hospital settings: 20%

*Lazarus JV et al J Int AIDS Soc. 2018*
How to Improve Access to Treatment of Hepatitis

➢ The role of pharma: tired pricing & generic licensing

➢ Decentralize services and integrate with HIV, TB, CDS and malaria

➢ Remove prescription barriers

Lazarus JV et al J Int AIDS Soc. 2018

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ASCEND. Nonspecialists Can Effectively Treat HCV Infection

Procurement of Generic Medicines

- Sixty-two % of HCV individuals live in countries where generic HCV medicines are available.

- > 100 countries access generic medicines for $200 or less per curative treatment; at these expenditures, HCV treatment is cost-saving.

Generic DAA in HIV/HCV Co-infected Patients

Hill A et al CROI Seattle 2017 569

Where Therapy of Hepatitis C Stands Now

➢ SVR in >95% of patients

➢ Difficult-to-cure populations no longer difficult
  HIV co-infections, renal failure
  Cirrhosis, transplant population
  DAA failures

➢ Current «suboptimal» treatment outcomes
  Decompensated cirrhosis
  Rare african genotypes

➢ Areas of uncertainty
  Patients with active HCC
Effectiveness of DAA in Chronic Hepatitis C
16,567 Patients in UK

Drysdale K et al EASL ILC Vienna 2019
HCC and All-cause Mortality Reduced by DAA in Veterans with Advanced HCV

HCC developing in SVR patients

- 44.8% HCC classified as stage I
- Predictors of persistent HCC risk after SVR: age, cirrhosis, diabetes

Kanwal et al Gastroenterology 2017

Backus L et al Hepatology 2019
Increased Risk of HCC Persists up to 10 Years After Virus Eradication in Patients with Advanced HCV

- 29,033 VA patients with an SVR to DAA and 19,102 with an SVR to IFN
- During 5.4 yr follow-up, 1509 incident HCCs were identified
HCV Proteins Able to Hijack Molecular Pathways that Control Cell Cycle

Lemon et al Gastroenterology 2012
### DAA Therapy of HCV in People Who Use or Inject Drugs
A Systematic Review and Meta-analysis

38 studies, 3634 pts with DU in the past 6 months, initiation/during DAA

<table>
<thead>
<tr>
<th></th>
<th>Studies</th>
<th>Participants</th>
<th>Tx Completion</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent DU</td>
<td>21</td>
<td>1408</td>
<td>97.5%</td>
<td>87.7%</td>
</tr>
<tr>
<td>OS</td>
<td>36</td>
<td>2987</td>
<td>97.4%</td>
<td>90.7%</td>
</tr>
<tr>
<td>Recent injecting DU</td>
<td>8</td>
<td>670</td>
<td>96.9%</td>
<td>87.4%</td>
</tr>
</tbody>
</table>

Meta-regression analysis: clinical trials (vs observational studies) and higher age were associated with higher SVR and lower % lost to follow-up.
Testing and Treatment Uptake among PWIDs in Australia. The ETHOS Study
Testing and Treatment Uptake among PWIDs in Australia. The ETHOS Study
HCV Reinfection Rate Among HIV Infected People
EUROSIDA

RISK OF REINFECTION

Lower odds:
Female vs male: aOR 0.46, 95% CI 0.21 to 0.99
SVR year 2014 or later vs earlier: aOR 0.44, 95% CI 0.23 to 0.84

Higher odds:
Central-West vs South region: aOR 3.88, 95% CI 1.66 to 9.07
East/Central-East vs South region: aOR 4.39, 95% CI 1.60 to 12.05
CD4 count above 500 vs lower: aOR 1.74, 95% CI 1.03 to 2.94
F3 or greater vs lower fibrosis stage: aOR 2.41, 95% CI 1.00 to 5.80.
Retreatment of HIV Coinfected Patients with Sof/Vel/Vox. Phase 2b RESOLVE

89 patients consented and screened
- 12 patients ineligible
  - 4 with lab abnormalities
  - 3 with HCV RNA not detectable
  - 3 with HCC
  - 2 lost to follow-up
  - 2 with reinfection (GT discrepancy)

77 patients enrolled and started SOF/VEL/VOX retreatment
- 6 patients without SVR determination
  - 3 discontinued early
  - 1 died on treatment
  - 2 lost to follow-up

71 patients completed retreatment and follow up assessments

![Graph showing SVR results](image)

**SVR**

- **Overall-ITT**: 90.9% (70/77)
- **HIV-ITT**: 82.4% (14/17)
- **Non completion ITT**: 81.2% (18/22)
- **Overall-per protocol**: 99.6% (70/70)

Wilson E et al J Hepatol 2019
The Burden of Pediatric Hepatitis C

Women with HCV and active IDU less likely to use contraception (56% vs. 81%) at greater risk of unplanned pregnancy than the general population (89% vs. 31–47%).

Perinatal HCV difficult to detect due to a lack of screening, slow onset symptoms, and poor adherence (43%) to the required 18 months of follow-up after birth.
The Burden of Pediatric HCV Infection in US

- Women of childbearing age: 1-1.6% are infected by HCV
- Pregnant wo. with HCV: 1998 vs 2007: $17 \times 10^5$ vs. $125 \times 10^5$
  vertical transmission = 5.8%
- Children with HCV: 0.15% < 11 y.o.
  0.40% > 12 y.o.
- Vertical transmission: 1 / 20, related to viremia in mother
- Adolescents: risky behaviors
- Overall HCV+ children: 23,000-46,000

* Florida
Faster Cirrhosis Development in Perinatally Infected Persons Calls for PMTCT of HCV

1049 HCV pos. in UK: IDU (53%), blood products (24%), perinatal infection (11%)

Cirrhosis increased the risk of death: OR = 6.2 (2.6 – 14.7, p < 0.001)

Working against HCV elimination in children:

- GP and Sof + NS5A inhibitors can be prescribed to >12 y.o. adolescents, only

FDA & EMA
Suboptimal SVR Rates in African Patients with Atypical(non a,non b)HCV-1 Subtypes

- Of 91 African patients, 47 (52%) were infected with an unusual subtype.
- Pre-treatment sequences were available on 22 unusual G1 patients. 18/22 (82%) had NS5A resistance associated substitutions (RASs).

- SVR was achieved in 56/63 (89%) overall.
- SVR in only 21/28 (75%) of those with unusual G1 subtypes.
- Failure in 3/16 G1*, 1/2 G1p and 3/3 in G11.
- Six treatment failures were with SOF/LBP compared with one failure on a PI based regimen.
Frequent Antiviral Therapy Failures in HCV-4r Patients of African Origin

University Hospital Henry Mondor

- 2015-2018 : 537 DAA treatment failures
- #121 HCV-4 , #27 subtype 4r (African)
- All HCV-4r with 2 or 3 NS5A RAS (28,30)
- All 27 HCV-4r relapsed after treatment completion (CT)
- #8 retreated (7/7 CT achieved SVR)

#13 received SOF + NS5A inhibitors

Fourati S et al Hepatology 2019
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# Improving Diagnostics

## Available Molecular Assays for HCV RNA

<table>
<thead>
<tr>
<th>Principle</th>
<th>RealTime HCV (Abbott)</th>
<th>CAP/CTM HCV 2.0 (Roche)</th>
<th>Xpert® HCV VL (Cepheid)</th>
<th>Xpert HCV VL FS (Cepheid)</th>
<th>Genedrive® HCV ID Kit</th>
<th>Aptima® HCV Quant Dx (Hologic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume required (µL)</td>
<td>500</td>
<td>650</td>
<td>1,000</td>
<td>100</td>
<td>30</td>
<td>500</td>
</tr>
<tr>
<td>Extraction</td>
<td>Automated</td>
<td>Automated</td>
<td>Automated</td>
<td>Automated</td>
<td></td>
<td>Automated</td>
</tr>
<tr>
<td>Linear range (UI/mL)</td>
<td>12-10⁸</td>
<td>15-10⁸</td>
<td>10-10⁸</td>
<td>10⁻²⁻¹⁰⁸</td>
<td>-</td>
<td>10⁻¹⁻¹⁰⁸</td>
</tr>
<tr>
<td>LLOQ (UI/mL)</td>
<td>12</td>
<td>15</td>
<td>10</td>
<td>100</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>LOD (UI/mL)</td>
<td>10.5/7.2</td>
<td>9.3/8.8</td>
<td>4.0/6.1</td>
<td>40</td>
<td>2,362</td>
<td>4.3/3.9</td>
</tr>
<tr>
<td>Time-to-result (min)</td>
<td>276*</td>
<td>345*</td>
<td>105</td>
<td>&lt;60</td>
<td>90</td>
<td>150*</td>
</tr>
<tr>
<td>Random access</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Better HCV Treatments Will Allow Simplified Diagnostic Pathway

**Present**

- **Diagnosis**
  - HCV antibody (EIA/RDT)
  - HCV Antigen (NAT/Ag)

- **Treatment assessment**
  - HCV Viral load
  - HCV genotype
  - Fibrosis assessment

- **Treatment monitoring**
  - HCV Viral load
  - Toxicity monitoring

- **Post-Rx**
  - HCV Viral load

**Future**

- HCV Antigen RDT
- HCV Antigen RDT

---

Adapted from UNITAID Hepatitis C Medicines and Diagnostics in the Context of HIV/HCV Co-Infection. 2013

EIA: enzyme immunoassay; NAT: nucleic acid test; RDT: rapid diagnostic test
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Elimination Programs Not in Place in Most Countries

National Prevention Plans (2016)

Only half of countries with national prevention plans had the data needed to estimate HCV prevalence.¹

VH prevention plans in place (2017)

Only 82/132 countries had action plans in place for VH prevention, few include elimination targets and strategies.²

Countries Step Up to Eliminate Viral Hepatitis

The number of countries in our Region with national hepatitis plans increased from 13 (in 2013) to 30 (in 2019).

- Endorsed hepatitis action plans (30 countries)
- Developing hepatitis action plans (15 countries)

WHO Report 2019
Egypt. National Screening Campaign for HCV

- Oct 2018 - May 2019: 49,630,319 screened, 2,229,328 HCV+ (4.6%)
- 1,6 M (72%) treated with SOF/DAC
- Plan with elimination goals by 2020
- Political commitment: test all persons 18-59 yrs
- Affordable diagnostics (< $5 PCR test, DAA 50-100$)
- Network of 60 treatment centers
- Serologic surveys and case registry data

Courtesy of J Ward
Educate, Test and Treat Model Toward Elimination of Hepatitis C Infection in Egypt

- A study in 73 villages across Egypt.

- 92.3% of 221,855 eligible villagers screened for anti-HCV and HBsAg: 33,839 (16.5%) and 763 (0.4%) positive.

- 15,892 (47.0%) HCV RNA positive: overall prevalence = 7.8%.

- 14,495 (91.2%) treated within 2.1 weeks from serological diagnosis.

- 98.3% achieved a virological cure.
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Averhoff G et al J Hepatol 2019

April 2015 - April 2019 : 36,098/37,582 (96.1%) achieved SVR

1,327 initiated 2° round of Tx with 94.2% SVR
Towards the WHO Target of HCV Elimination by 2030

The goal: averting 15.1 million new infections and 1.5 million HCV-related deaths by 2030

Requirements

Massive screening programme and demands a rapid increase in new treatment courses in the short term: 51 +/- 8 million courses of DAA treatment by 2030.