



Lo screening e la terapia dell'epatite C

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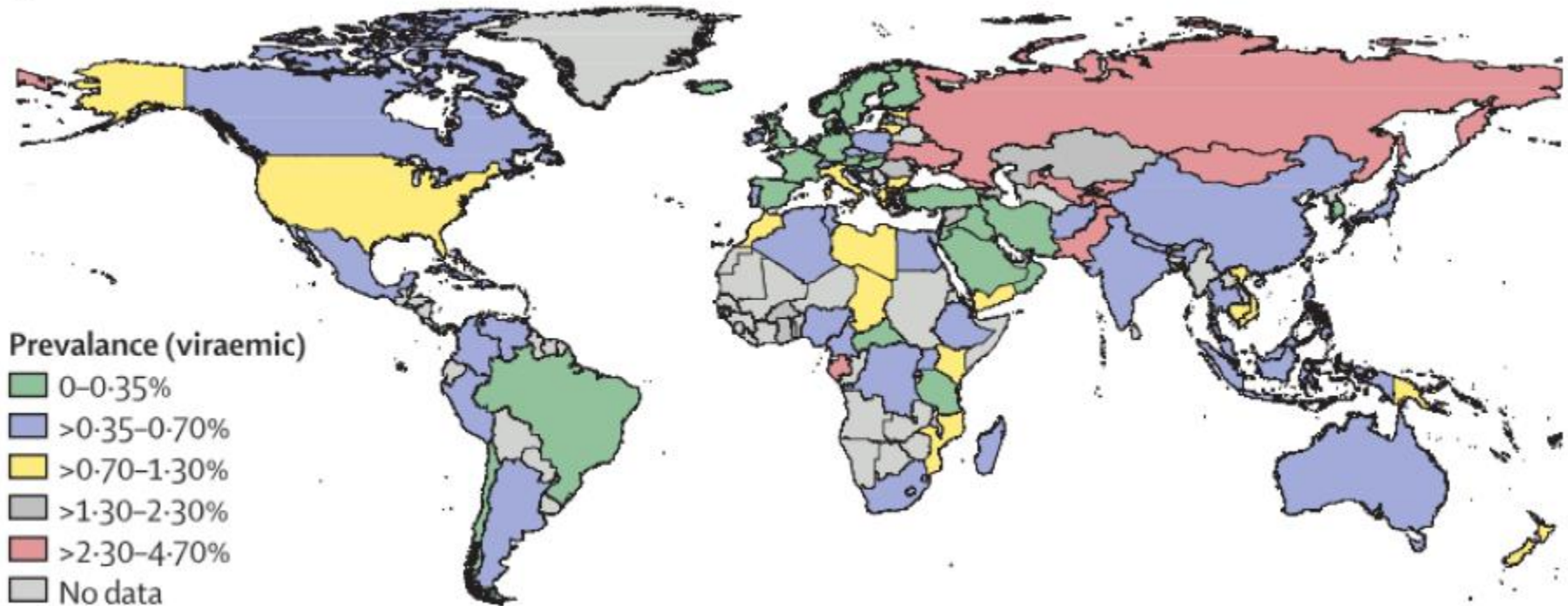
Outline

- Epidemiologia
- Storia naturale
- Terapia
- Screening
- Verso l'eliminazione?

Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2020: a modelling study

*The Polaris Observatory HCV Collaborators**

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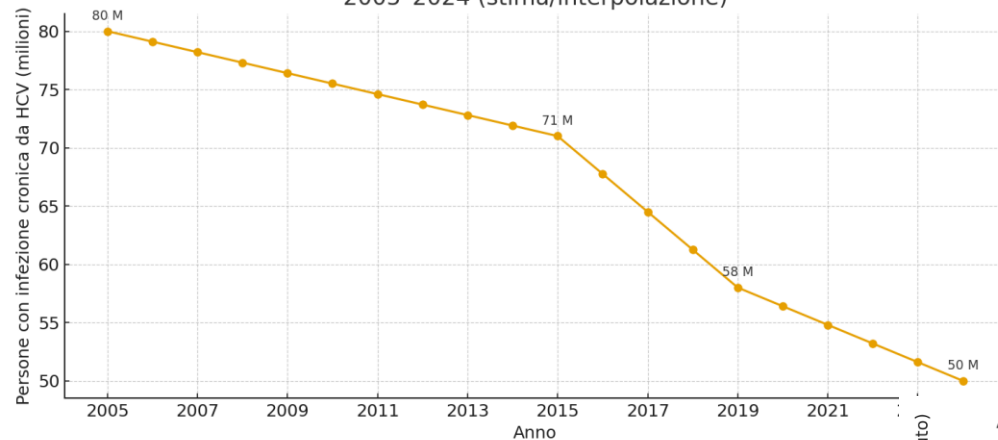


Estimated 71 Million Persons Living With HCV

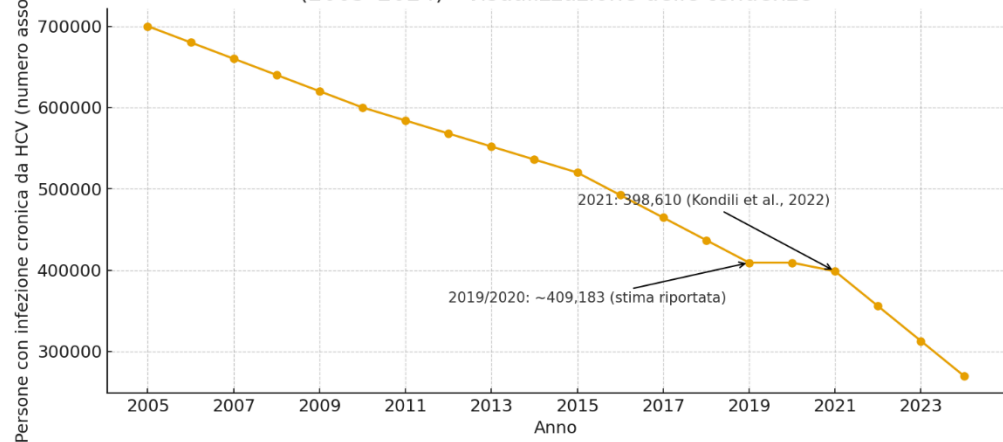
Funding John C Martin Foundation, Gilead Sciences, AbbVie, ZeShan Foundation, and The Hepatitis Fund.

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Andamento stimato della prevalenza globale di HCV (persone con infezione cronica)
2005-2024 (stima/interpolazione)

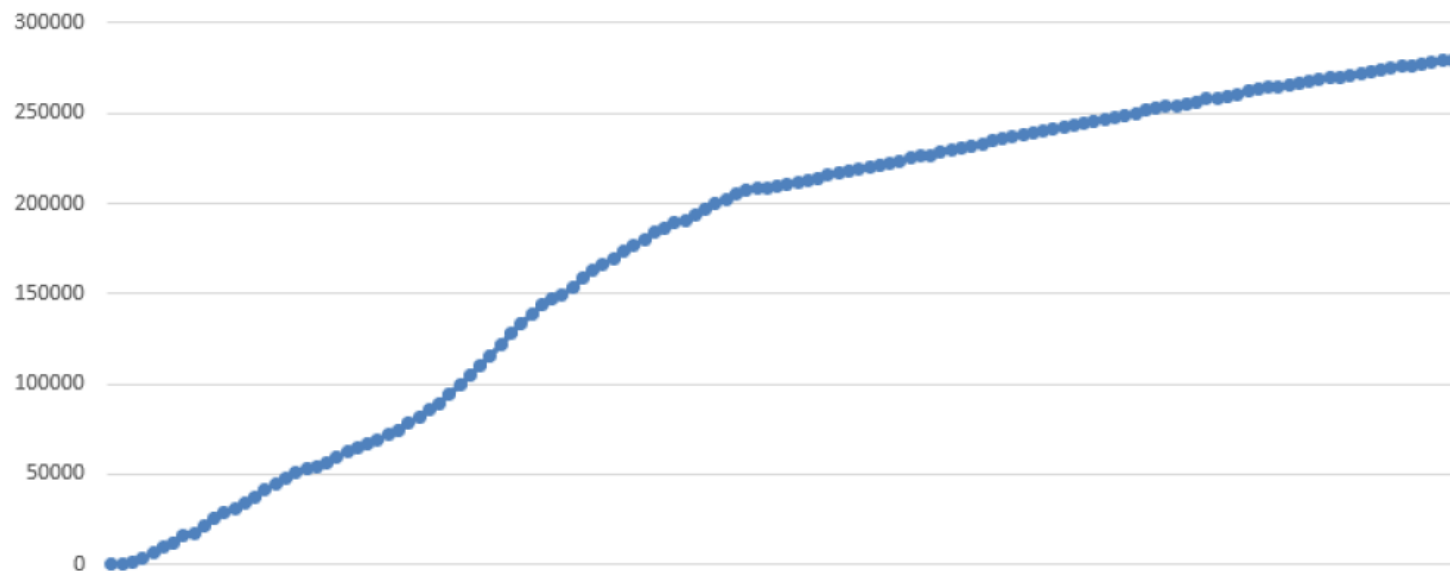


Andamento stimato del numero di persone con infezione cronica da HCV in Italia
(2005-2024) - visualizzazione delle tendenze



Trend cumulativo dei trattamenti avviati

N° DI TRATTAMENTI CUMULATI



MESE INIZIO TRATTAMENTO

**279.247 «avviati» sono i trattamenti (solo pazienti eleggibili)
con almeno una scheda di dispensazione farmaco**

Diagnosis and cure of HCV globally in 2022

WHO. Global Hepatitis Report 2024

WHO region	Total number of hepatitis C infections including cured (all ages) in 2022	Number of people with hepatitis C infection diagnosed (including those cured), end 2022	Number of people receiving hepatitis C treatment, end 2022	Diagnosis coverage, end 2022 (%)	Treatment coverage, end 2022 (%)
African Region	8 000 000	1 000 000	200 000	13%	3%
Region of the Americas	7 000 000	3 100 000	1 800 000	44%	26%
South-East Asia Region	10 600 000	2 700 000	1 600 000	26%	15%
European Region*	7 700 000	2 100 000	1 300 000	29%	9%
Eastern Mediterranean Region	17 700 000	13 000 000	6 300 000	49%	35%
Western Pacific Region	8 300 000	3 800 000	1 300 000	45%	16%
Global	61 200 000	25 700 000	12 500 000	36%	20%

Note: Hepatitis C virus has a cure and those cured are included in the denominator to assess coverage and gaps. For example if 500 out of 1000 people with hepatitis C virus are cured, the coverage is 500/1000. The baseline of 2015 is therefore used here as the denominator.

Source: Global Hepatitis Reporting System, WHO.

Prevalence of hepatitis C virus estimates of undiagnosed individuals in different Italian regions: a mathematical modelling approach by route of transmission and fibrosis progression with results up to January 2021

Loreta A. Kondili¹, Massimo Andreoni², Alessio Aghemo^{3,4}, Claudio Maria Mastroianni⁵, Rocco Merolla⁶, Valentina Gallinaro⁶, Antonio Craxi⁷



Figure 1 - Map showing the estimated prevalence of active HCV infection in the 4 macroareas of Italy up to January 2021.

Table 2 - Estimates of the absolute number and percentage of viraemic HCV individuals in Italy according to fibrosis stage and risk factor for route of transmission up to January 2021.

<i>Transmission route/fibrosis stage</i>	<i>Absolute number and 95% CI</i>	<i>Percent of attributable risk and 95% CI (%)</i>	<i>Percentage</i>
Glass syringe			
F0-F3	9,516 (8,617-10,415)	0.016 (0.014-0.017)	3.3
F4	37,159 (35,511-38,808)	0.06 (0.06-0.06)	33.5
Total	46,675 (45,552- 47,799)	0.08 (0.08-0.08)	11.7
Transfusion			
F0-F3	4,037 (3,532-4,541)	0.007 (0.006-0.008)	1.4
F4	5,914 (5,347-6,482)	0.01 (0.009-0.011)	5.3
Total	9,951 (9,374-10,528)	0.02 (0.02-0.02)	2.5
PWID*			
F0-F3	144,307 (139,845-148,768)	0.24 (0.23-0.25)	50.2
F4	49,404 (45,371-53,437)	0.082 (0.075-0.089)	44.6
Total	193,710 (192,186-195,235)	0.32 (0.32-0.33)	48.6
Sex			
F0-F3	42,141 (41,117-43,165)	0.07 (0.068-0.072)	14.6
F4	3,496 (2,915-4,078)	0.006 (0.005-0.007)	3.2
Total	45,637 (44,837-46,438)	0.08 (0.07-0.08)	11.4
Tattoo			
F0-F3	86,491 (84,161-88,822)	0.14 (0.14-0.15)	30.1
F4	13,681 (11,895-15,466)	0.023 (0.02-0.026)	12.3
Total	100,172 (98,922-101,423)	0.17 (0.16-0.17)	25.1
Vertical			
F0-F3	1,237 (1,034-1,440)	0.002 (0.002-0.002)	0.4
F4	1,227 (997-1,458)	0.002 (0.002-0.002)	1.1
Total	2,464 (2,233-2,695)	0.004 (0.004-0.005)	0.6

Epidemiologia HCV in PWID

15.6 milioni di PWID nel mondo

- 83% prevalentemente oppioidi
- 33% prevalentemente stimolanti
- 58% storia di reclusione

52.3% HCV+ (8.2 milioni)

17.8% HIV+ (2.77 million people)

9% Hepatitis B surface antigen (HBsAg)+

179 of 206 countries or territories report IDU (31 new compared to 2008)



The majority of existing HCV cases occur in PWID

60% OF EXISTING INFECTIONS ARE
AMONG **CURRENT & FORMER PWID**



PEOPLE LIVING WITH HCV INFECTION

The majority of new HCV cases occur in PWID

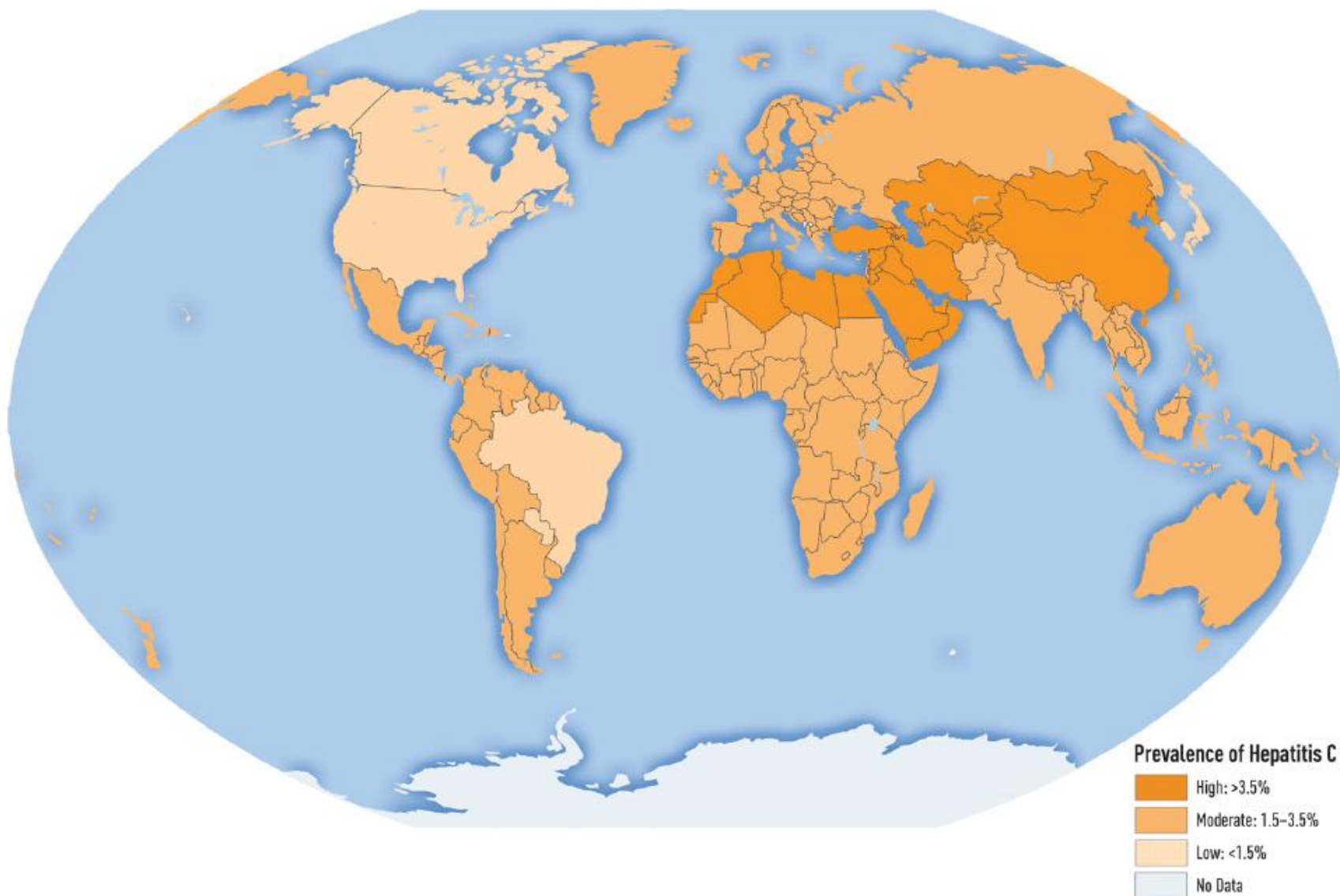
80% OF NEW INFECTIONS OCCUR
AMONG CURRENT PWID



PEOPLE LIVING WITH HCV INFECTION

HCV & Migrations

- There is a continuous flow of immigrants from the south of the world to north-western countries
- Often immigrants originate from areas of high-prevalence of viral hepatitis and pose a challenge to the healthcare systems of the host nations
- The prevalence of HCV infection varies according to the countries of origin



MAP 3-5. DISTRIBUTION OF HEPATITIS C VIRUS INFECTION¹

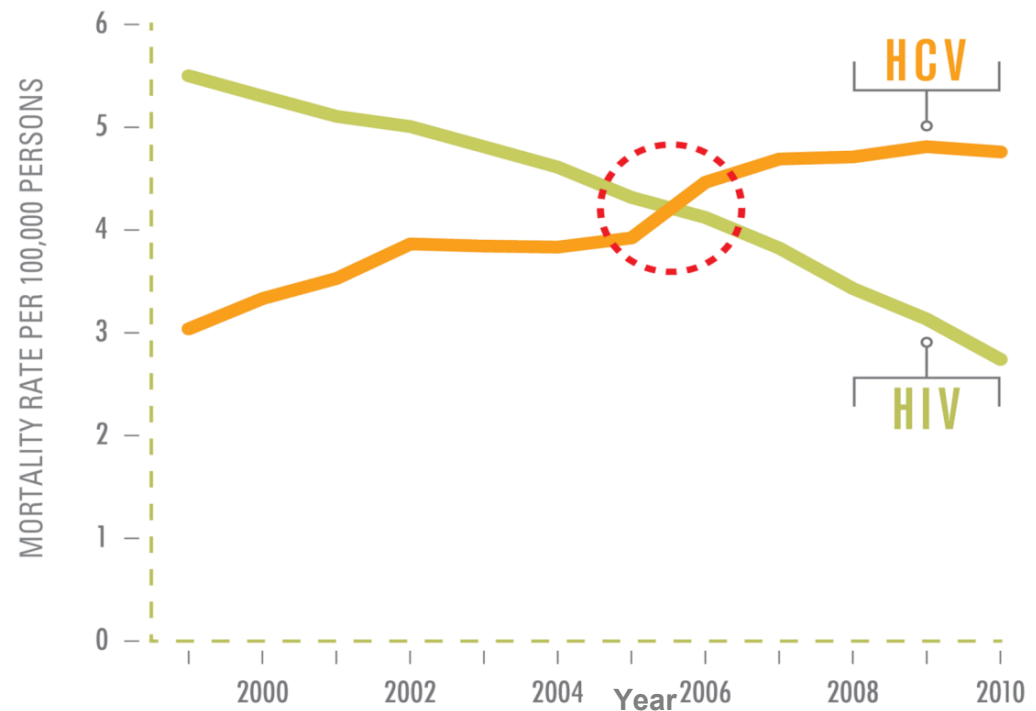
¹ Disease data source: Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. "Global Epidemiology of Hepatitis C Virus Infection; New Estimates of Age-Specific Antibody to HCV and Seroprevalence." *Hepatology* 2013; 57:1333-1342.

Hepatitis C virus (HCV) and HIV co-infection

- 36,9 million people were living with HIV in 2014, 2 million were newly infected, and 1,6 million died
- 115 million people were estimated to be HCV antibody positive in 2014
- Individuals with HIV/HCV co-infection have a 3-fold greater risk for liver cirrhosis or decompensation and 10-fold greater risk for liver related mortality than patients with HCV mono-infection
- Sustained virologic response (SVR) following HCV treatment is associated with a 90% reduction in the risk for liver-related mortality and liver transplantation as well as considerable patient-reported improvements in quality of life

Mortality From Viral Hepatitis in the US

- Analysis of US multiple-cause mortality data from the National Center for Health Statistics
 - Death certificate data in all US states and District of Columbia
 - Approximately 21.8 million decedents
- Change in age-adjusted mortality rates (per 100,000 person-years)
 - HCV: increased 0.18 ($P=0.002$)
 - HIV: decreased 0.21 ($P=0.001$)
- Deaths from HCV surpassed those from HIV in 2007 and are continuing to increase.



*Because a decedent can have multiple causes of death, a record listing >1 type of infection was counted for each type of infection.

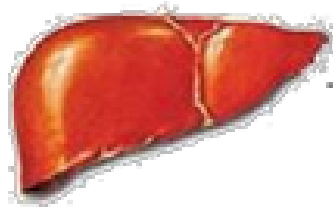
Ly KN et al. Ann Intern Med. 2012;156(4):271-278.

CDC. <http://www.cdc.gov/hepatitis/statistics/2010surveillance>.

Murphy SL et al. http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf.

Storia naturale

Acute HCV



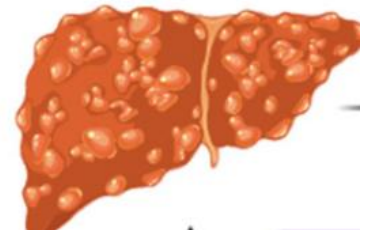
Spontaneous
Resolution
15-45%

Chronic Infectic
55-85%

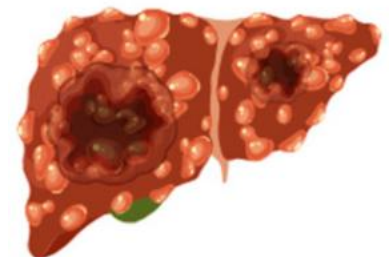


~25-30 Years

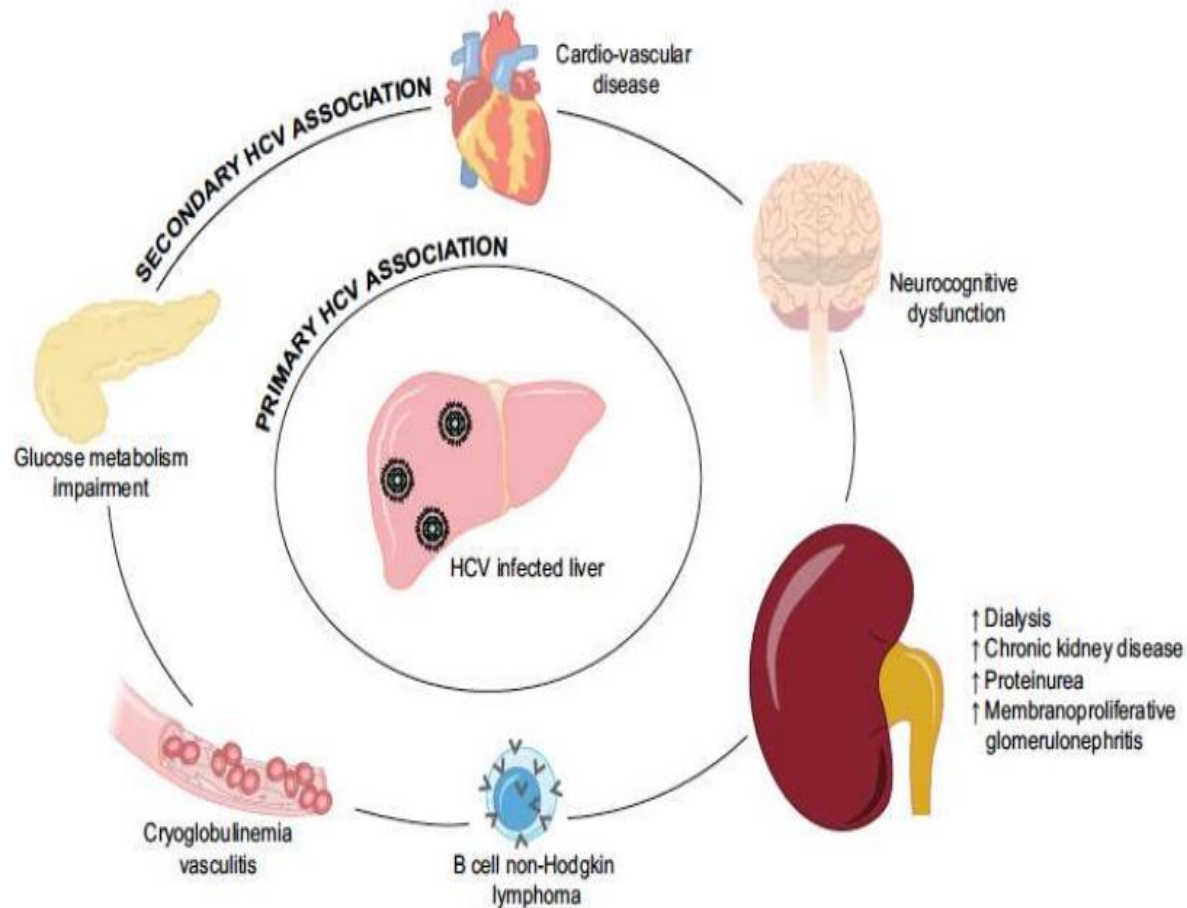
Cirrhosis
20-30%



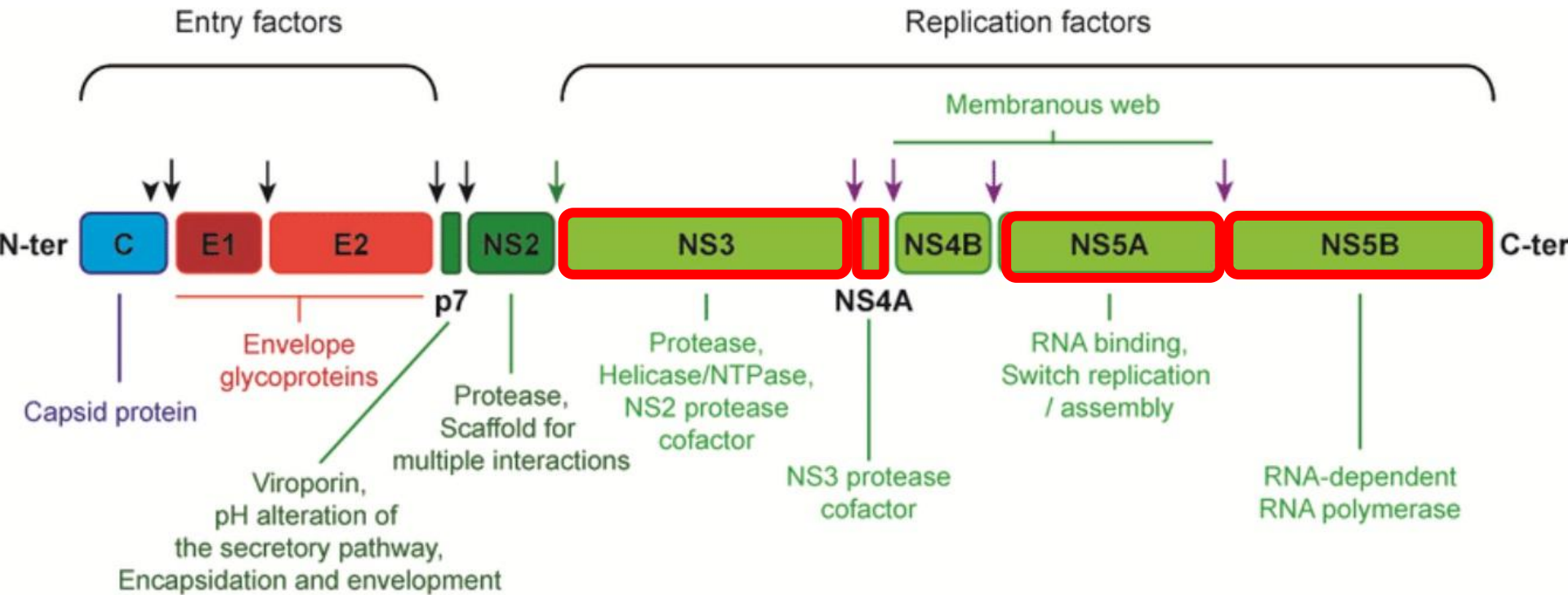
Hepatocellular
Carcinoma
1-4%/Year



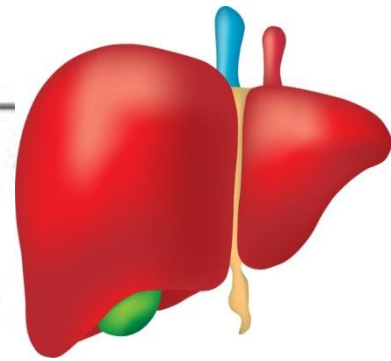
La malattia da HCV è sindromica



DAA



Mechanisms of Action



Receptor binding
and endocytosis

Transport
and release

Fusion and
uncoating

Replication,
Assembly & Release

Translation and
polyprotein
processing

(+) RNA

Virion
assembly

Replication

NS3/4
protease
inhibitors

ER lumen

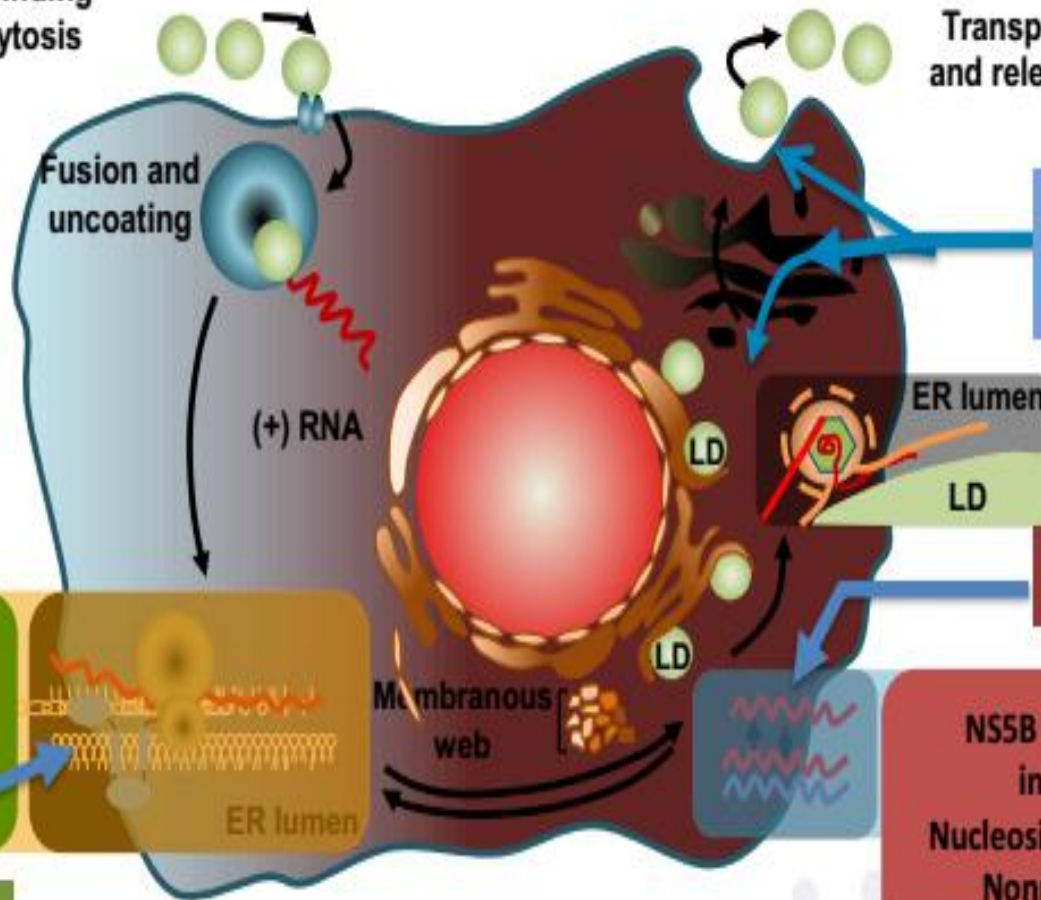
Membranous
web

NS5B polymerase
inhibitors
Nucleoside/nucleotide
Nonnucleoside

Translation, &
Polyprotein cleavage

NS5A* inhibitors

*Block replication complex formation, assembly





Elbasvir/Grazoprevir
12-16 sett



Sofosbuvir/Velpatasvir
12-24 sett



Glecaprevir/Pibrentasvir
8-16 sett



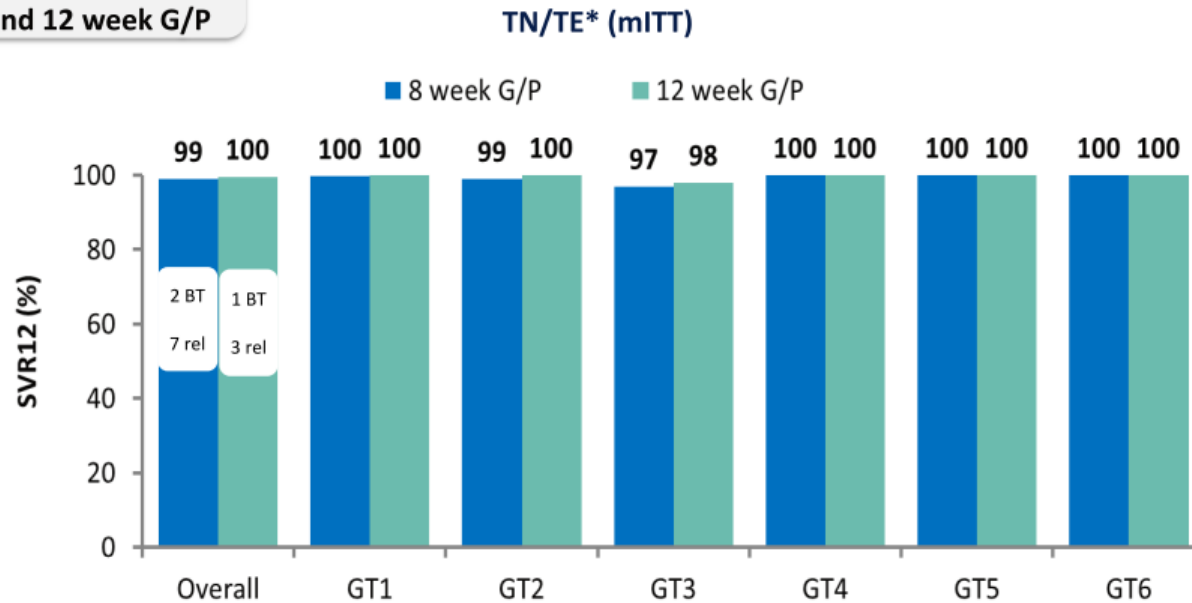
Sofosbuvir/Velpatasvir/Voxilaprevir
8-12 sett

DAA Treatment Regimen	NS3/4A Protease Inhibitor	NS5B Nucleotide Polymerase Inhibitor	NS5A Polymerase Inhibitor
LDV/SOF ± RBV		✓	✓
EBR/GZR ± RBV	✓		✓
GLE/PIB	✓		✓
SOF/VEL ± RBV		✓	✓
SOF/VEL/VOX	✓	✓	✓

Integrated Efficacy Analysis: High SVR Rates with 8 and 12 Weeks of G/P in GT1–6 Patients without Cirrhosis

Integrated efficacy analysis of 8- or 12-weeks G/P treatment in non-cirrhotic patients with GT1–6 infection across 7 phase 2 or 3 clinical trials

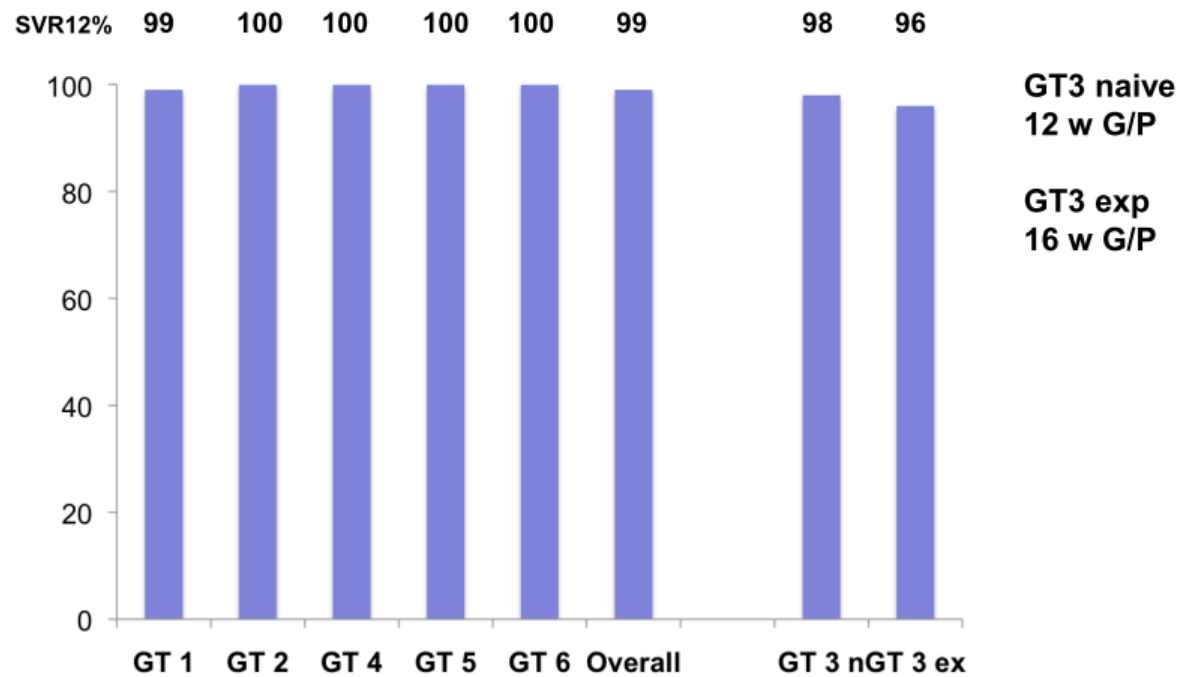
Failure rate was
similar between
8 and 12 week G/P



Puoti M, et al. J Hepatol 2017; 66(Suppl):S721 (poster presentation SAT-233).

Glecaprevir/Pibrentasvir in patients with HCV GT 1-6 and compensated cirrhosis

233 patients, 146 (GT1-2,4-6-Expedition -1) and 87 (GT3, Surveyor-II)



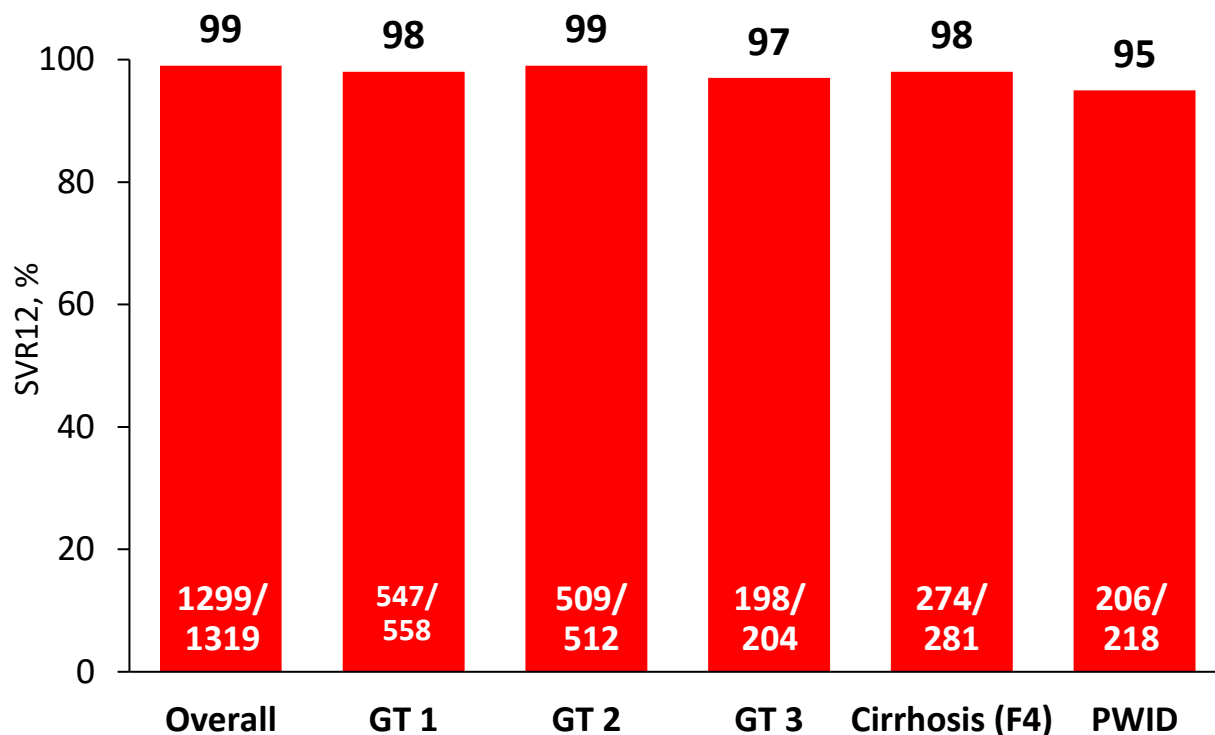
SOF/VEL $\pm$ RBV in Italian Patients with HCV GT 1, 2, 3, 4, 6

Regional registry of patients treated with SOF/VEL $\pm$ RBV for 12 weeks

Baseline Demographics

N=1319	
Mean age, years (range)	64 (18–91)
Male, %	59
GT, % 1 / 2 / 3 / 4 / 6	42 / 39 / 16 / 3 / <1
Mean LSM, KPa $\pm$ SE	10 (0.33)
F0-F2, n (%)	732 (55)
F3-F4, n (%)	587 (45)
CTP B7-9, n (%)	19 (7)
PWID, n (%)	218 (17)
+RBV, n (%)	41 (3)

SVR12 (ITT)



SOF/VEL for 12 weeks without RBV results in high SVR12 regardless of cirrhosis and HCV GT

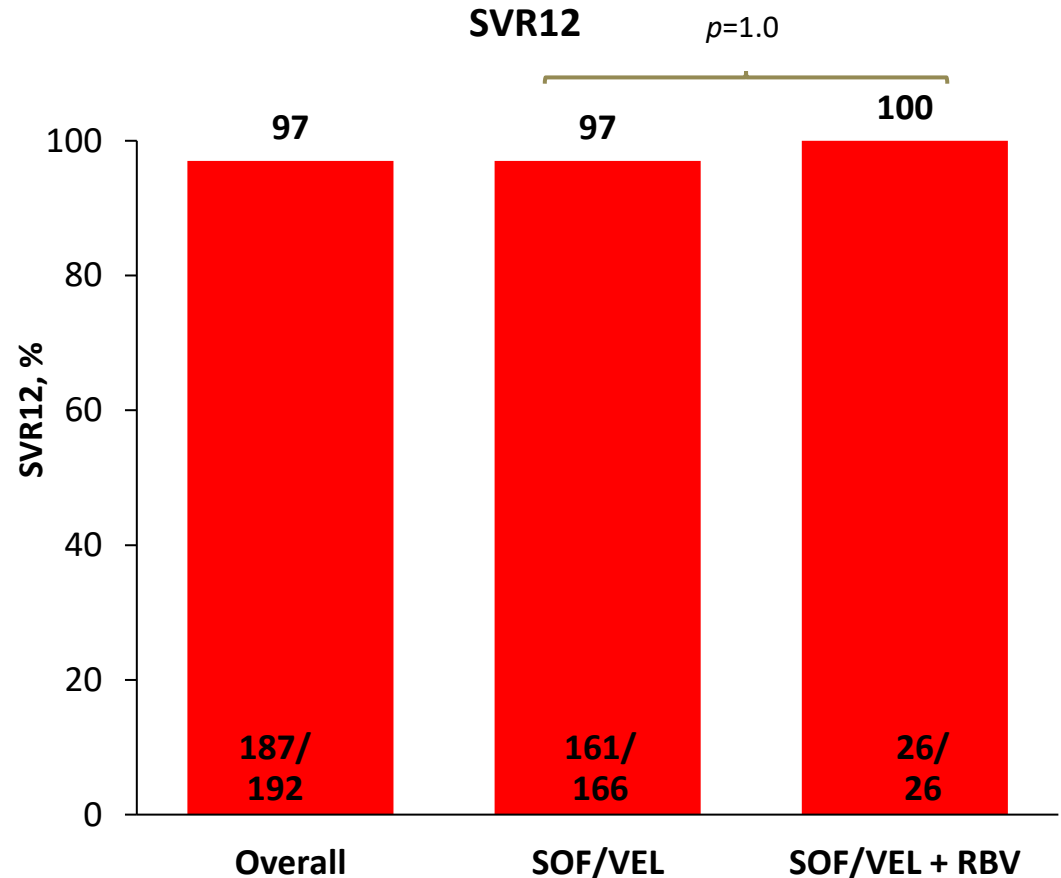
- 8 deaths [HCC (2), others 6-12 months after EOT]
- 16 (1%) D/C treatment, none due to AE
- Most common AEs: fatigue, headache

SOF/VEL in Italian Patients with GT 3 and Cirrhosis

Real-world, multicenter study of SOF/VEL $\pm$ RBV for 12 weeks

Baseline Demographics

	Overall N=192	RBV no N=166	RBV yes N=26
Male, n (%)	166 (87)	142 (86)	24 (92)
Mean age, years	52 (25-80)	53 (25-85)	52 (34-66)
CPT A, n (%)	185 (96)	161 (97)	24 (92)
CPT B/C, n (%)	7/0 (4)	26 (3)	2 (8)
Prior IFN/RBV failures, n (%)	55 (29)	43 (26)	12 (46)
Mean LSM, kPa	22.9 (10.1-69)	25.3 (13-59.3)	22.08 (10.1-22)
APRI score >2	74 (42)	65 (43)	9 (35)
Mean FIB-4 >3.25	92 (48)	78 (47)	14 (54)



SVR12 achieved in patients with GT 3 and compensated clinical cirrhosis who received SOF/VEL without RBV in real life are comparable to those of clinical trials

Mangia, AASLD 2018, 615 Cirrhosis defined by TE value > 12,5 kPa, and FIB-4 > 3.25 or APRI >2, presence of esophageal varices or ultrasonographic signs of cirrhosis (nodular liver surface or signs of portal hypertension as splenomegaly).

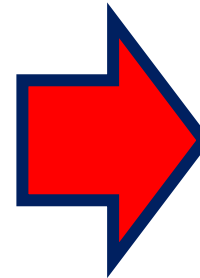
Effect of treatment on natural history

Chronic HCV, no cirrhosis

- Halts progression of fibrosis
- Marked reduction in risk of progression to cirrhosis
- Marked reduction in risk of developing HCC
- ? Reversal of fibrosis

Chronic HCV with cirrhosis

- Reduced risk of developing HCC
- Reduced risk of decompensation
- ? Reversal of cirrhosis – in the early stages



Reduced
viral
circulation



World Health
Organization

Long-term liver morbidity and mortality after HCV elimination by direct-acting antivirals in patients with chronic hepatitis C: Results from a large-scale, multicenter cohort study

Eiichi Ogawa
Kyushu University Hospital, Fukuoka, Japan

Patients and Methods

❖ Multicenter, retrospective cohort study

❖ Inclusion criteria

- Adults (18 and over)
- Achievement of SVR by all oral DAAs (between 2014 and 2023)

❖ Exclusion criteria

- Treatment failure
- Decompensated cirrhosis
- Active malignancy
- Past history of transplantation
- Coinfection with HBV or HIV
- Inadequate medical records

❖ 3,024 CHC patients

Mean age of 64.8 years

HCC-naïve: 2,689

Non-cirrhosis: 2,130

Compensated cirrhosis: 559

HCC-experienced: 333

❖ Index date

- At the end of DAAs treatment
- Median follow-up duration: 6.5 years

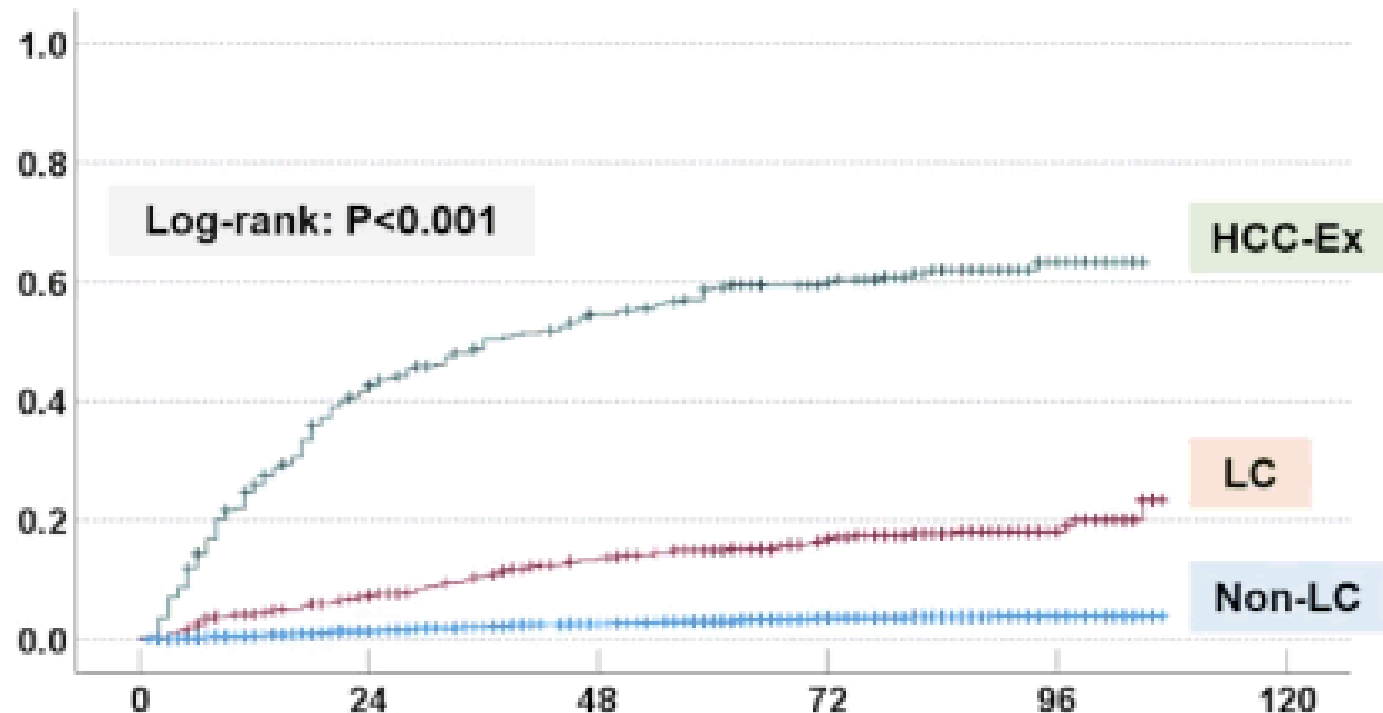
❖ Primary / secondary endpoints

1. Development of HCC (de novo and recurrence)
2. Survival rate
3. Causes of death

Long-term liver morbidity and mortality after HCV elimination by direct-acting antivirals in patients with chronic hepatitis C: Results from a large-scale, multicenter cohort study

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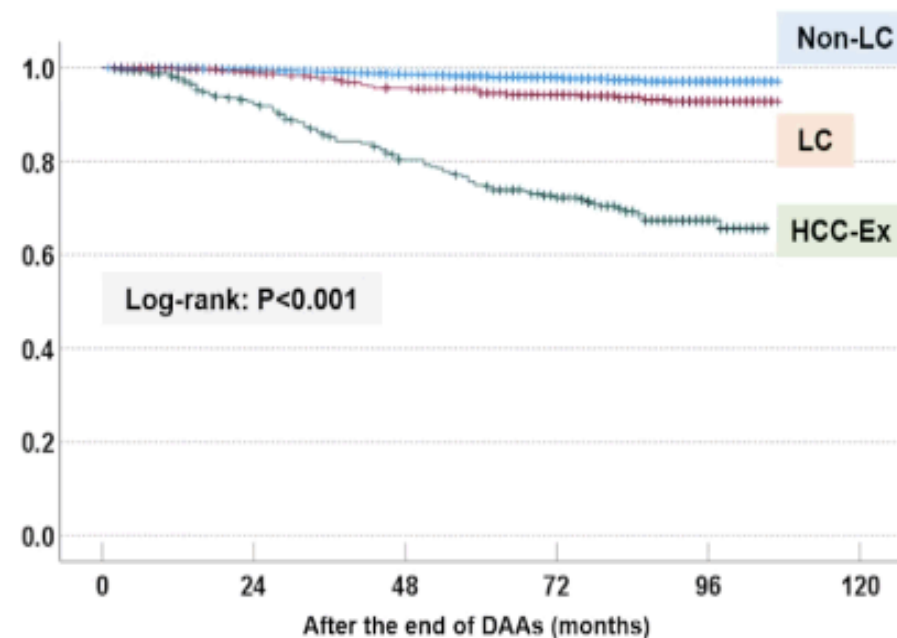
Cumulative HCC development rate after HCV elimination



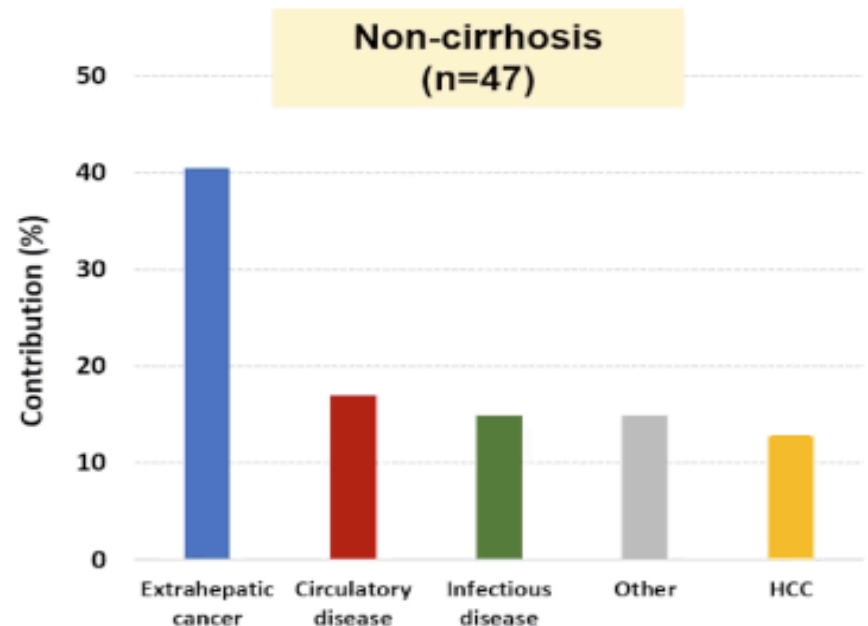
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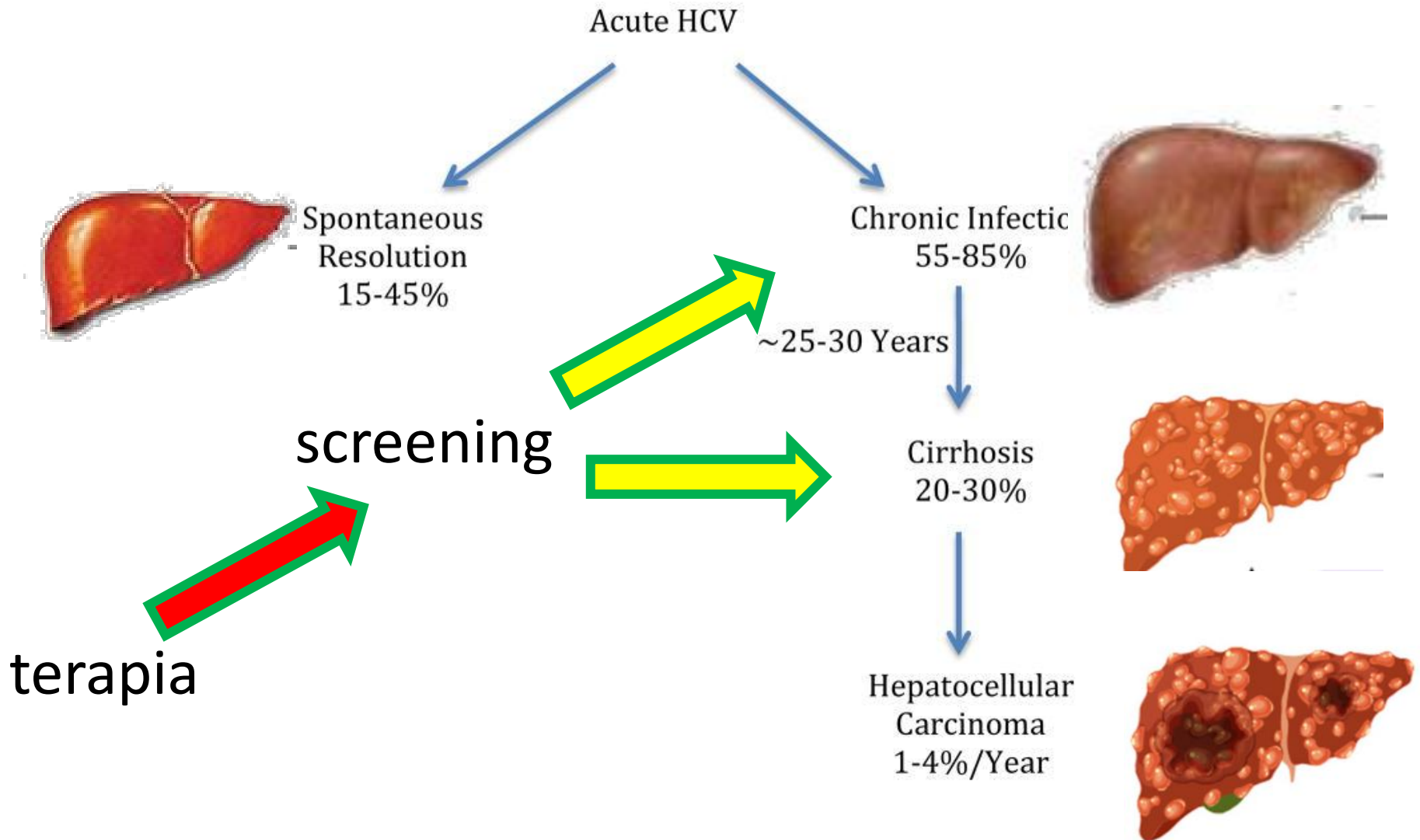
Survival rates after HCV elimination



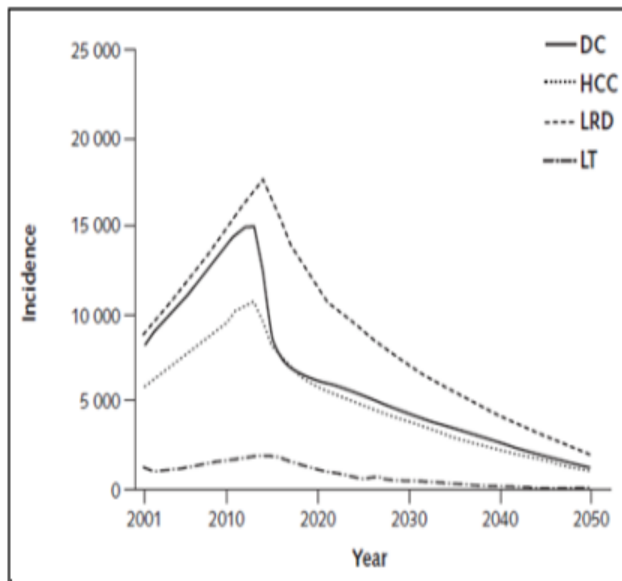
Causes of death after HCV elimination



Storia naturale



HCV Infection Could Become a Rare Disease in the Next 20 Years



By 2050 highly effective therapies could prevent:

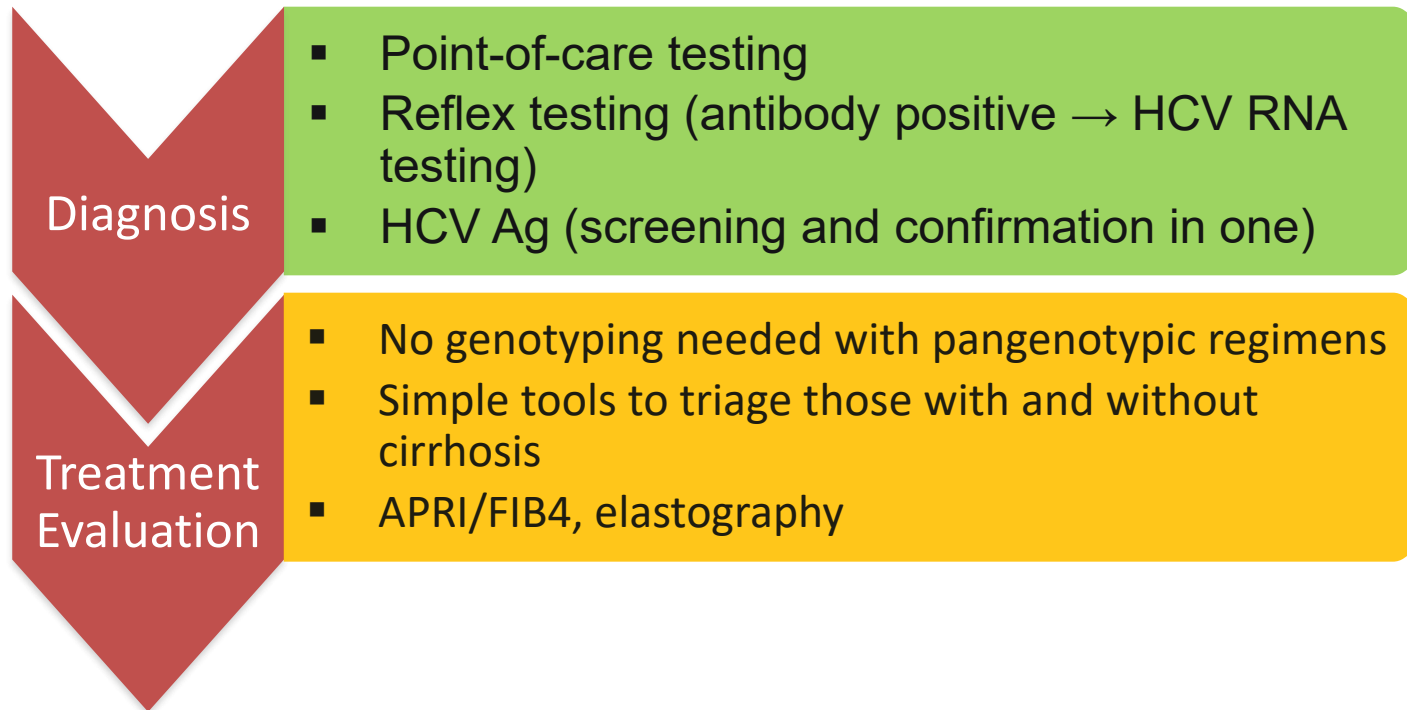
24,200 cases of decompensated cirrhosis

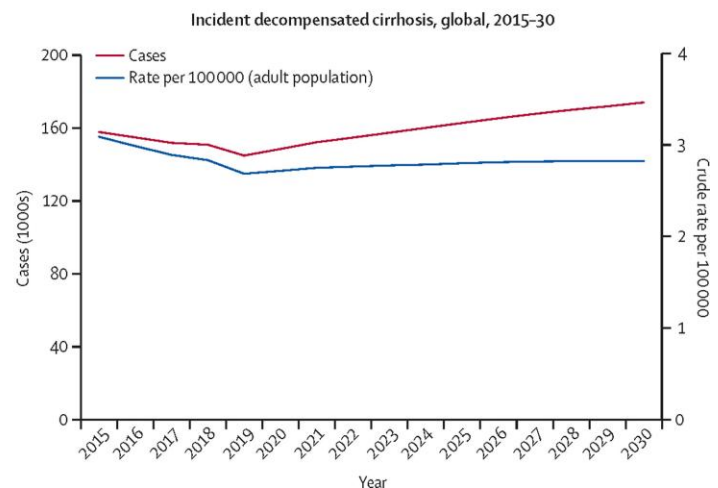
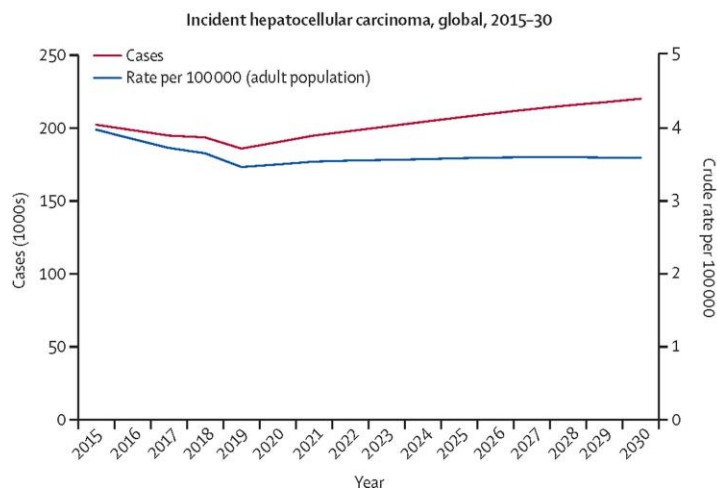
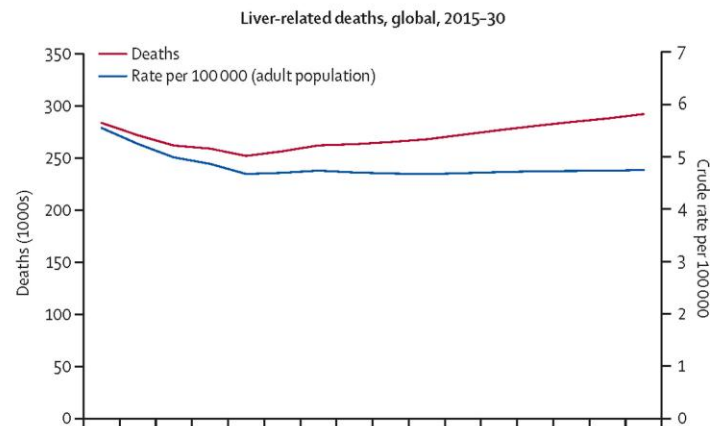
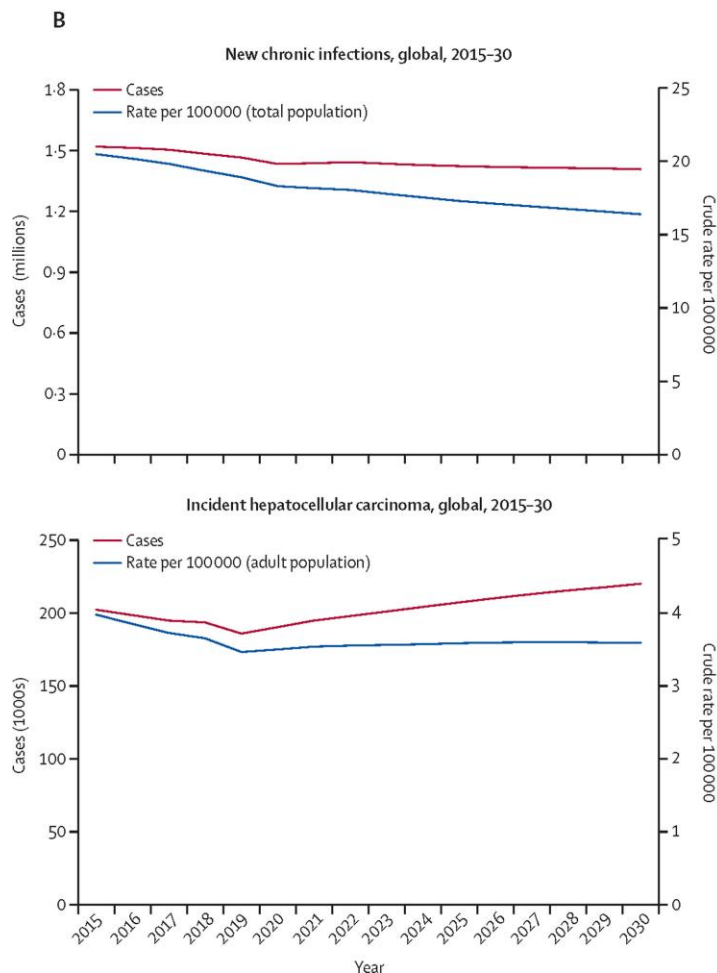
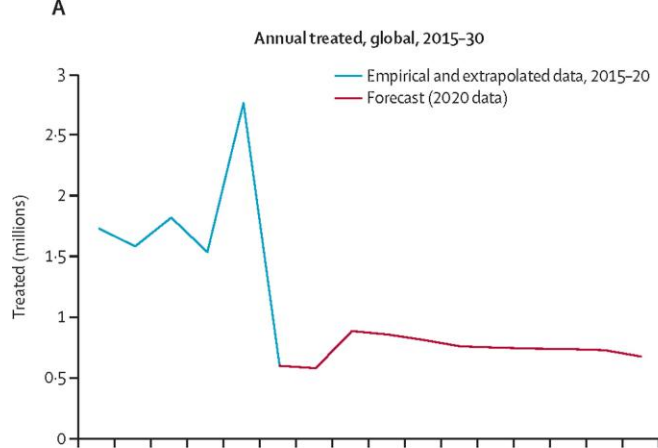
78,800 cases of HCC

126,500 liver-related deaths

9,900 liver transplantations

HCV Elimination: Simplifying and Streamlining Care







Elimination of hepatitis
by 2030

Lo screening nazionale

- L'Italia (art. 25-sexies, legge 8/2020), ha istituito un fondo di 71,5 M € per uno screening gratuito dell'Epatite C:
 - nati negli anni dal 1969 al 1989
 - soggetti seguiti dai SerD
 - soggetti detenuti in carcere

Risultati *in itinere* dei dati regionali

Popolazione generale (nati tra il 1969 e il 1989)

- **Estensione**: 65,5% delle persone target ha ricevuto l'invito o è stata informata
- **Copertura** (persone testate rispetto alla popolazione target): 15%
- **Adesione** (persone testate rispetto a quelle invitate): 23%
- **Prevalenza anticorpale**: 0,8%
- **Test di conferma (HCV RNA)**: adesione 73%; positività 23%
- **Linkage to care** (persone con infezione attiva collegate ai centri cura): 64%
- **Screening**: coinvolte circa 2.580.787 persone, con 3.299 infezioni attive rilevate

Utenti afferenti ai SerD

- **Estensione**: 72% ←
- **Copertura**: 46% ←
- **Adesione**: 64%
- **Prevalenza anticorpale**: 19% ←
- **Test di conferma**: adesione 90%; positività 44%
- **Linkage to care**: 50% ←
- **Screening**: coinvolti 135.469 utenti SerD, con 9.862 infezioni attive rilevate

Popolazione carceraria

- **Estensione**: 93% ←
- **Copertura**: 78% ←
- **Adesione**: 85%
- **Prevalenza anticorpale**: 9,6% ←
- **Test di conferma**: adesione 86%, positività 41%
- **Linkage to care**: 64% ←
- **Screening**: coinvolti 85.561 detenuti, con 2.925 infezioni attive rilevate

Criticità

- Disomogeneità regionale.
- Difficoltà nel collegamento diagnosi-trattamento:

Prospettive

- Omogeneizzazione dell'attività fra le varie regioni
- Realizzare campagne di comunicazione/informazione
- Potenziare e armonizzare il percorso di cura prendendo esempi virtuosi
- Screening ospedaliero una tantum



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