FESTIVAL DELLE SCIENZE INFETTIVOLOGICHE

FERRARA

20 - 21 SETTEMBRE 2018

SALA IMBARCADERO

CASTELLO ESTENSE

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale della Romagna

Infezione da HCV

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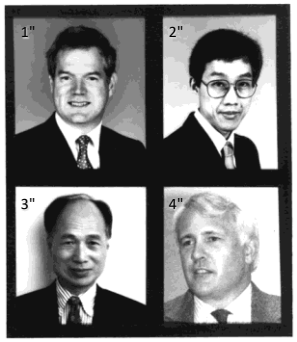
Ospedale Faenza e Ravenna
Alta Specializzazione Epatologia
AUSL Romagna

From Virus Discovery to Plans for Elimination in 30 years



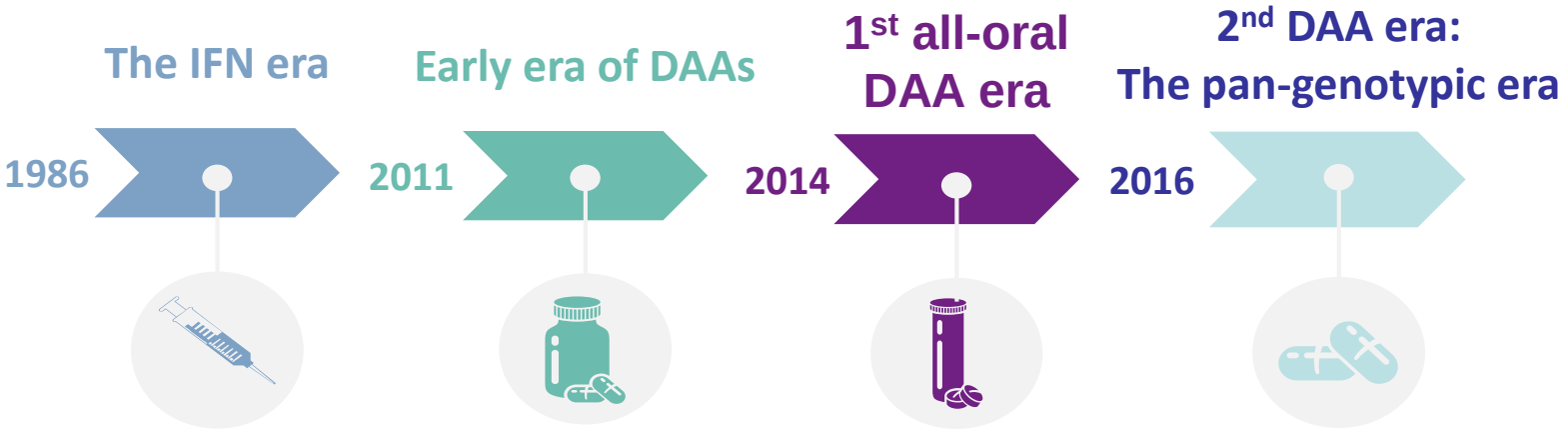
Science 21.4.1989

Isolation of a cDNA Clone Derived from a Blood-Borne Non-A, Non-B Viral Hepatitis Genome

QUI-LIM CHOO, GEORGE KUO, AMY J. WEINER, LACY R. OVERBY, DANIEL W. BRADLEY, MICHAEL HOUGHTON

2016: The WHO Global Health Sector established the goal of HCV elimination as a major public health target by 2030

World Health Organization



HCV epidemiology

Status of hepatitis C

HCV

Prevalence:

71 million infected, all regions

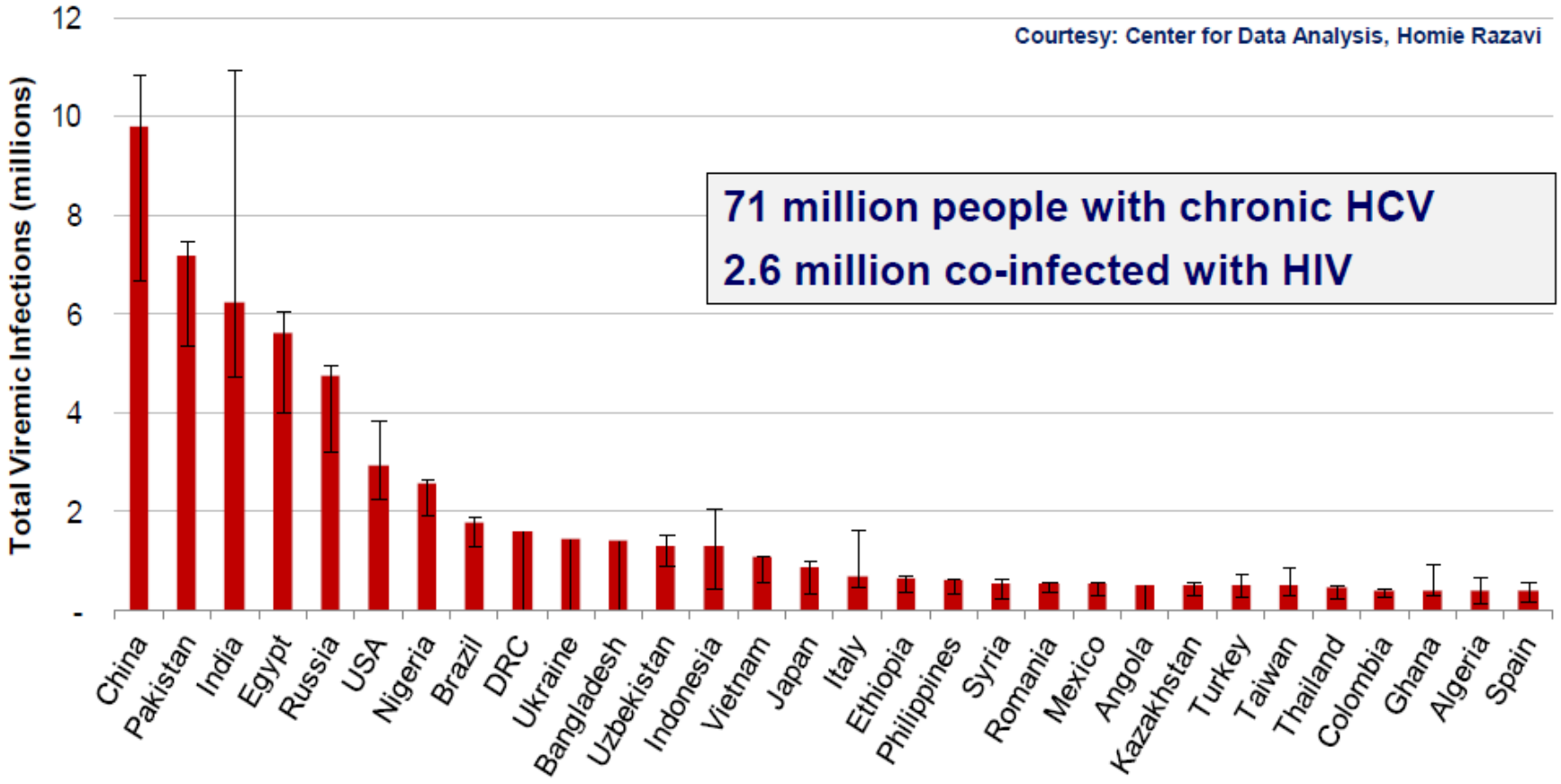
Incidence:

1.75 million new infections / year (Unsafe health care and injection drug use)

Sources – WHO (Center for Disease Analysis)

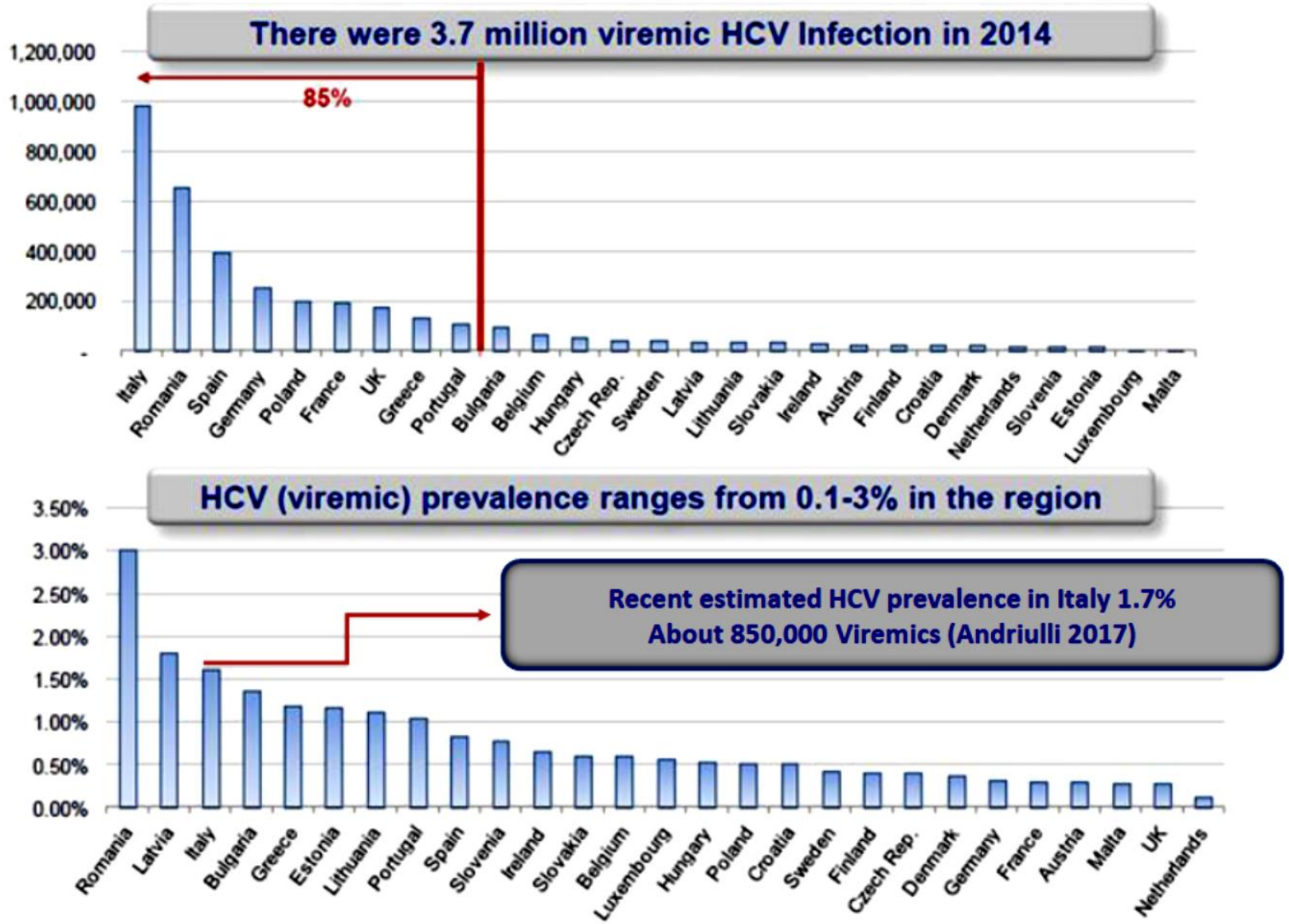
World Health Organization

Countries with high numbers of Hepatitis C infections

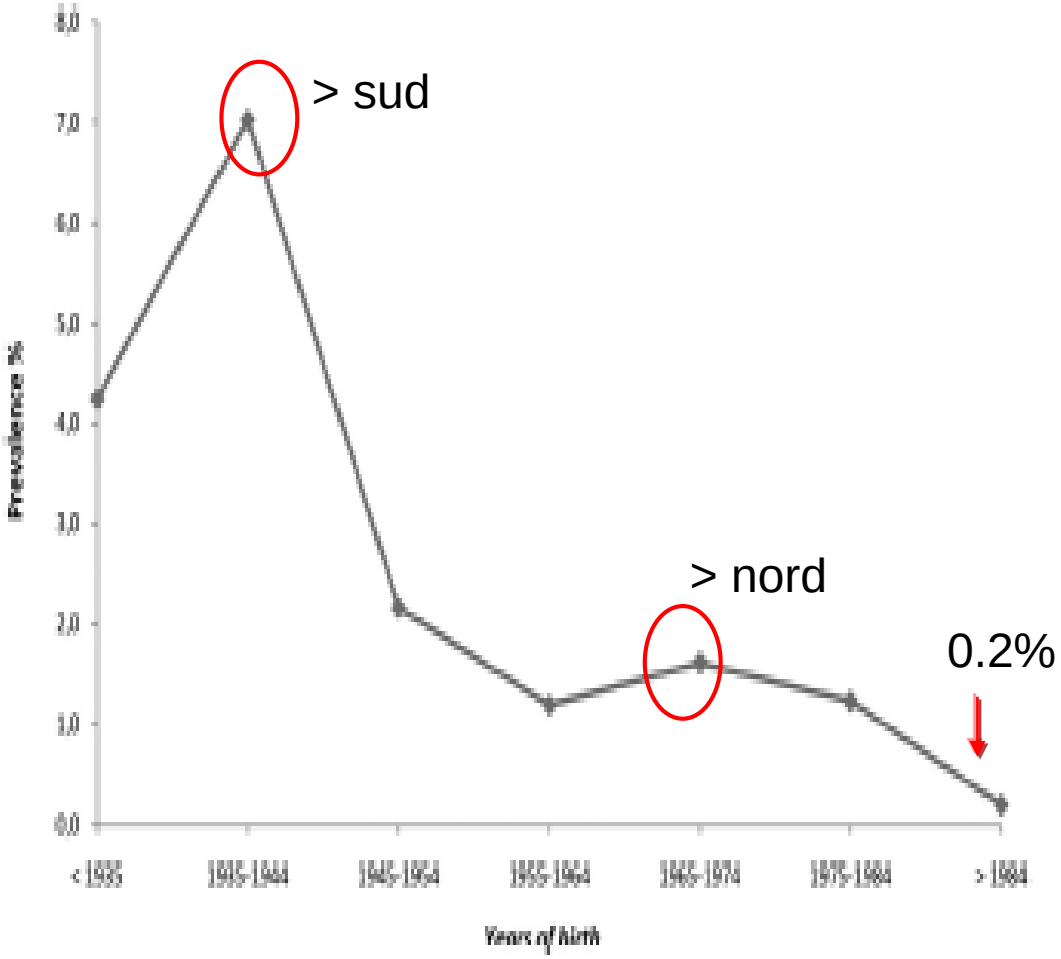


World Health Organization

Italy, Romania, Spain, Germany, Poland , France , UK, Greece and Portugal account for 85% of total infections in EU



Prevalence of anti-HCV positivity by cohort of birth in 5 Italian metropolitan areas, 2015.



Adjusted Odds Ratios (OR) for the association of anti-HCV with different variables and population attributable risks (PAR) for risk factors for anti-HCV. Italy, 2015.

Characteristics	OR (CI 95%)	PAR
Age > 70 years	2,7 (1,7–4,3)	-
Years of school (≤8)	1,9 (1,2–3,0)	32%
Blood transfusion	3,1 (1,9–5,1)	14%
History of IDU	30,2 (12,7–71.9)	12%
Household contact with a HCV+ subject	3,0 (1,7–5,3)	11%
Male gender	1,3 (0,9–2,0)	-
Past use of glass syringes	1,7 (1,0–2,7)	25%
Previous surgery	1,0 (0,6–1,7)	-

4907 subject were randomly selected from the list of GP;
79,5 were aware of their infection

Andriulli A et, al Eur J Intern Med. 2018

SERT Romagna

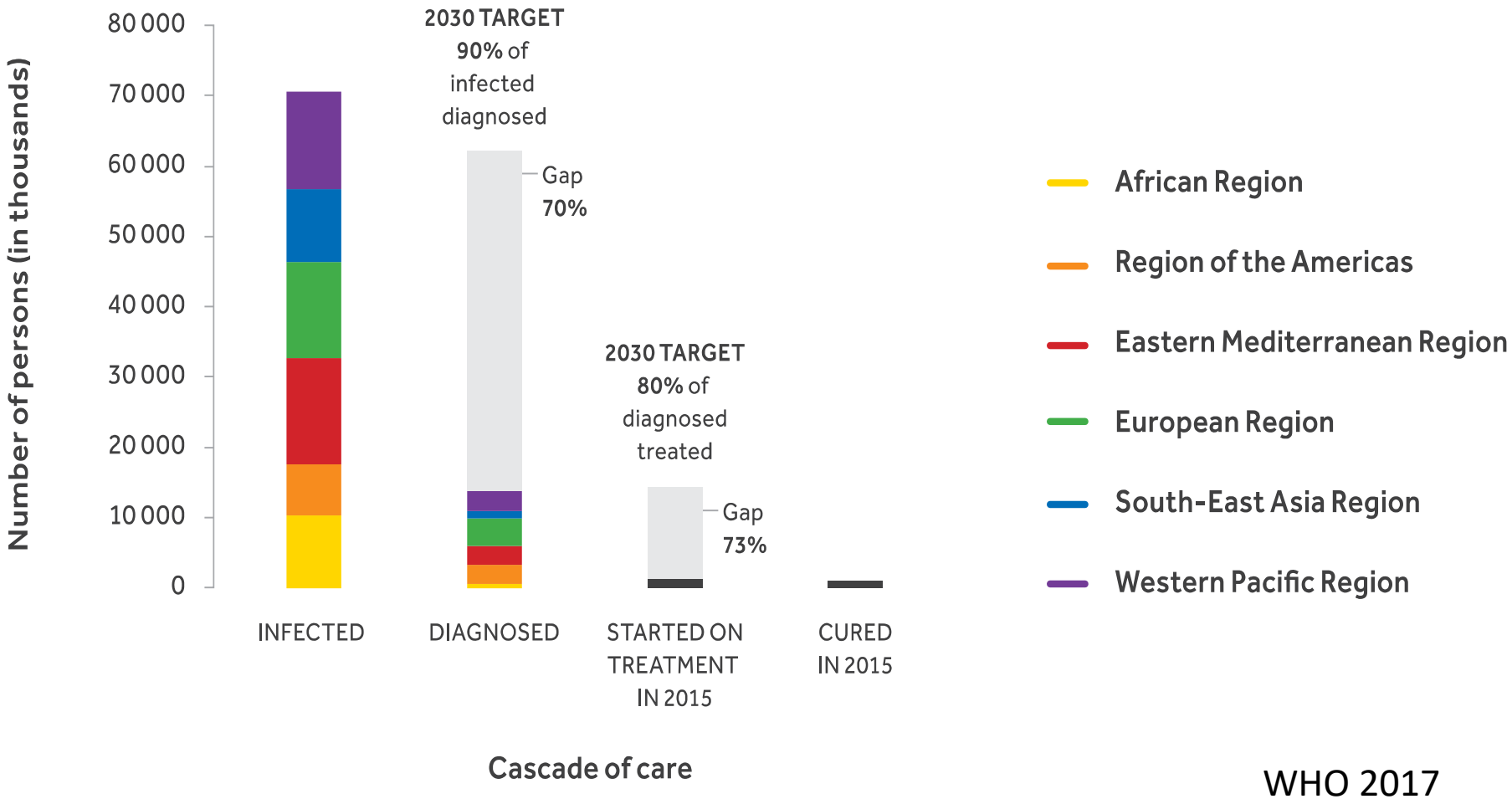
- I pazienti in carico all'UO Dipendenze Patologiche della Romagna per uso di Droghe sono 2861.
- I pazienti HCV positivi sono 1058; 351 non sono testati;
- Molte persone non sono state testate
- Seguiti per Problemi alcol correlati 1536 (1.1% positivo per HIV e l'11.6% positivo per HCV; 321 mon sono testati)

Rapporto delle dipendenze patologiche 2017

HCV elimination strategy and special population

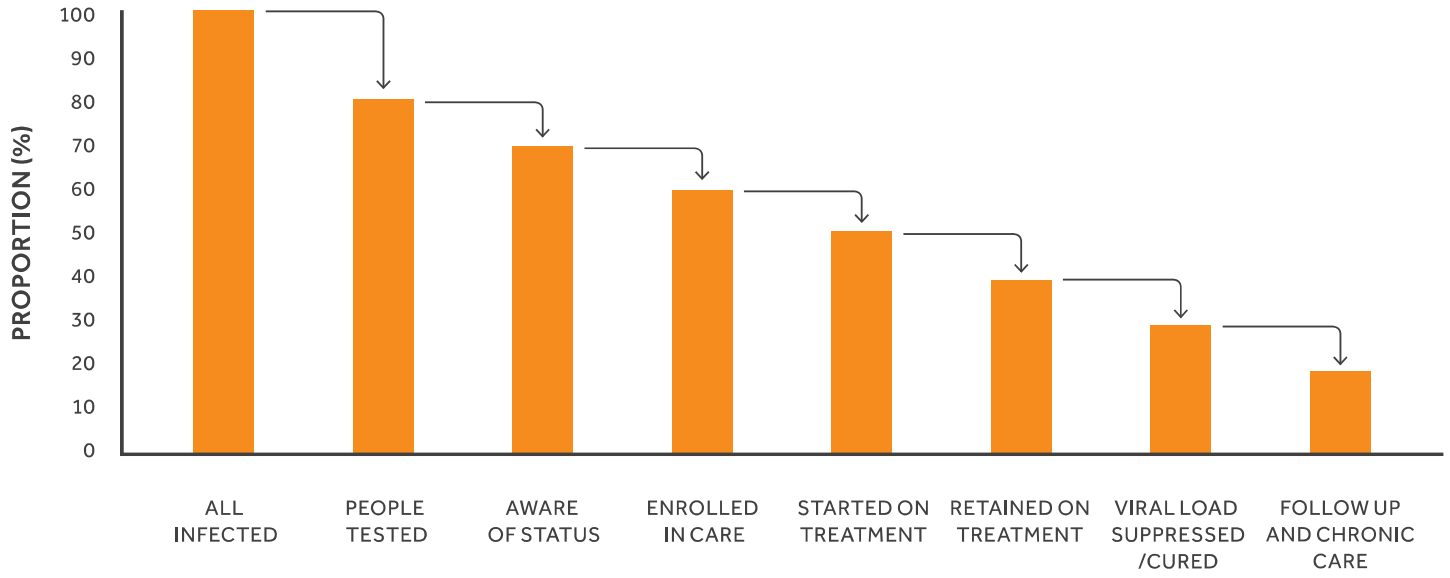
- **Prisoners**
- **MSM**
- **PWID**
- **Sex workers**
- **Migrants**

Cascade of care for HCV infection, by WHO region, 2015



WHO 2017

The continuum of viral hepatitis services and the retention cascade

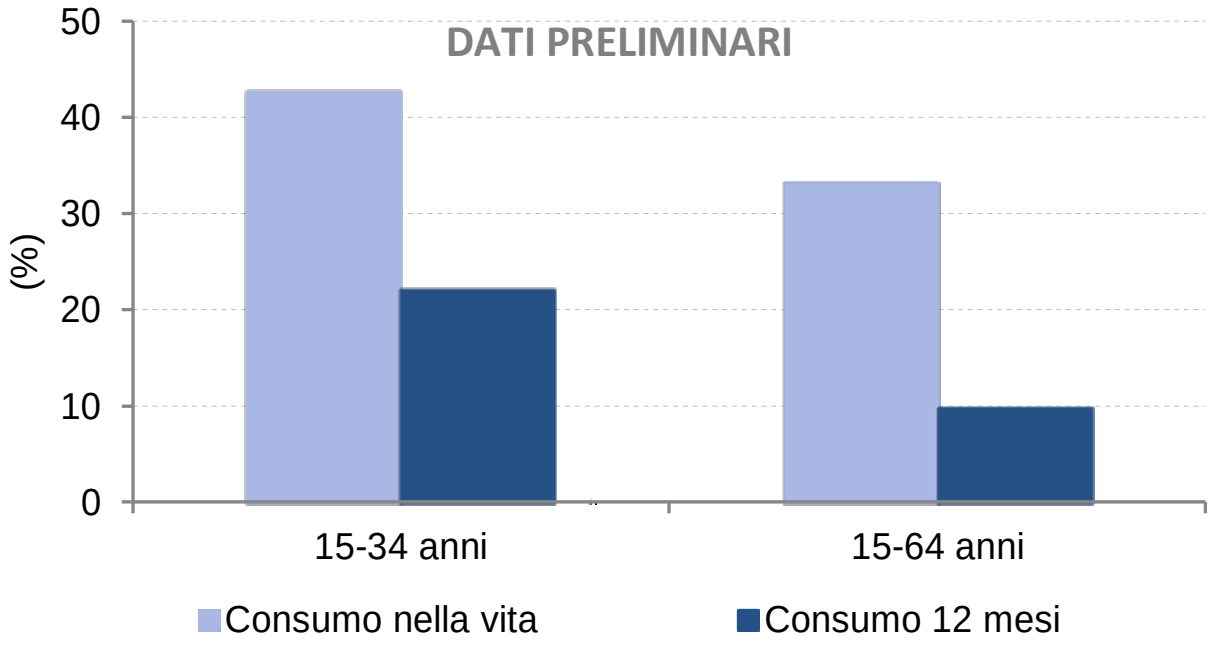


WHO 2017

HCV Screening

- Adulti nati tra il 1945-1965
- Familiari di persone infette
- Immigrati provenienti da regioni ad alta endemia
- Soggetti con infezione da HIV
- Soggetti che abbiano un’attività sessuale promiscua (che presentano storia di malattie sessualmente trasmesse)
- Uso passato o attuale di droghe somministrate per via endovenosa
- Soggetti sottoposti a trasfusione di emoderivati prima del 1992
- Bambini nati da madri HCV positive

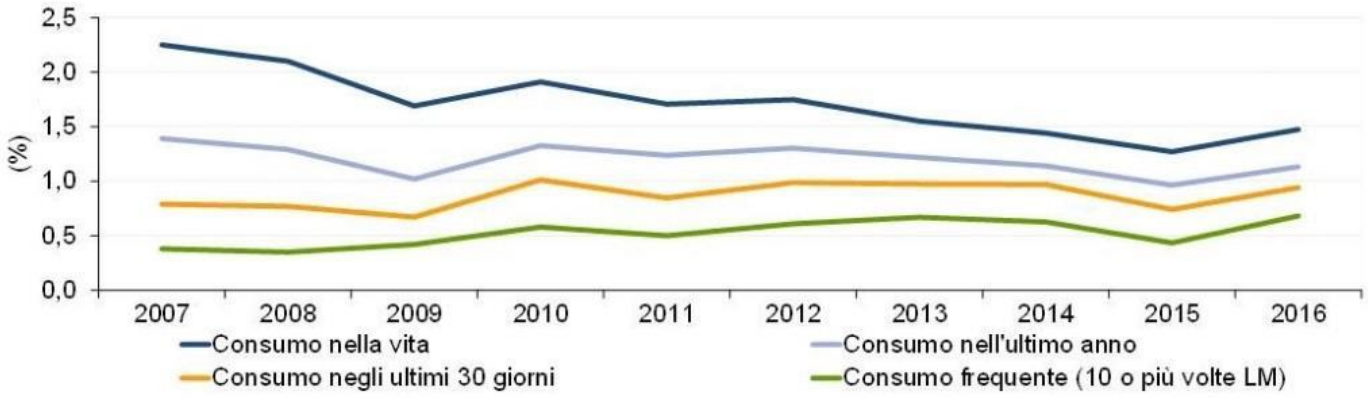
Percentuali di consumatori di almeno una sostanza stupefacente nella popolazione generale e tra i giovani adulti, nella vita e negli ultimi 12 mesi (Anno 2017)

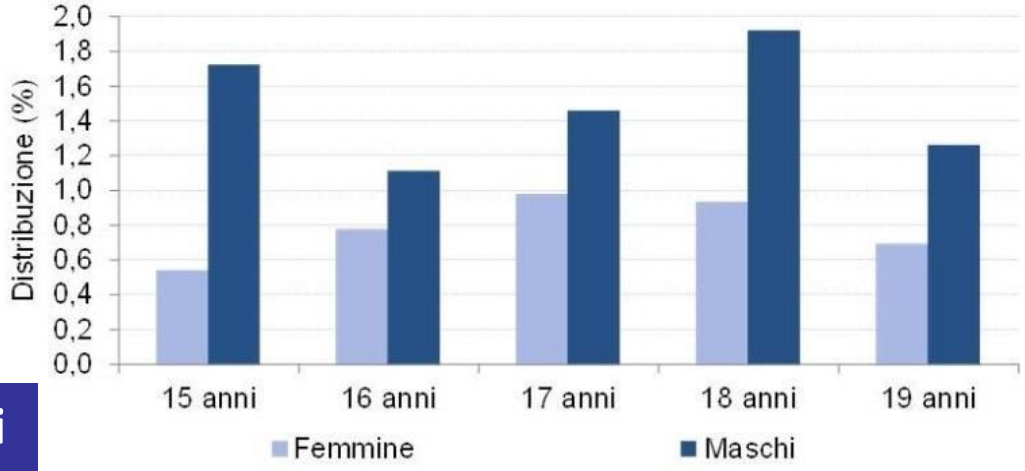


Il 33% degli italiani di 15-64 anni ha provato almeno una volta nella vita una sostanza psicoattiva illegale

Presidenza del Consiglio; Relazione al Parlamento 2017

Consumo di eroina





Quasi 17.000 studenti fanno uso di eroina 10 o più volte al mese

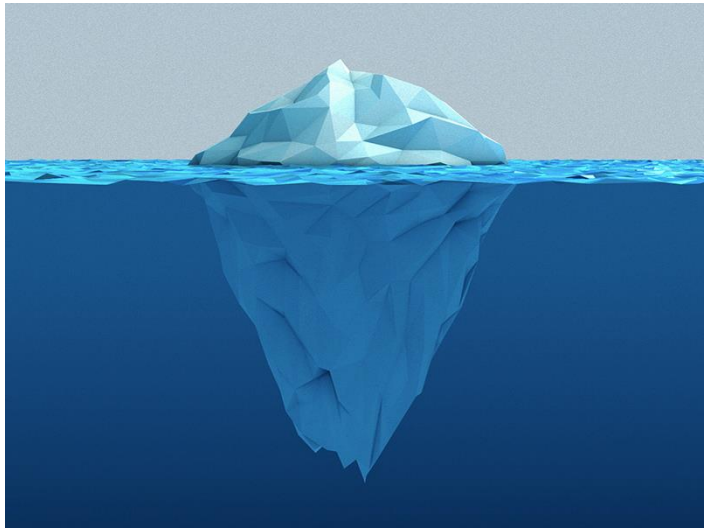
Presidenza del Consiglio; Relazione al Parlamento 2017

Chi sono i PWID?

- Chi si è iniettato una volta
- Chi si inietta regolarmente
- Chi si inietta occasionalmente
- Chi si è iniettato negli ultimi 35 anni
- Chi è in OST e non si inietta più

Larney S. et al. Int. J. Drug Policy 2015; 26: 950-957 Grebely J., Dore G.J. Antiviral Res 2014; 104: 62-72

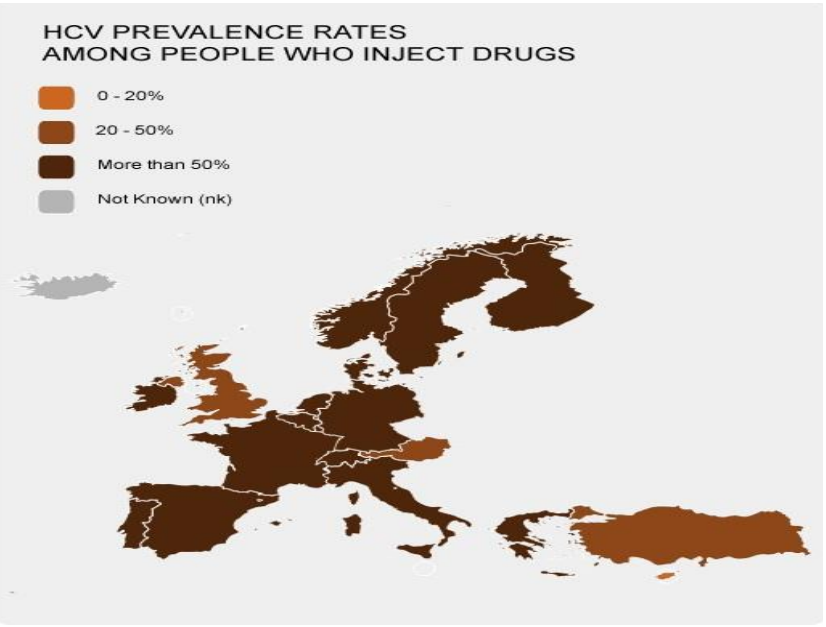
HCV among PWID in europe



- I Europe, PWID are a major, if not the main HCV transmission risk group
- One in two PWID has HCV antibodies (6 milion)
- A significant proportion has not been diagnosed
- There is a lack of access to testing and treatment

Hickman and martin (Eds) EMCDDA 2016; Who global Hepatitis Report 2017

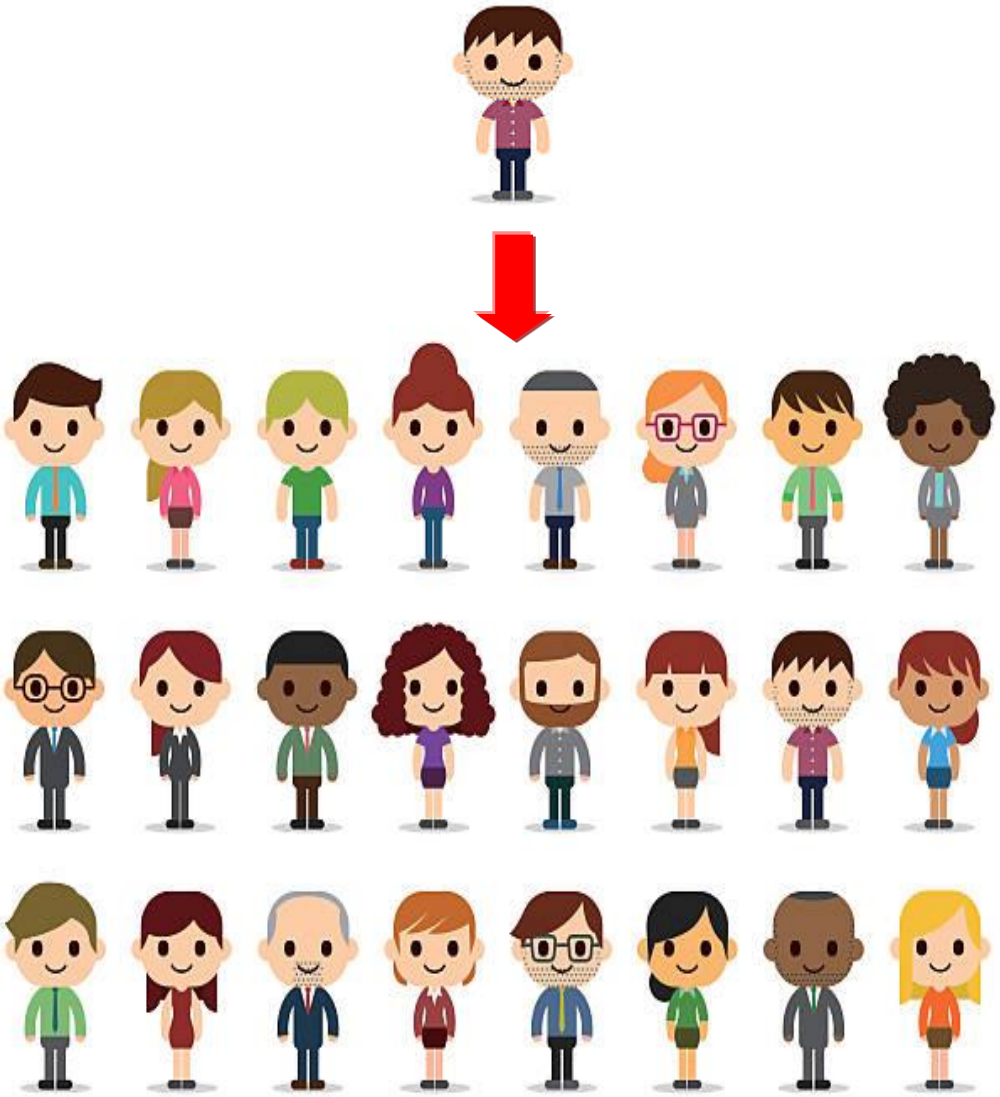
Hepatitis C virus infection among PWID: epidemiology



Countries/territory with reported injecting drug use	People who inject drugs*	Adult HIV prevalence amongst people who inject drugs**	Adult HCV prevalence amongst people who inject drugs***
Andorra	nk	nk	nk
Austria	17,500	7.1%	48%
Belgium	25,800	4.3%	50-80.7%
Cyprus	305	0%	9.1%
Denmark	15,416	2.1%	58%
Finland	15,650	0.2%	23-56.6%
France	122,000	12.2%	44-66%
Germany	94,250	2.9%	75%
Greece	9,720	0.5%	43.3-61.7%
Iceland	nk	nk	nk
Ireland	6,289	5.8%	72.3%
Italy	326,000	12.1%	61.4%
Liechtenstein	nk	nk	nk
Luxdmbourg	1,715	2.8%	71.8-90.7%
Malta	nk	0%	30.4%
Monaco	nk	nk	nk
Netherlands	3,115	9.5%	64.6%
Normway	10,049	3.2%	69%
Portugal	32,287	15.6%	38.4-84.3%
San Marino	nk	nk	nk
Spain	83,972	39.7%	59.1-73.3%
Sweden	nk	5.4%	83.8%
Switzerland	31,653	1.4%	91%
Turkey	nk	2.65%	47.4%
United Kingdom	156,398	2.3%	41%

*Mathers, B. et al. Reference Group to the United Nations on HIV and injecting drug use (2008). The global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. The Lancet 2008, Volume 372.
***Cook, C & Kanaef, N (2008) The Global State of Harm Reduction: Mapping the global response to drug-related HIV and hepatitis C epidemics. Harm Reduction International, UK

Trattare per prevenire

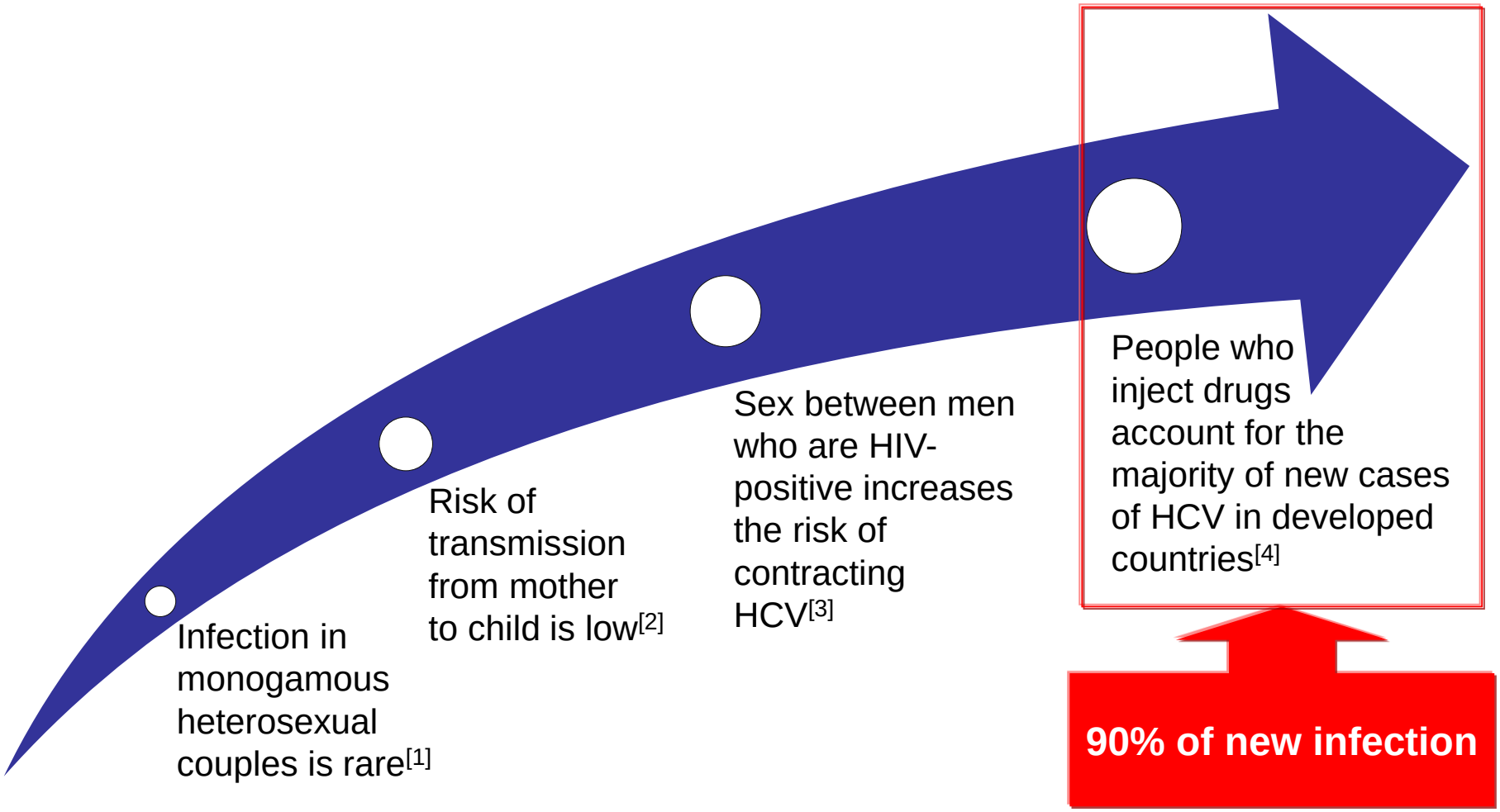


-L'uso iniettivo di sostanze è responsabile del 23% delle nuove infezioni da HCV

-Ogni PWID con infezione da HCV è capace di infettare almeno altri 20 consumatori entro i primi tre anni dall'inizio del contagio

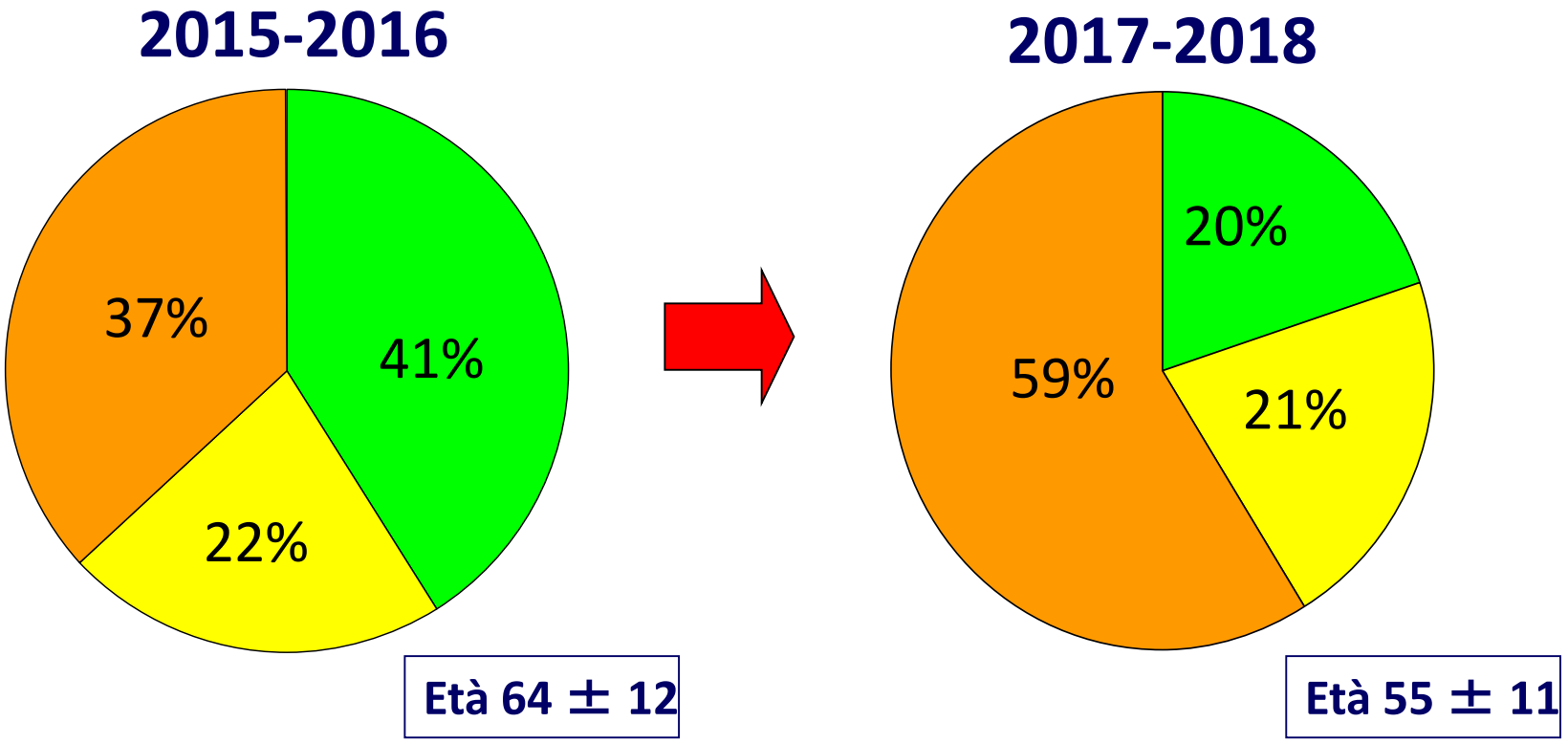
WHO Global Hepatitis Report 2017; Magiorkinis G et al. Plos Comput Biol, 2013. 9(1).

Hepatitis C Is an INFECTIOUS Virus: Treatment as Prevention

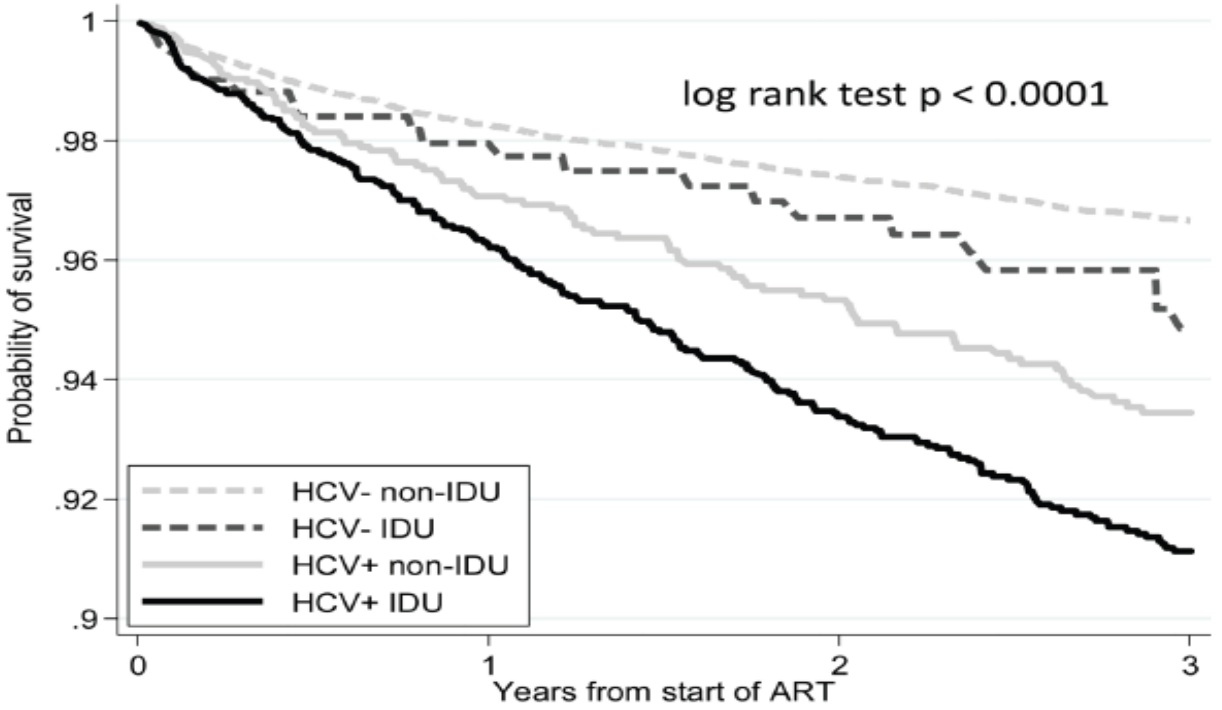


1. Terrault NA, et al. Hepatology. 2013;57:881-899. 2. Thomas SL, et al. Int J Epidemiol. 1998;27:108-117. 3. Larsen C, et al. PLoS One. 2011;6:1-9. 4. Shepard CW, et al. Lancet Infect Dis. 2005;5:558-567.

Cambiamento della tipologia di Pazienti HCV Positivi afferenti all'Ambulatorio di Faenza



Contribution of IDU and HCV to the risk of death

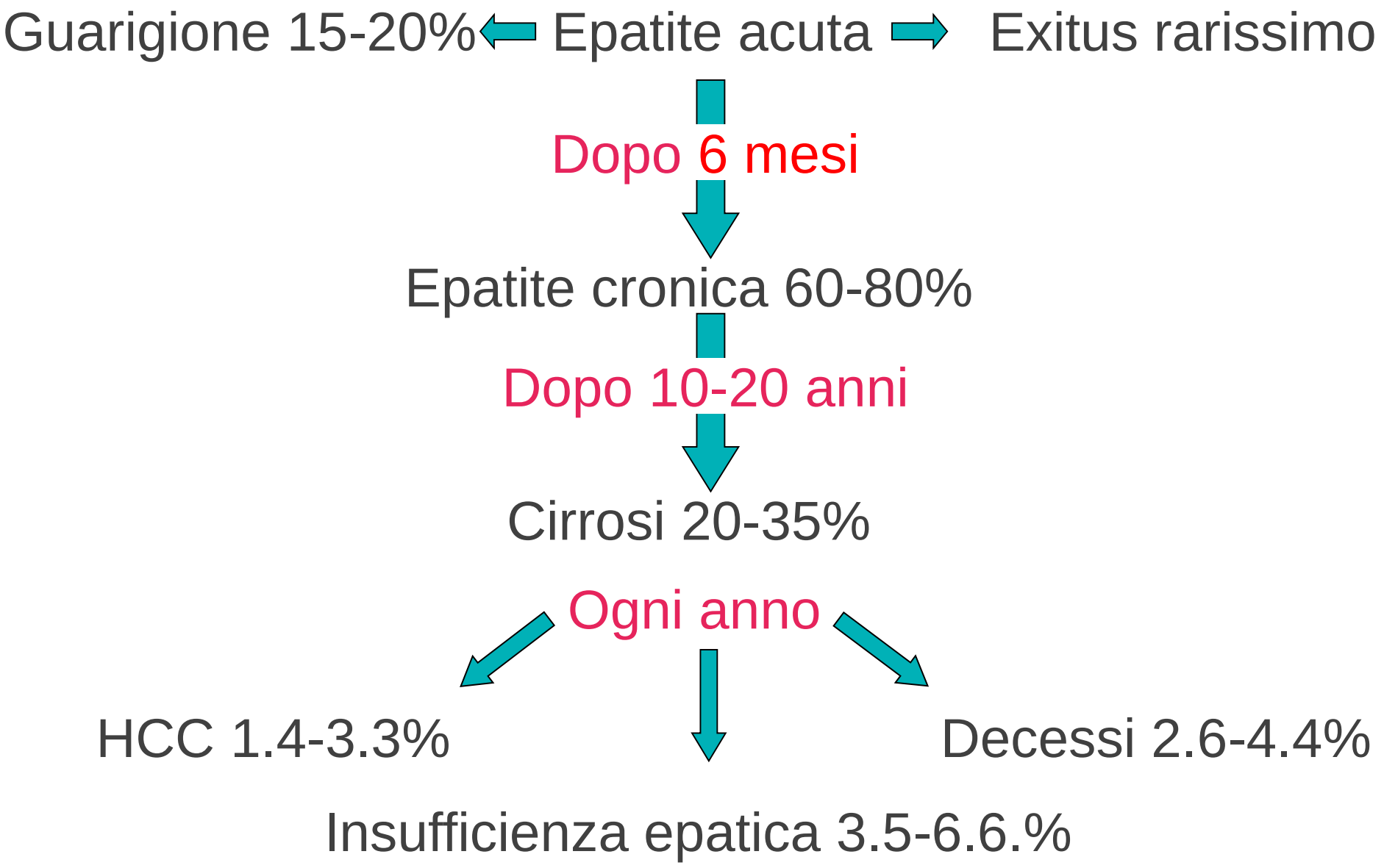


Number at risk:	Yr 0	Yr 1	Yr 2	Yr 3
HCV- non-IDU	27567	23729	19625	15919
HCV- IDU	506	426	353	289
HCV+ non-IDU	1762	1485	1209	953
HCV+ IDU	2868	2400	1958	1553

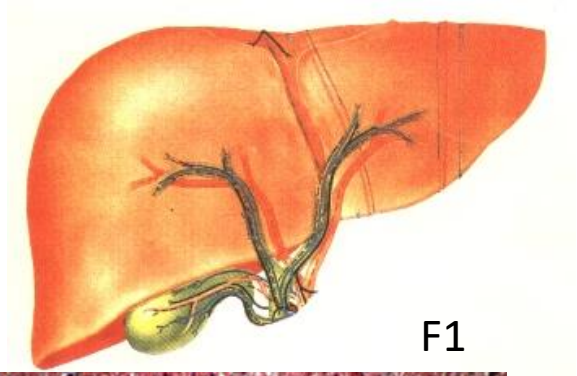
Justice A. et al J Acquir Immune Defic Syndr. 2015

HCV Hepatic and extrapetic diseases

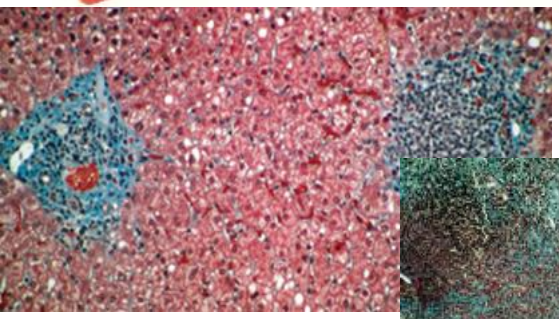
Epatite C: storia naturale



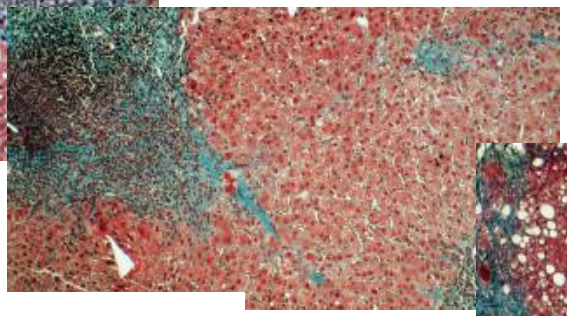
Natural Hystory of Chronic Hepatitis C



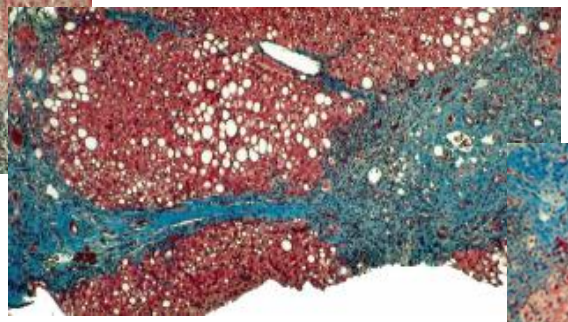
F1



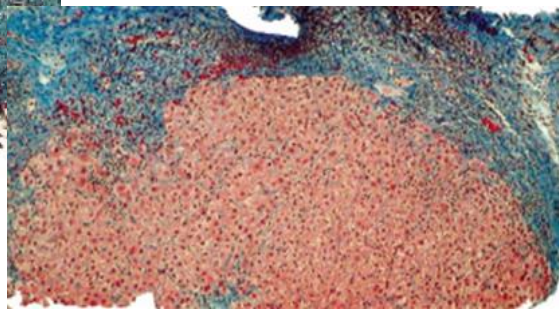
F2

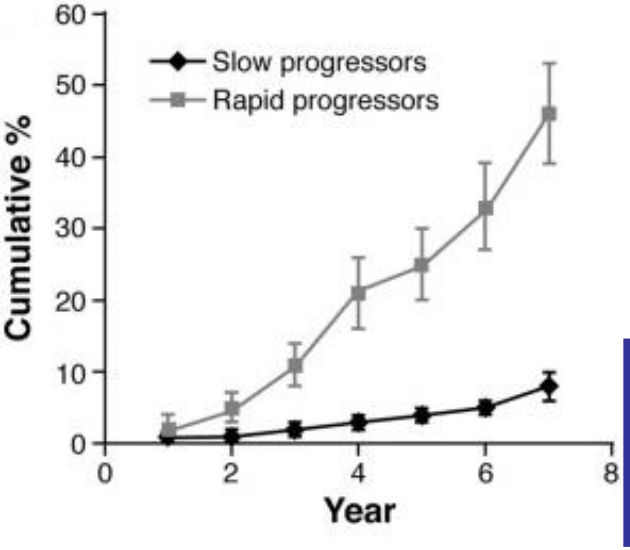


F3



F4

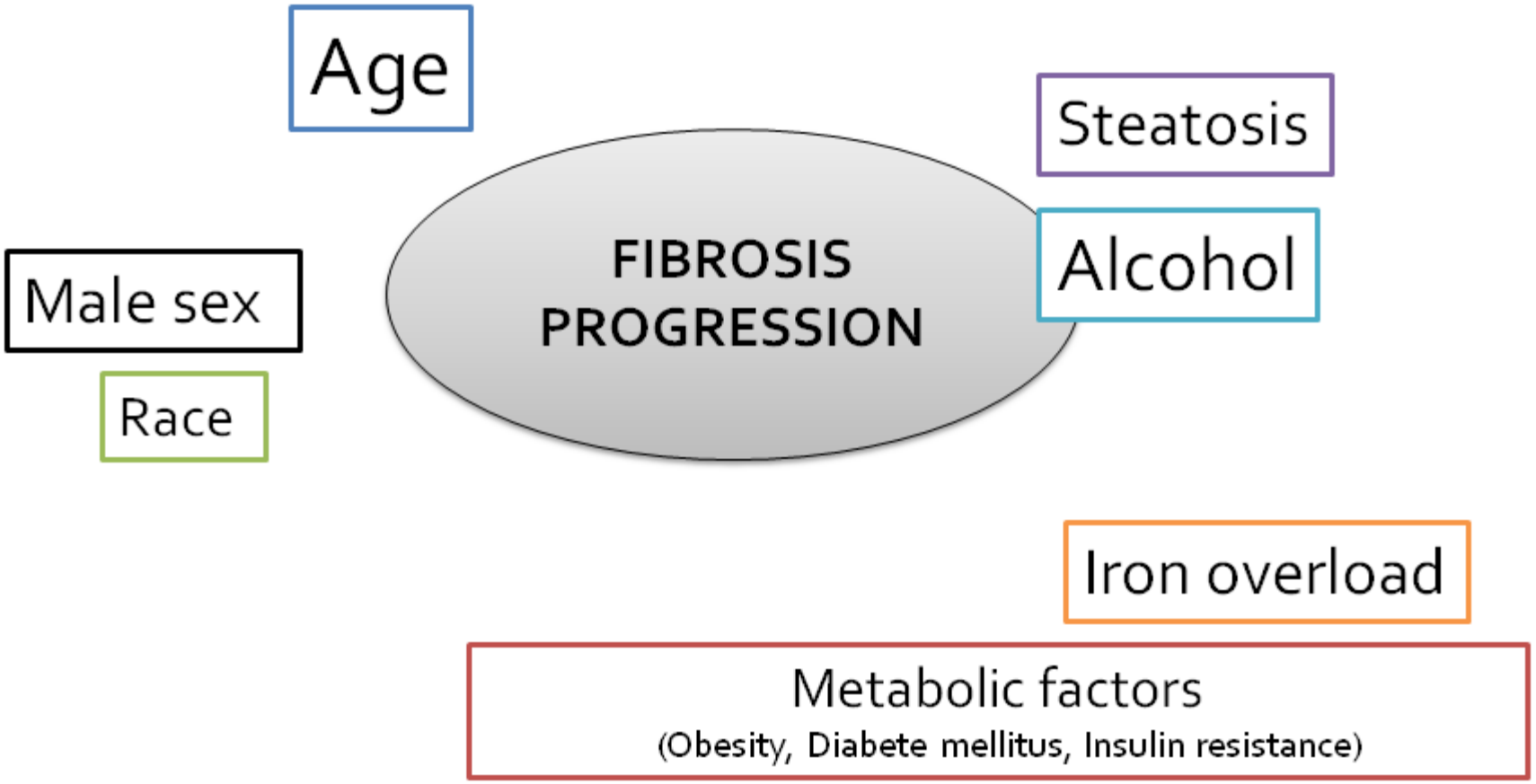




✓Progression of fbrosis appears to be "non-linear"
✓For smplicity sake, fibrosis can be estimated to progress "1 Metavir Unit every 5 years".

Hoefs JC et al Gastroenterol 2011

Modifiable and nonmodifiable factors in disease progression in chronic hepatitis C



However the role played by each factor may change over time according to the phase of infection, the stage of disease and the age of the patient

HCV e Manifestazioni Sistemiche

Immuno-relate

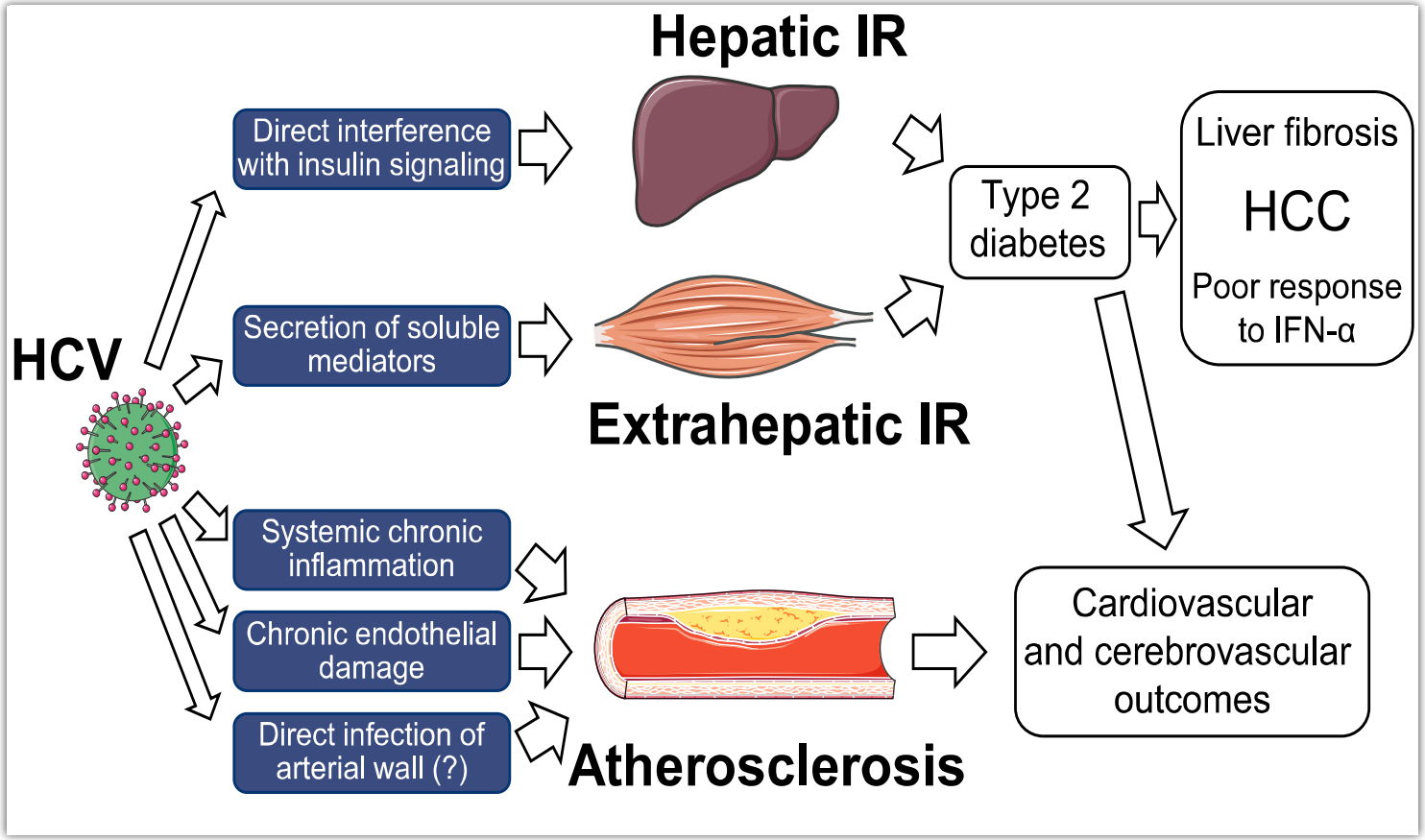
- Crioglobulinemia mista
- Vasculite crioglobulinemica
- Linfoma B
- Gammopatia monoclonale
- Porpora trombocitopenica
- Sindrome Sicca
- Artralgia/mialgia
- Produzione di autoanticorpi
- Poliarterite nodosa

Infiammatorio-relate

- Disordini cardiovascolari
- Diabete mellito
- Resistenza insulinica
- Glomerulonefrite
- Insufficienza renale
- Astenia
- Decadimento cognitivo
- Depressione
- Peggioramento qualità della vita

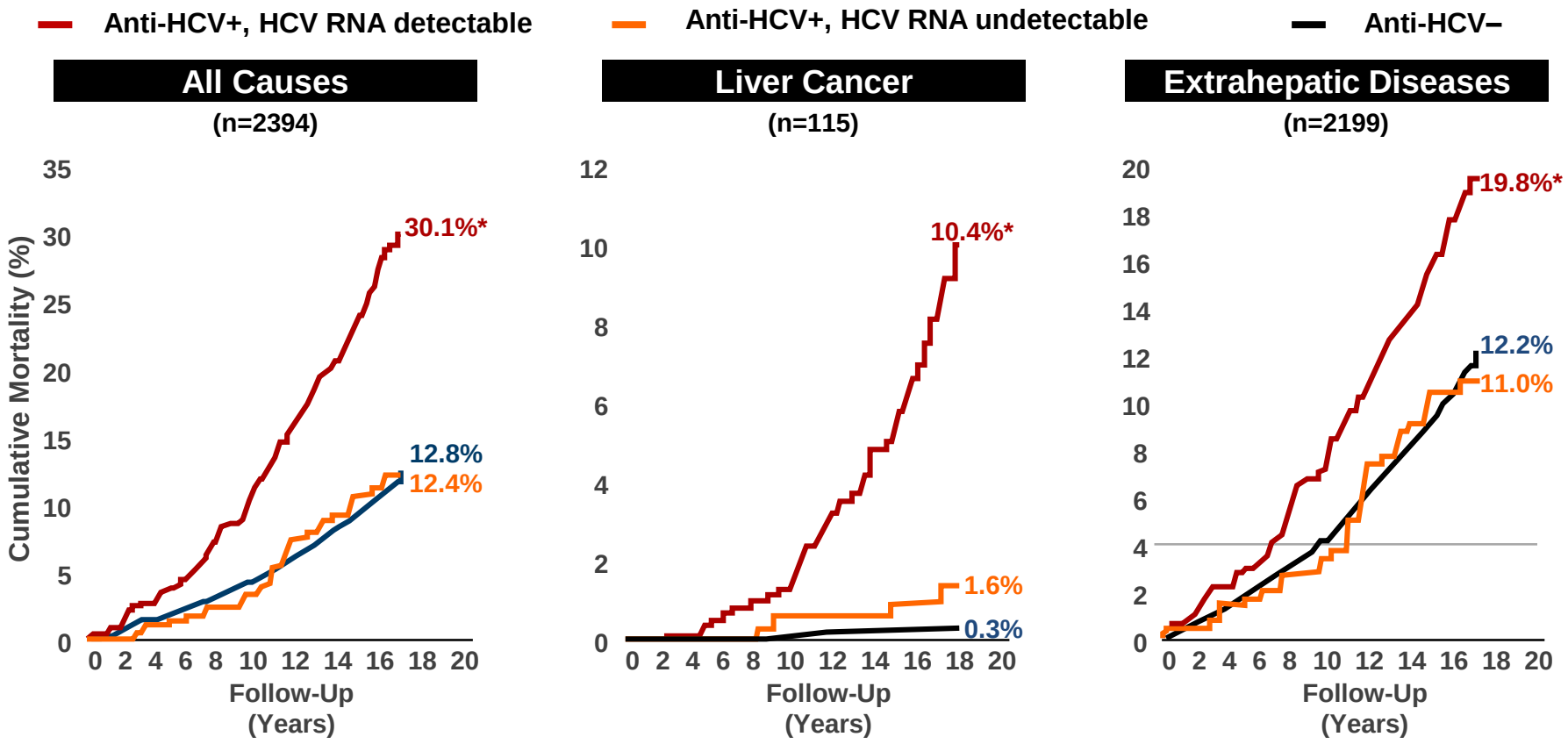
Cacoub P et al, Ther Adv Inf Dis 2016

HCV, Aterosclerosi & Diabete



Negro F, J Hepatol 2014

HCV e Mortalità



Cacoub P, et al. DLD 2014; Lee MH, et al J Infect Dis 2012; Backus LI, et al. Clin Gastroenterol Hepatol 2011; El-Kamary S, et al. Clin Infect Dis 2011; Hsu YC, et al. Hepatology 2014; Kawamura Y, et al. Am J Med 2007; Adinolfi LE, et al. WJG 2014

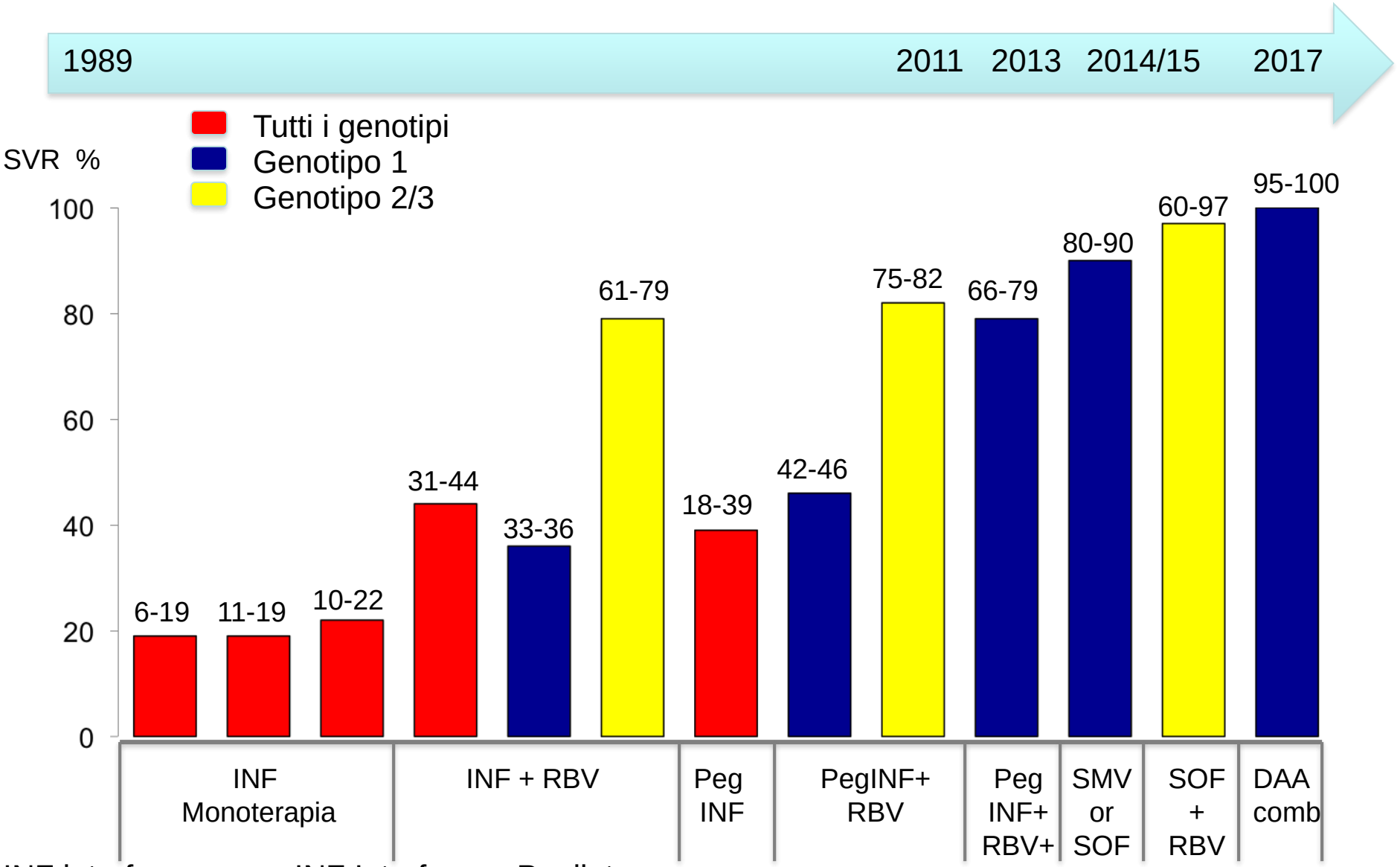
Epatite C e rischio di morte: cause epatiche ed extraepatiche

Cause di morte	Anti HCV+/ HCV Rna Negativo	Anti HCV +/HCV Rna Positivo	P
Tutte le cause	0.97 (0.70-1.35)	2.20 (1.90-2.55)	<0.0001
Malattie epatiche	2.19 (0.81-5.97)	16.36 (12.09-22.13)	<0.0001
Tumore fegato	4.70 (1.68-13.11)	28.02 (18.96-41.41)	<0.0001
Malattie croniche di fegato e cirrosi		7.37 (4.22-12.87)	<0.0001
Malattie extraepatiche	0.90 (0.64-1.28)	1.47 (1.23-1.77)	<0.0002
Malattie cardiocircolatorie	1.16 (0.62-2.17)	1.53 (1.05-2.23)	<0.026
Sindrome nefrosica /nefrite	1.66 (0.40-6.81)	2.98 (1.43-6.22)	<0.0032
Tumore esofago		5.86 (1.98-17.35)	<0.0014
Tumore prostata		5.83 (1.64-20.77)	<0.0065
Tumore tiroide		7.07 (0.73-68.35)	<0.09

Lee M-H, J Infect Dis 2012

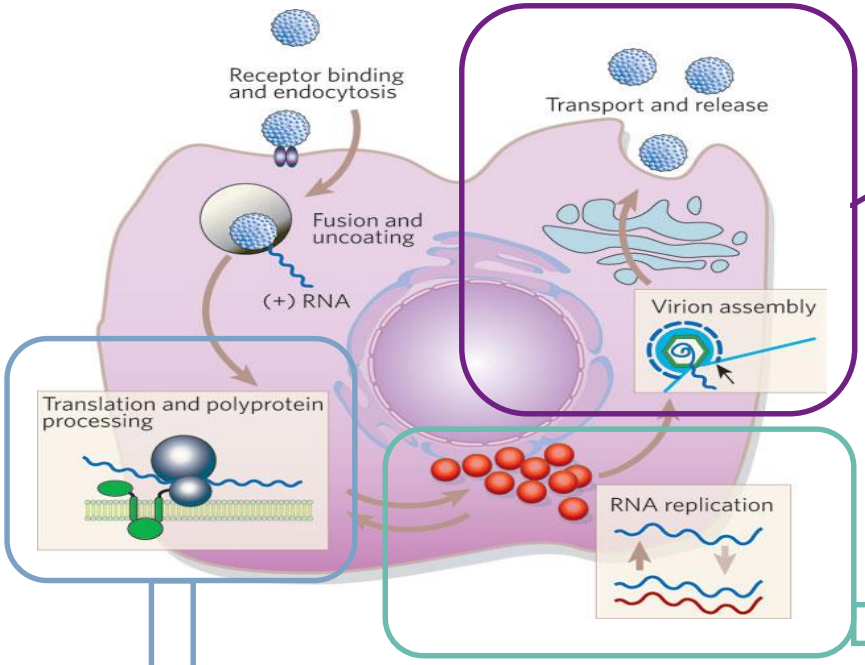
HCV Treatment

EVOLUZIONE DEL TRATTAMENTO DELL'EPATITE DA HCV



INF interferone; peg INF Interferone Pegilato;
RBV Ribavirina; BOC Bocepreir, TVR telaprevir;
SMV Simeprevir; SOF Sofosbuvir; DAA Antivirali diretti
SVR Risposta virologica sostenuta

Direct-Acting Antivirals for the Treatment of Hepatitis C Infection



NS5A inhibitor

- Ombitasvir (OBV)*
- Ledipasvir (LDV)†
- Daclatasvir (DCV)
- Elbasvir (EBR)‡
- Pibrentasir (PIB) §
- Velpatasvir (VEL)‖

NS5B polymerase inhibitor

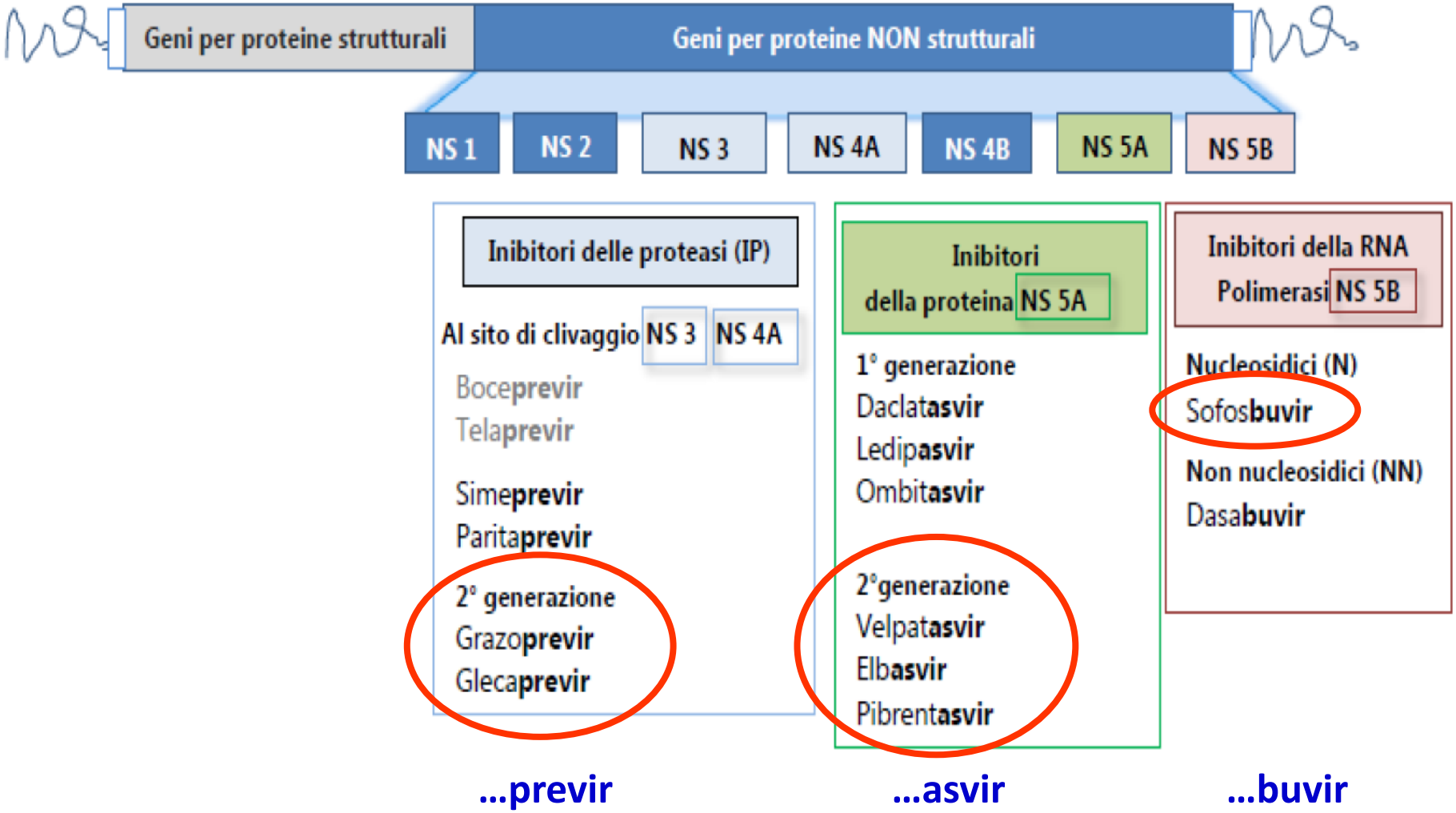
- Sofosbuvir (SOF)† ‖
- Dasabuvir (DSV)*

NS3/4A protease inhibitors

- Paritaprevir (PTV)*
- Simeprevir (SMV)
- Grazoprevir (GZR)‡
- Glecaprevir (GLE) §
- Voxilaprevir (VOX)

* OBV/PTV/r co-formulated (Viekirax), DSV (Exviera); † LDV/SOF co-formulated (Harvoni);
‡ EBR/GZR co-formulated; ‖ SOF/VEL co-formulated; § GLE/PIB co-formulated (Maviret)

Antivirali ad azione diretta anti HCV (DAA)

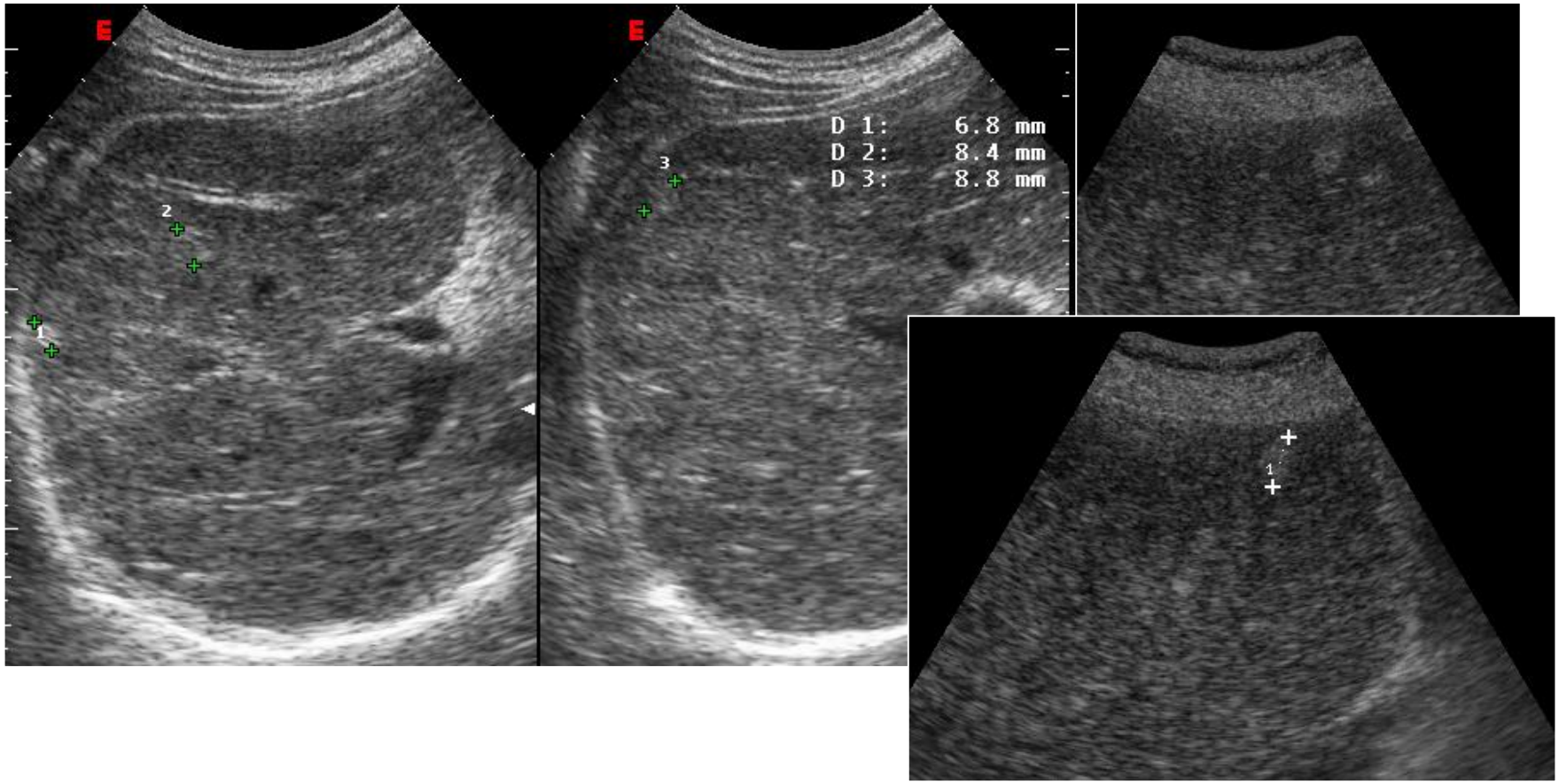


Valutazione del malato affetto da infezione da HCV

E' indispensabile eseguire una ecografia nel pazienete HCV+ per:

- Valutare l'ecostruttura del parenchima epatico, la presenza e il grado di una eventuale steatosi (cofattore di danno epatico)
- Valutazione di una epatopatia evoluta (ecostruttura granulosa, Ipertrofia del lobo di sinistra, profili irregolari, presenza di ascite)
- Valutazione di lesioni focali (sorveglianza semestrale nell'epatopatia evoluta unita al dosaggio dell'alfa fetoproteina)
- Valutazione della presenza ipertensione portale (aumento di calibro della vena porta, della vena splenica , splenomegalia, flusso portale)
- Valutazione di complicanze vascolari (trombosi portale etcc)

Lesioni "hemangioma-like"



44 noduli "hemangioma-like"
alla prima osservazione (*casi prevalenti*): → 22 HCC e 22 angiomi

26 noduli "hemangioma-like" durante
follow-up (*casi incidenti*): → 22 HCC e 4 HGDN

Caturelli et al, Radiology 2001

Nuovi Criteri AIFA per il trattamento dell'epatite HCV correlata

Criterio 1: Pazienti con cirrosi in classe di Child A o B e/o con HCC con risposta completa a terapie resettive chirurgiche o loco-regionali non candidabili a trapianto epatico nei quali la malattia epatica sia determinante per la prognosi.
Criterio 2: Epatite ricorrente HCV-RNA positiva del fegato trapiantato in paziente stabile clinicamente e con livelli ottimali di immunosoppressione.
Criterio 3: Epatite cronica con gravi manifestazioni extra-epatiche HCV-correlate (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B, insufficienza renale).
Criterio 4: Epatite cronica con fibrosi METAVIR F3 (o corrispondente Ishak).
Criterio 5: In lista per trapianto di fegato con cirrosi MELD <25 e/o con HCC all'interno dei criteri di Milano con la possibilità di una attesa in lista di almeno 2 mesi.
Criterio 6: Epatite cronica dopo trapianto di organo solido (non fegato) o di midollo in paziente stabile clinicamente e con livelli ottimali di immunosoppressione.

Criterio 7: Epatite cronica con fibrosi METAVIR F2 (o corrispondente Ishak) e/o comorbilità a rischio di progressione del danno epatico [coinfezione HBV, coinfezione HIV, malattie croniche di fegato non virali, diabete mellito in trattamento farmacologico, obesità (body mass index ≥30 kg/m^2), emoglobinopatie e coagulopatie congenite].
Criterio 8: Epatite cronica con fibrosi METAVIR F0-F1 (o corrispondente Ishak) e/o comorbilità a rischio di progressione del danno epatico [coinfezione HBV, coinfezione HIV, malattie croniche di fegato non virali, diabete mellito in trattamento farmacologico, obesità (body mass index ≥30 kg/m^2), emoglobinopatie e coagulopatie congenite].
Criterio 9: Operatori sanitari infetti.
Criterio 10: Epatite cronica o cirrosi epatica in paziente con insufficienza renale cronica in trattamento emodialitico.
Criterio 11: Epatite cronica nel paziente in lista d'attesa per trapianto di organo solido (non fegato) o di midollo.

Terapia Epatite C - 2018

- Terapia tutta solo orale
- Una sola somministrazione giornaliera
- Durata 8 - 12 settimane
- Effetti collaterali minimi o assenti
- Alcune (poche) interazioni farmacologiche di rilievo
- Eliminazione dell’infezione HCV > 95%
- Costo medio per intera terapia ~ 6.000 euro
- Tutti i pazienti possono essere trattati indipendentemente dallo stadio della malattia

Interazioni farmacologiche

www.hep-druginteractions.org

UNIVERSITY OF LIVERPOOL

Interaction Report

Report ID:
Date Produced: 27 November 2017

Hepatitis Treatment	Co-medications
Glecaprevir/Pibrentasvir	Amlodipine Bisoprolol Buprenorphine

This report lists the summaries of potential interactions (i.e. "red", "amber" and “yellow” classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown. Please note that some co-medications with a green classification may require dose adjustment due to hepatic impairment.

For full details of all interactions, see www.hep-druginteractions.org .

Description of the interactions

No clinically significant interaction expected (GREEN)

Glecaprevir/Pibrentasvir + Amlodipine

Glecaprevir/Pibrentasvir + Bisoprolol

Glecaprevir/Pibrentasvir + Buprenorphine

Interazioni farmacologiche

www.hep-druginteractions.org

UNIVERSITY OF LIVERPOOL

Interaction Report

- Seranase
- Seroquel
- Rivotril
- Depakin
- Medadone
- Akineton
- Cannabis

LG EASL Aprile 2018

Table 7. Treatment recommendations for HCV-monoinfected or HCV/HIV-coinfected patients with chronic hepatitis C without cirrhosis, including treatment-naïve patients (defined as patients who have never been treated for their HCV infection) and treatment-experienced patients (defined as patients who were previously treated with pegylated IFN-α and ribavirin; pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirin).

Patients	Prior treatment experience	SOF/VEL	GLE/PIB	SOF/VEL/VOX	SOF/LDV	GZR/EBR	OBV/PTV/r + DSV
Genotype 1a	Treatment-naïve	12 wk	8 wk	No	8-12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	No
	Treatment-experienced	12 wk	8 wk	No	No	12 wk (HCV RNA ≤800,000 IU/ml)	No
Genotype 1b	Treatment-naïve	12 wk	8 wk	No	8-12 wk	8 wk (F0-F2) 12 wk (F3)	8 wk (F0-F2) 12 wk (F3)
	Treatment-experienced	12 wk	8 wk	No	12 wk	12 wk	12 wk
Genotype 2	Treatment-naïve	12 wk	8 wk	No	No	No	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No
Genotype 3	Treatment-naïve	12 wk	8 wk	No	No	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 4	Treatment-naïve	12 wk	8 wk	No	12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No
Genotype 5	Treatment-naïve	12 wk	8 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No
Genotype 6	Treatment-naïve	12 wk	8 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

LG EASL Aprile 2018

Table 8. Treatment recommendations for HCV-monoinfected or HCV/HIV-coinfected patients with chronic hepatitis C with compensated (Child-Pugh A) cirrhosis, including treatment-naïve patients (defined as patients who have never been treated for their HCV infection) and treatment-experienced patients (defined as patients who were previously treated with pegylated IFN-α and ribavirin; pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirin).

Patients	Prior treatment experience	SOF/VEL	GLE/PIB	SOF/VEL/VOX	SOF/LDV	GZR/EBR	OBV/PTV/r + DSV
Genotype 1a	Treatment-naïve	12 wk	12 wk	No	12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	No
	Treatment-experienced	12 wk	12 wk	No	No	12 wk (HCV RNA ≤800,000 IU/ml)	No
Genotype 1b	Treatment-naïve	12 wk	12 wk	No	12 wk	12 wk	12 wk
	Treatment-experienced	12 wk	12 wk	No	12 wk	12 wk	12 wk
Genotype 2	Treatment-naïve	12 wk	12 wk	No	No	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 3	Treatment-naïve	No	12 wk	12 wk	No	No	No
	Treatment-experienced	No	16 wk	12 wk	No	No	No
Genotype 4	Treatment-naïve	12 wk	12 wk	No	12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 5	Treatment-naïve	12 wk	12 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 6	Treatment-naïve	12 wk	12 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

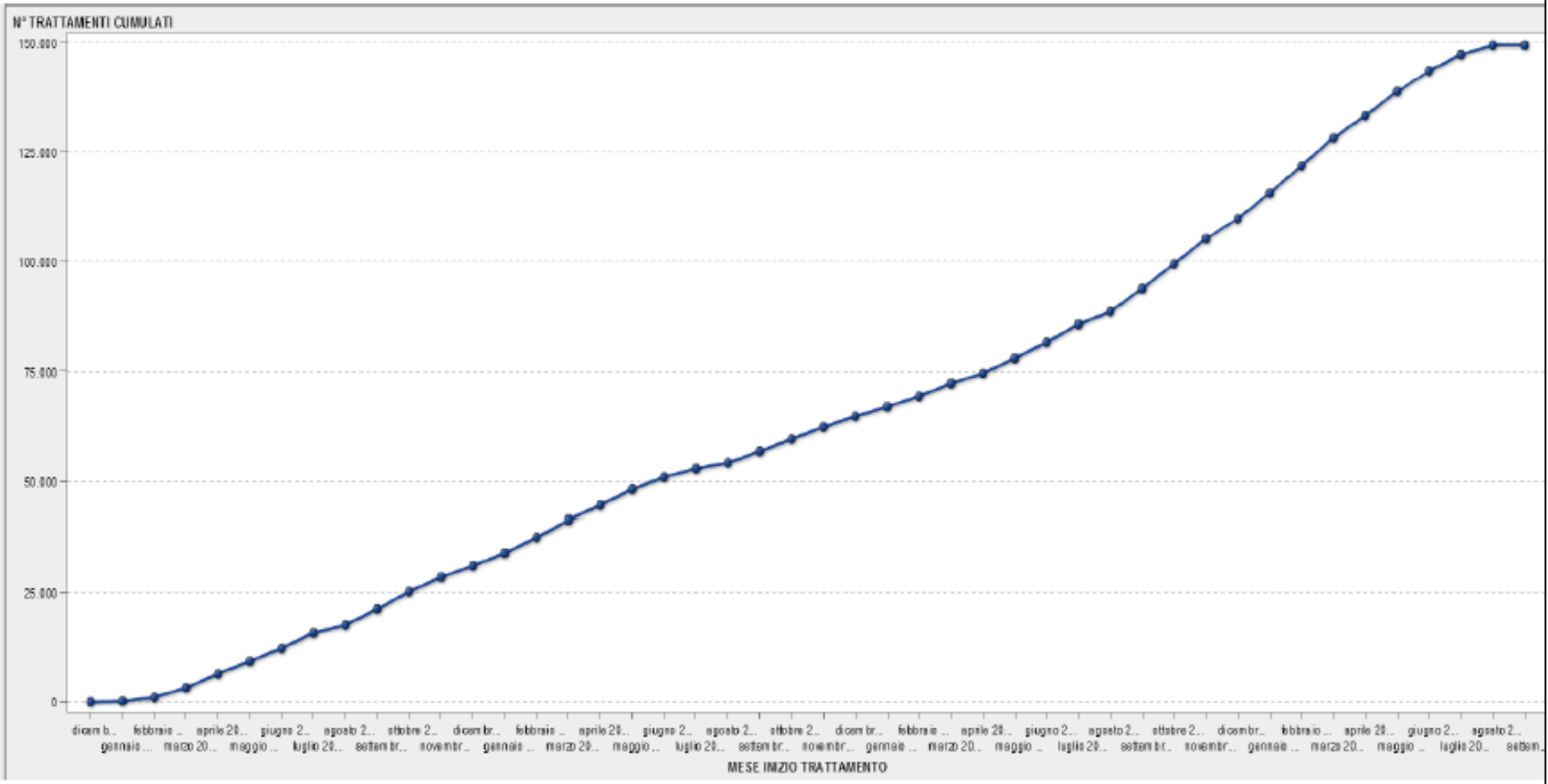
HCV Guidance: recommendations for testing, managing and treating Hepatitis C

Il trattamento è raccomandato per tutti i pazienti con infezione cronica da HCV, ad eccetto di quelli con un aspettativa di vita breve non modificabile dal trattamento dell'HCV, dal trapianto o da altre terapie

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

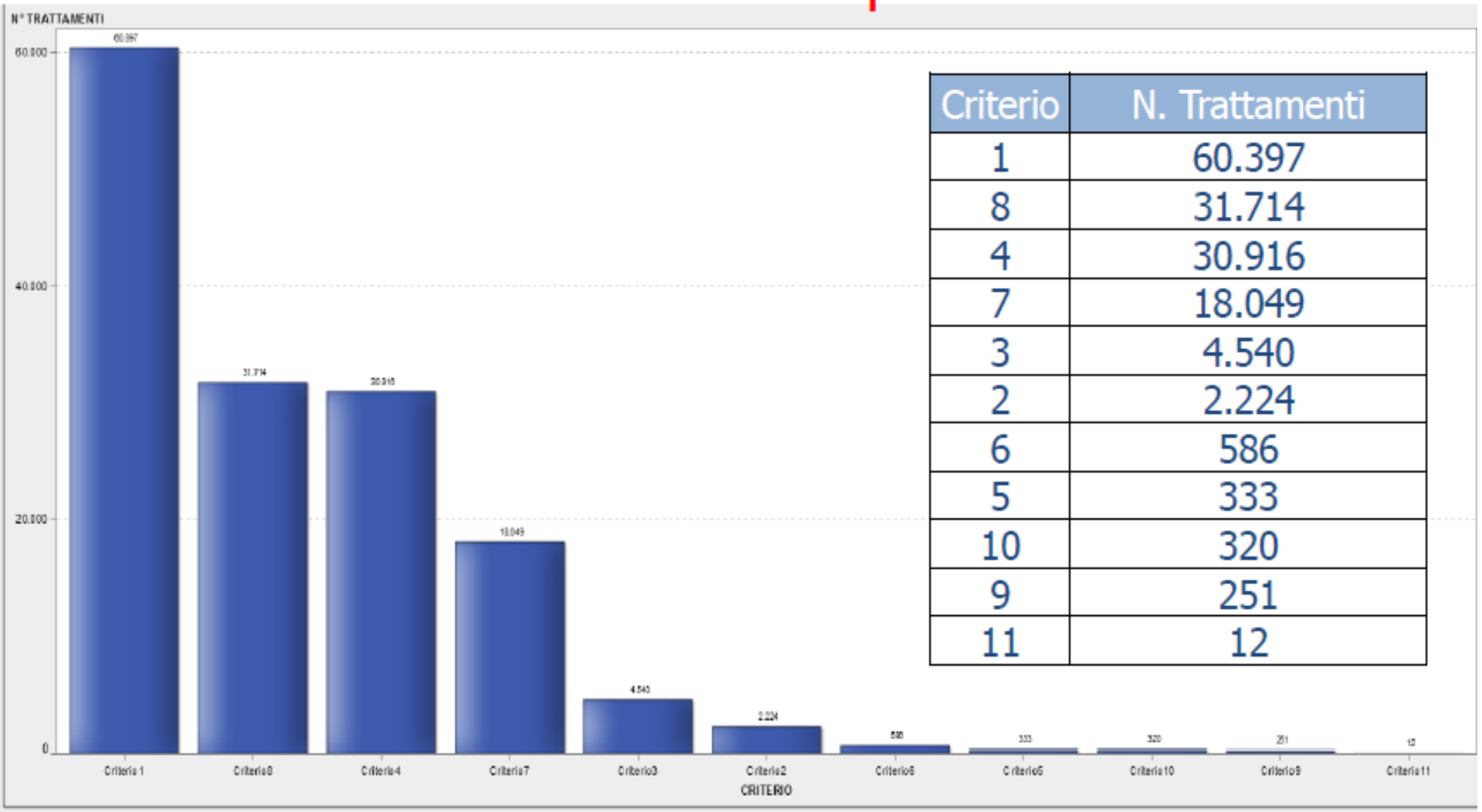
IDSA
Infectious Diseases Society of America

Trend cumulativo dei trattamenti avviati



149.342 «avviati» sono i trattamenti (solo pazienti eleggibili)
con almeno una scheda di Dispensazione farmaco

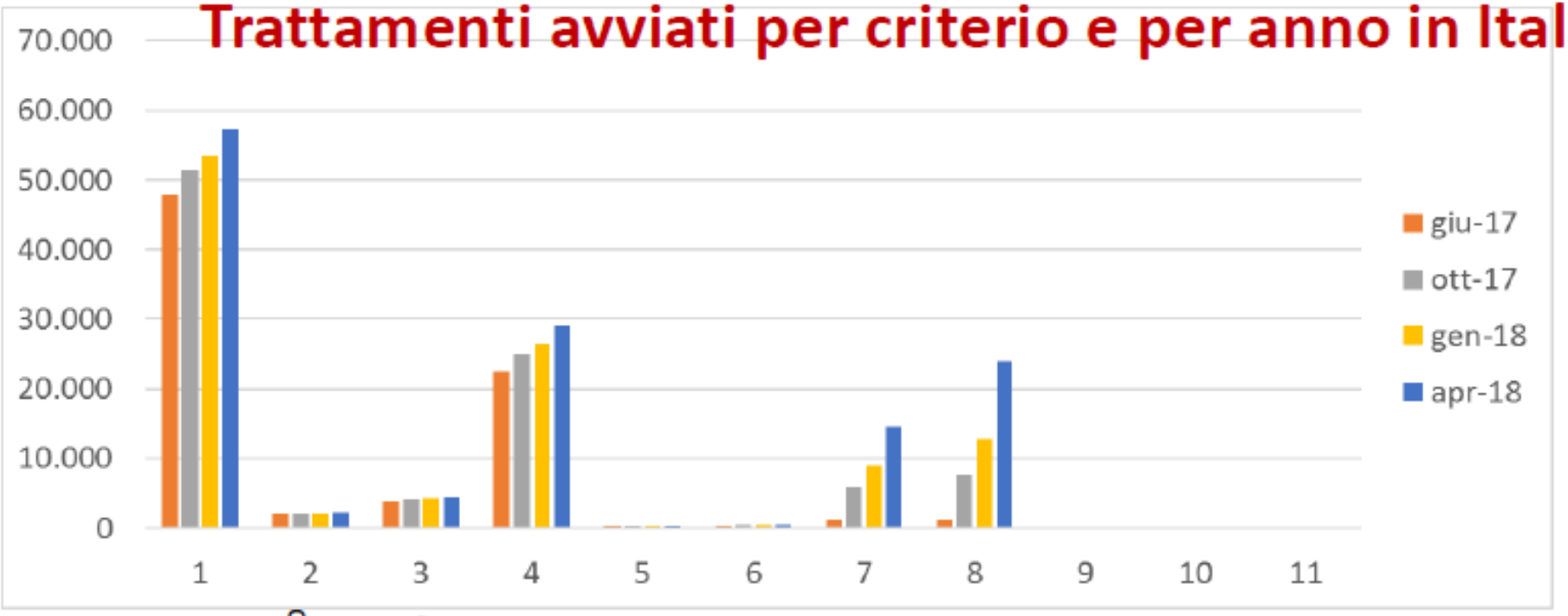
Trattamenti avviati per criterio



Criterio	N. Trattamenti
1	60.397
8	31.714
4	30.916
7	18.049
3	4.540
2	2.224
6	586
5	333
10	320
9	251
11	12

NB: I trattamenti avviati con il precedente criterio 7 sono stati distribuiti, sulla base della stadiazione METAVIR, nei nuovi criteri 7 e 8

Trattamenti avviati per criterio e per anno in Italia



criterio	giu-17	ott-17	gen-18	apr-18
1	47.912	51.422	53.550	57.294
2	1.979	2.056	2.091	2.165
3	3.828	4.101	4.242	4.425
4	22.498	25.036	26.483	29.015
5	309	321	322	326
6	401	457	487	552
7	**1.142**	**5.961**	**9.035**	**14.539**
8	**1.171**	**7.678**	**12.884**	**24.067**
9	**40**	**158**	**193**	**232**
10	**17**	**87**	**136**	**248**
11	0	5	5	9

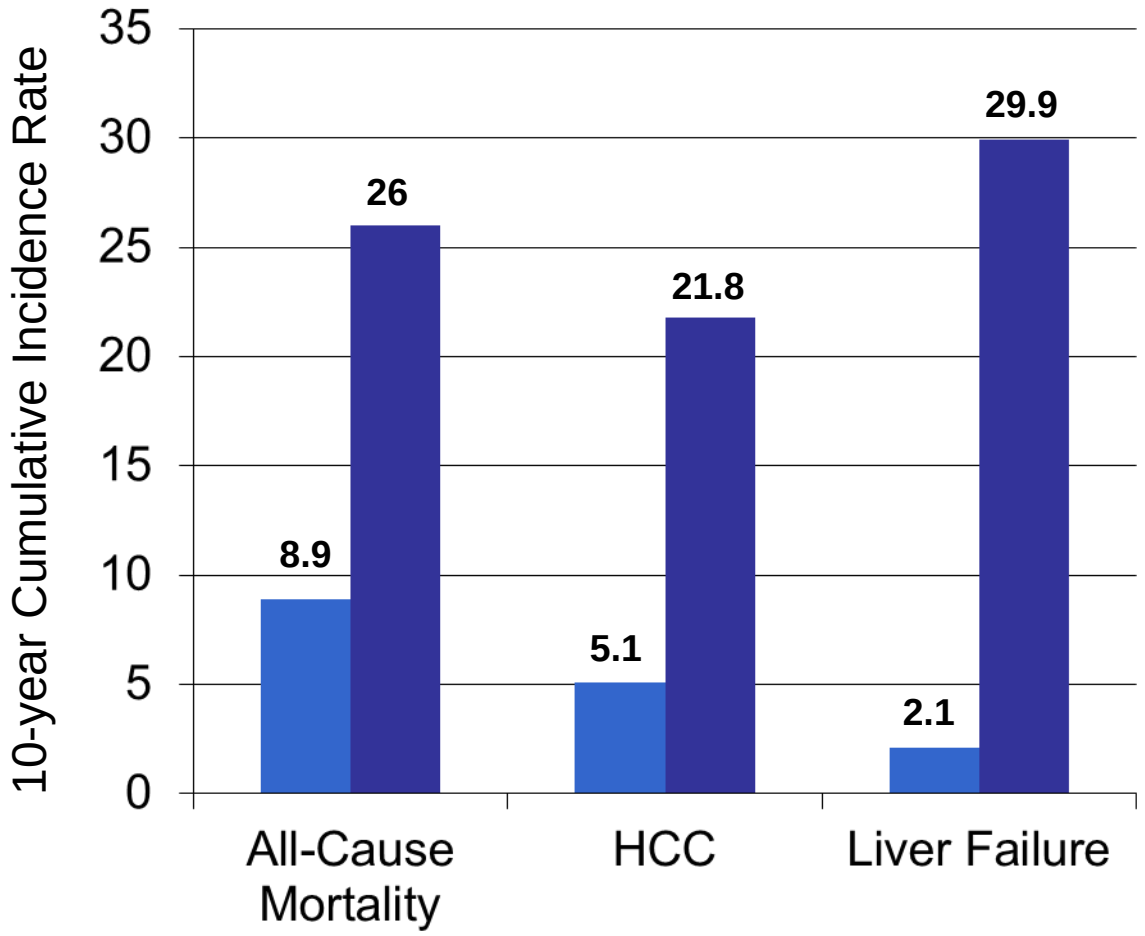
GENOTIPO PER CRITERIO AIFA

Genotipo	N pz	Pz Residenti	Pz domiciliati in RER	Pz Extra RER
1	10	9	1	
1a	458	418	34	6
1b	647	612	20	15
2	330	312	9	9
3	364	331	26	7
4	166	154	9	3
altro	3	3		
totale	**1.978**	**1.839**	**99**	**40**

	Criterio AIFA											
GENOTIPO	**1 cirrotici**	**2**	**3**	**4 F3**	**5**	**6**	**7 F2**	**8 F0-F1**	**9**	**10**	**11**	***totale per Genotipo***
1	1			3			3	3				*10*
1a	52	1	4	42		1	84	271	3			*458*
1b	71	1	11	65			126	364	6	3		*647*
2	34	2	8	20		3	58	204		1		*330*
3	56	1	2	49	1	1	91	162	1			*364*
4	22		4	10			38	92				*166*
altro							1	2				*3*
totale per criterio AIFA	*236*	*5*	*29*	*189*	*1*	*5*	*401*	*1.098*	*10*	*4*	*0*	*1.978*

HCV Advantage of treatment

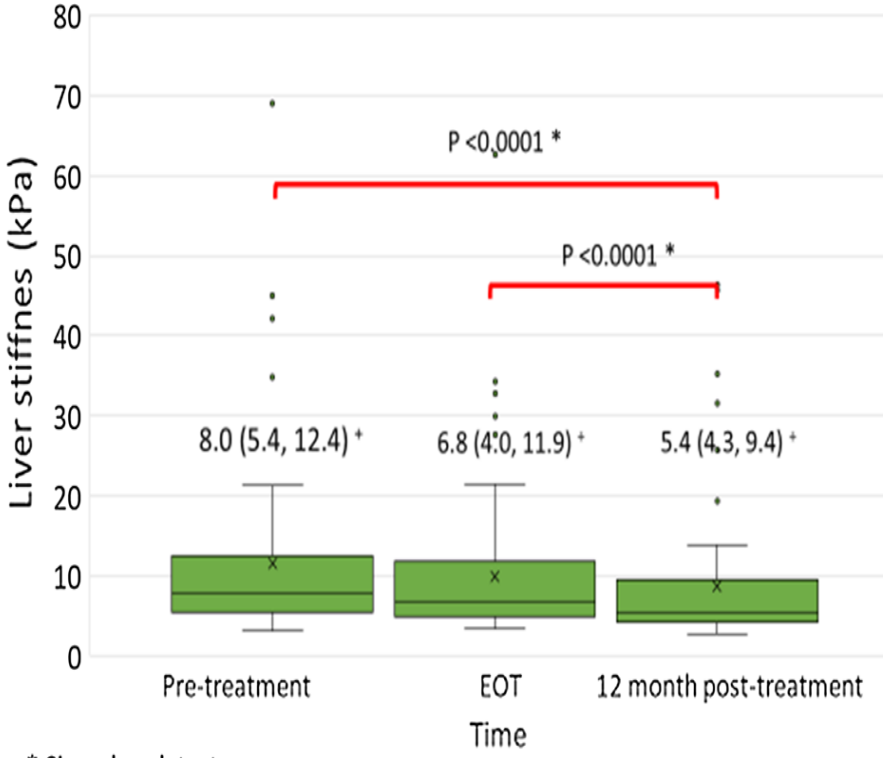
SVR (Cure) Associated with Decreased All-Cause Mortality



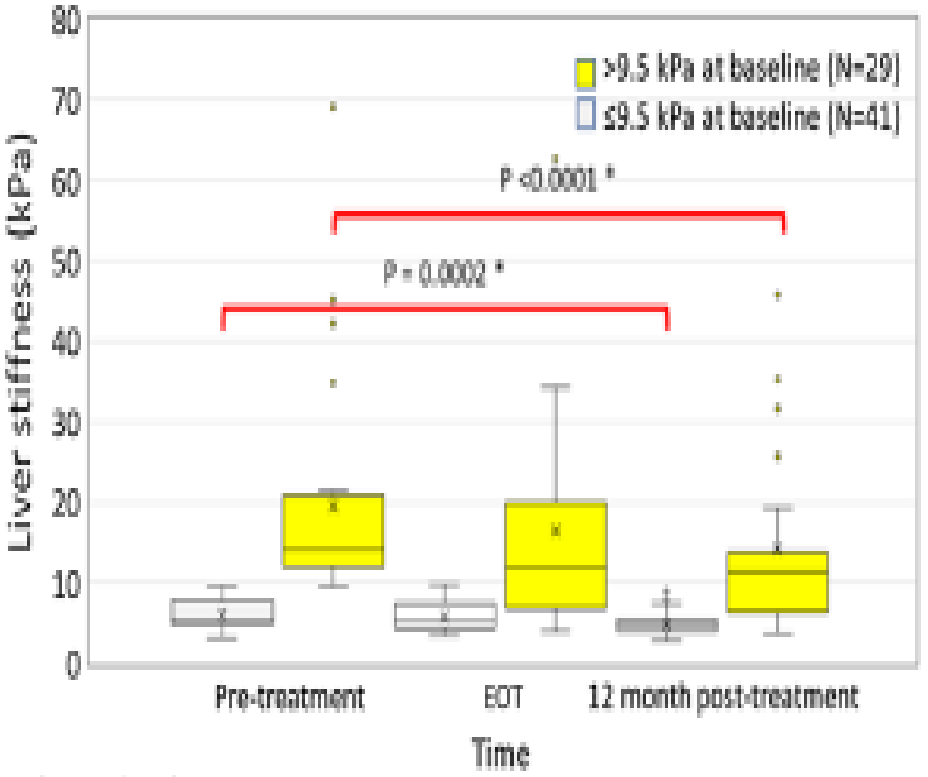
530 patients with advanced fibrosis, treated with interferon-based therapy, and followed for 8.4 (IQR 6.4-1.4) years

Van der Meer et al. JAMA 2012; 308:2584

Direct-Acting Antiviral Therapy for Chronic HCV Infection Results in Liver Stiffness Regression Over 12 Months Post treatment



* Signed rank test
+ Median and (IQR)
EOT = end of treatment

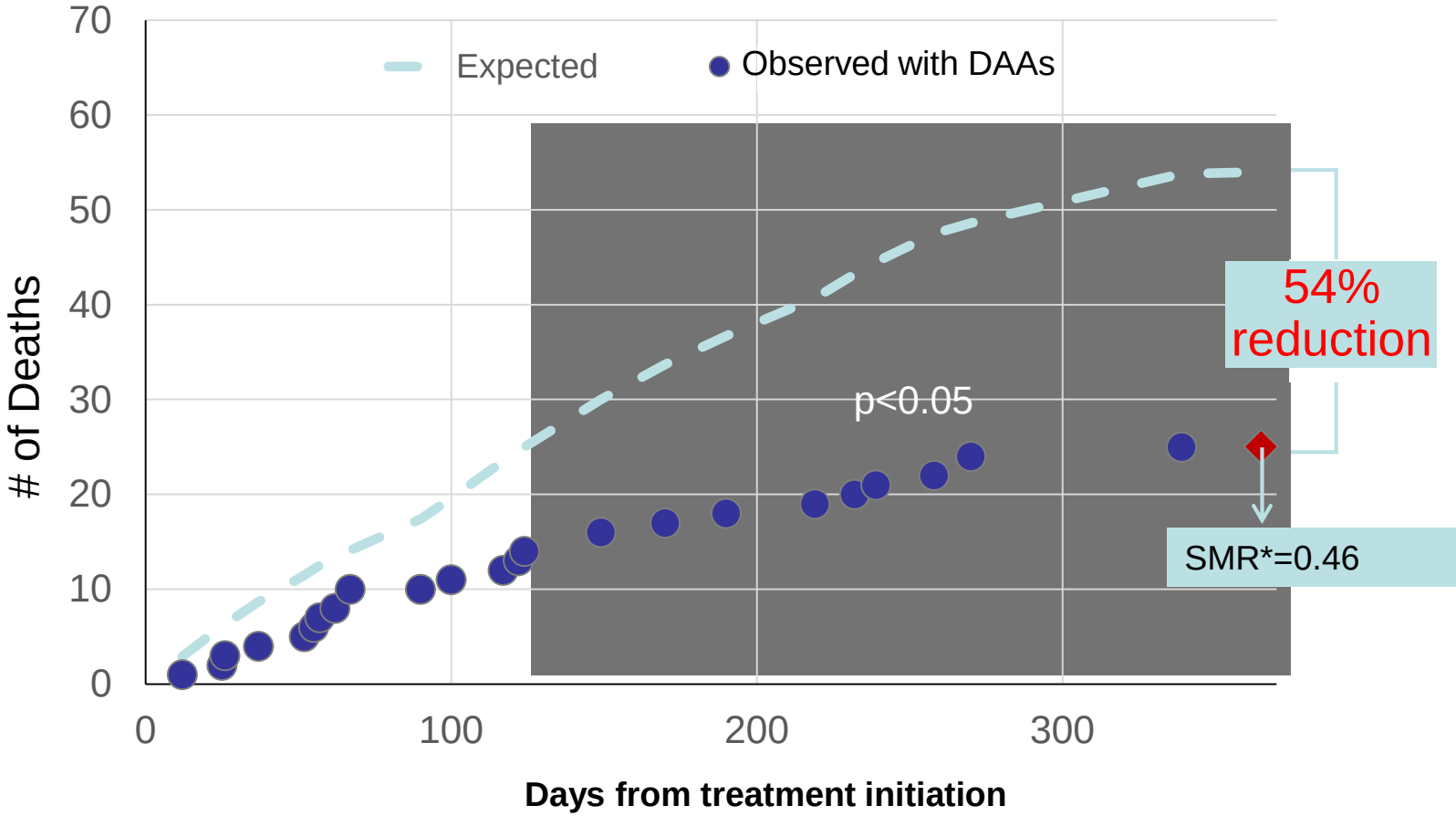


* Signed rank test
EOT = end of treatment

Chan J et al Dig Dis Sci (2018) 63:486–492

Survival Benefits of DAA in Patients with Decompensated Cirrhosis

Comparison of Incidence of deaths in 463 decompensated patients in SOLAR and ASTRAL-4 studies with the expected incidence.



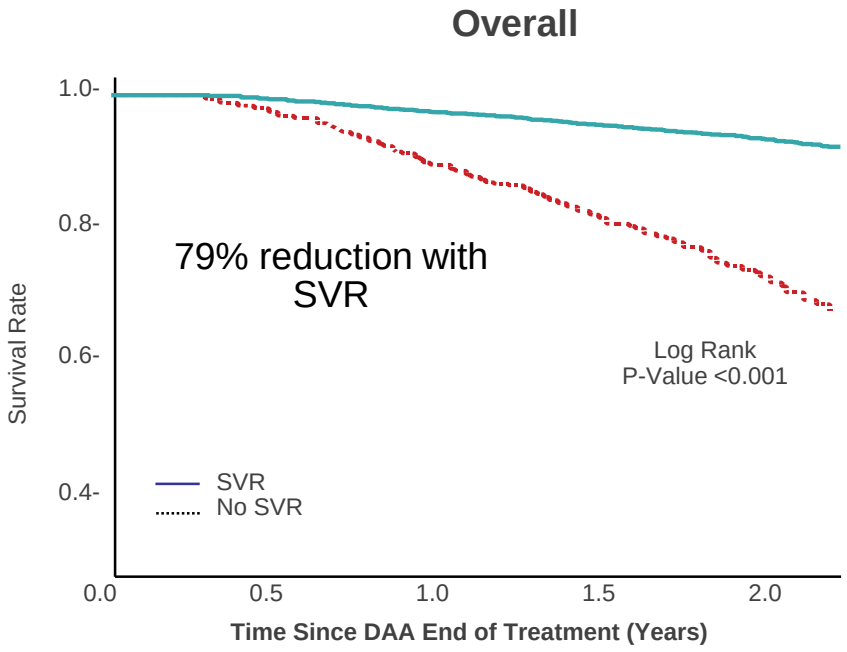
DAA treatment is associated with a significant decrease in mortality risk in patients with decompensated HCV cirrhosis.

Kim, EASL 2018, PS-151

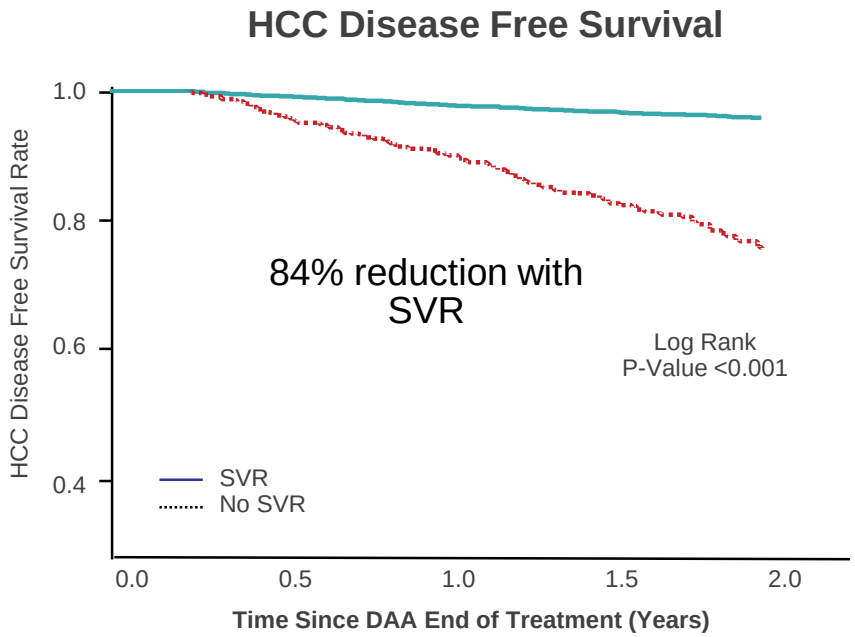
*Standardized Mortality Ratio

Survival Curves for ACLD Patients with and without SVR

Patients with HCV infection, FIB-4 > 3.25 in VA HCV Clinical Case Registry (N = 15,059)



No SVR	1067	923	650	326	105
SVR	13992	12939	9521	5437	1875

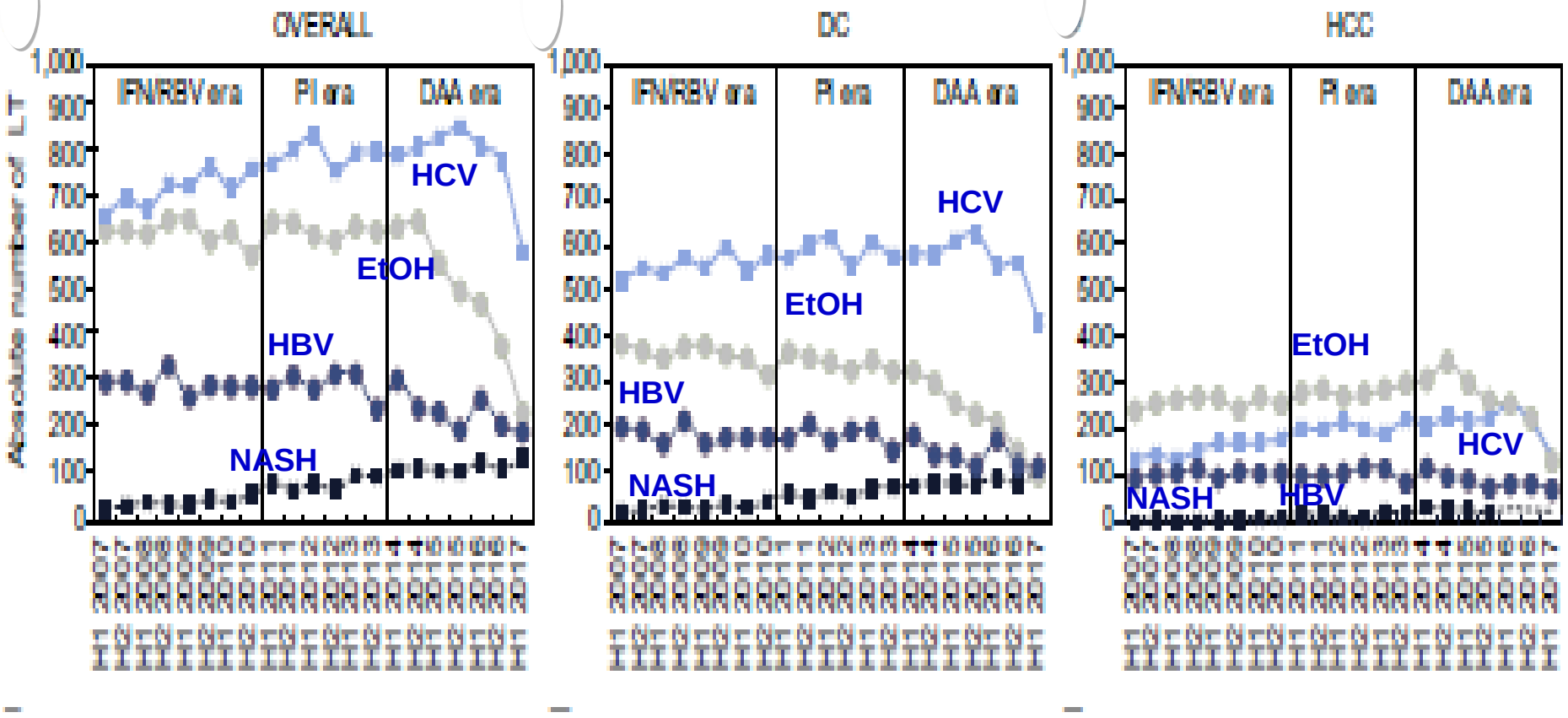


No SVR	871	844	650	425	181
SVR	13153	13070	10759	7482	3588

Increasing access to DAAs for ACLD patients should result in fewer overall deaths

Backus, AASLD, 2017, oral 78

Absolute number of LT by etiology of liver disease and indication for LT.



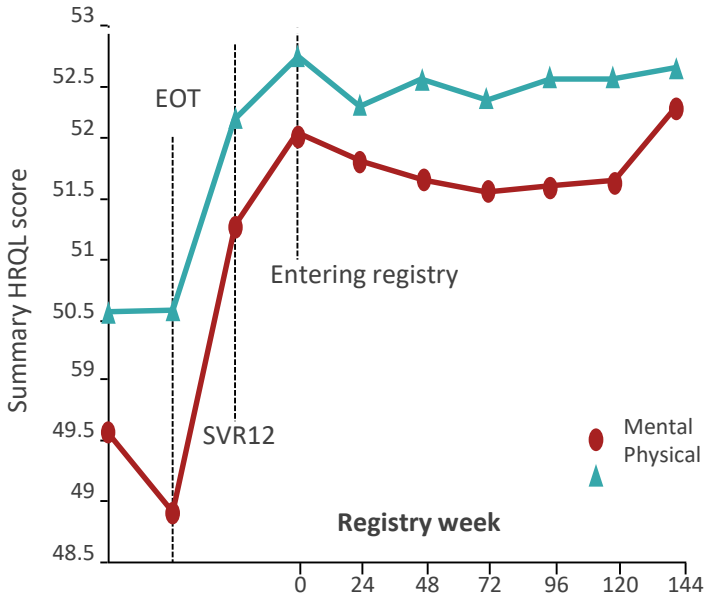
Number of LT -58% HCV- DC, HCV-HCC -41%;
Almost 30% HCV-DC Delisted (Waiting list and with low priority)
Survival improve from 65.1% to 76.9% in DAA era compared with HBV

Belli LS et al J Hepatol 2018

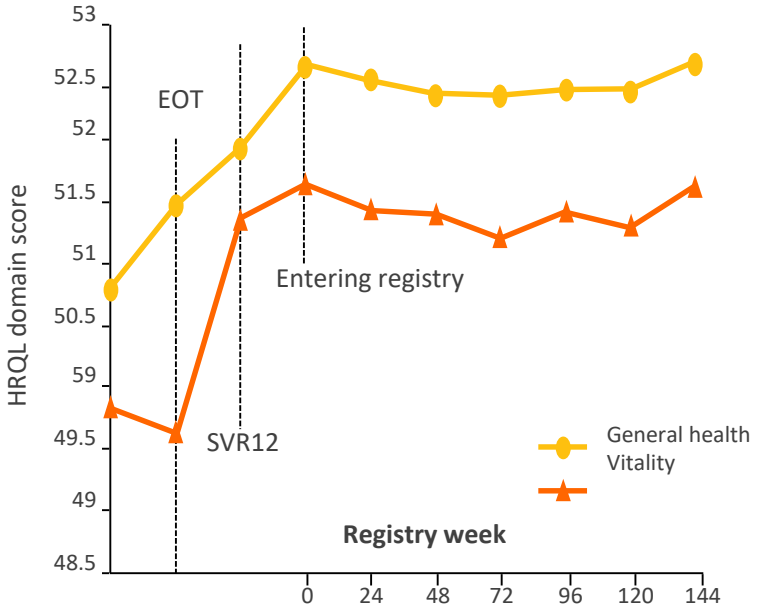
Health-Related Quality Of Life Scores In Patients With HCV and SVR

HRQL outcomes in 3486 patients with SVR12

SF-36 summary scores



Greatest HRQL gains consistently observed General Health and Vitality domains



Improvement in HRQL after achieving SVR is maintained in the long-term follow up

Younossi ZM, et al. AASLD 2017, #64

Characteristics of 182 patients with advanced fibrosis/compensated Cirrhosis due to HCV infection.

Variable	Chronic hepatitis C with advanced fibrosis/cirrhosis (N = 182)
Male gender (%)	56
Age (years)	63.1 ± 10.4
Age >65 years (%)	47.3
BMI (kg/m^2)	25.6 ± 3.7
BMI ≥30 (kg/m^2)	14.3
Blood glucose (mg/dl)	103.5 ± 23.2
Type 2 diabetes (%)	19.8
Arterial hypertension (%)	41.8
Total cholesterol (mg/dl)	159.9 ± 29.5
Smoking (%)	35.2
IMT (mm)	0.94 ± 0.29
IMT ≥1 mm (%)	42.9
Carotid plaques (%)	42.9
ALT (IU/L)	81.9 ± 49.5
PLT (10^3/μl)	153.3 ± 64.3
HCV genotype 1/1a/1b/2/3/4	0.5/8.2/83.4/1.1/2.2/1.6
HCV RNA (Log)	5.8 ± 0.6
Cirrhosis (%)	65.9

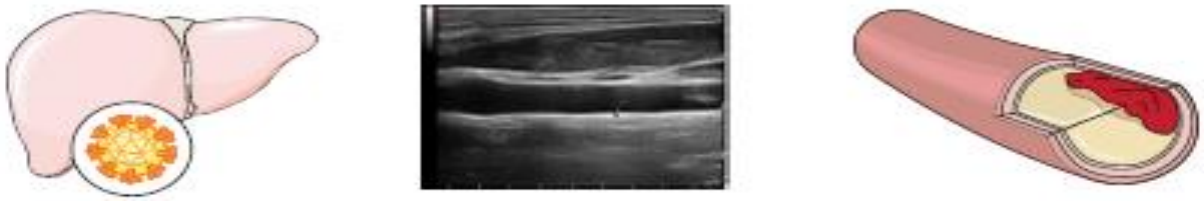
BMI, body mass index; IMT, intimamedia thickness, ALT, alanine aminotransferase; PLT, platelet;

Petta S et al J Hepatol 2018

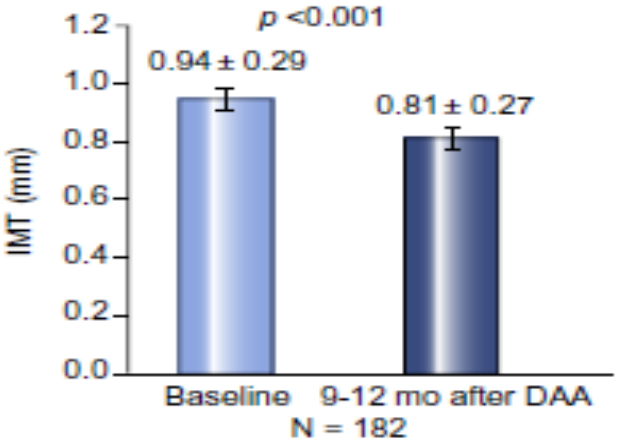
Research Article
Viral Hepatitis

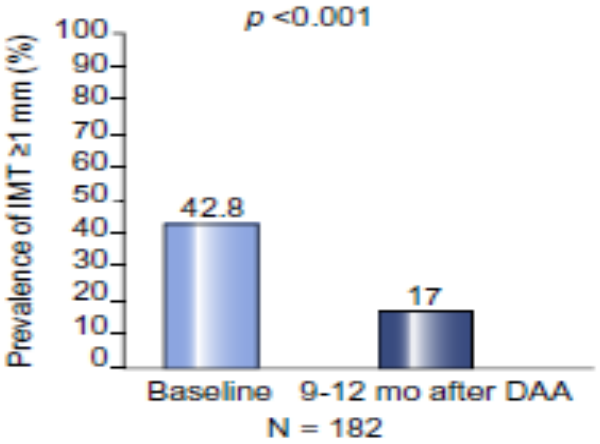
JOURNAL
OF HEPATOLOGY

Hepatitis C virus eradication by direct-acting antiviral agents improves carotid atherosclerosis in patients with severe liver fibrosis



Ultrasonographic assessment of intima-media thickness and carotid thickening in patients with advanced fibrosis/compensated cirrhosis due to HCV infection: Impact of SVR by DAA

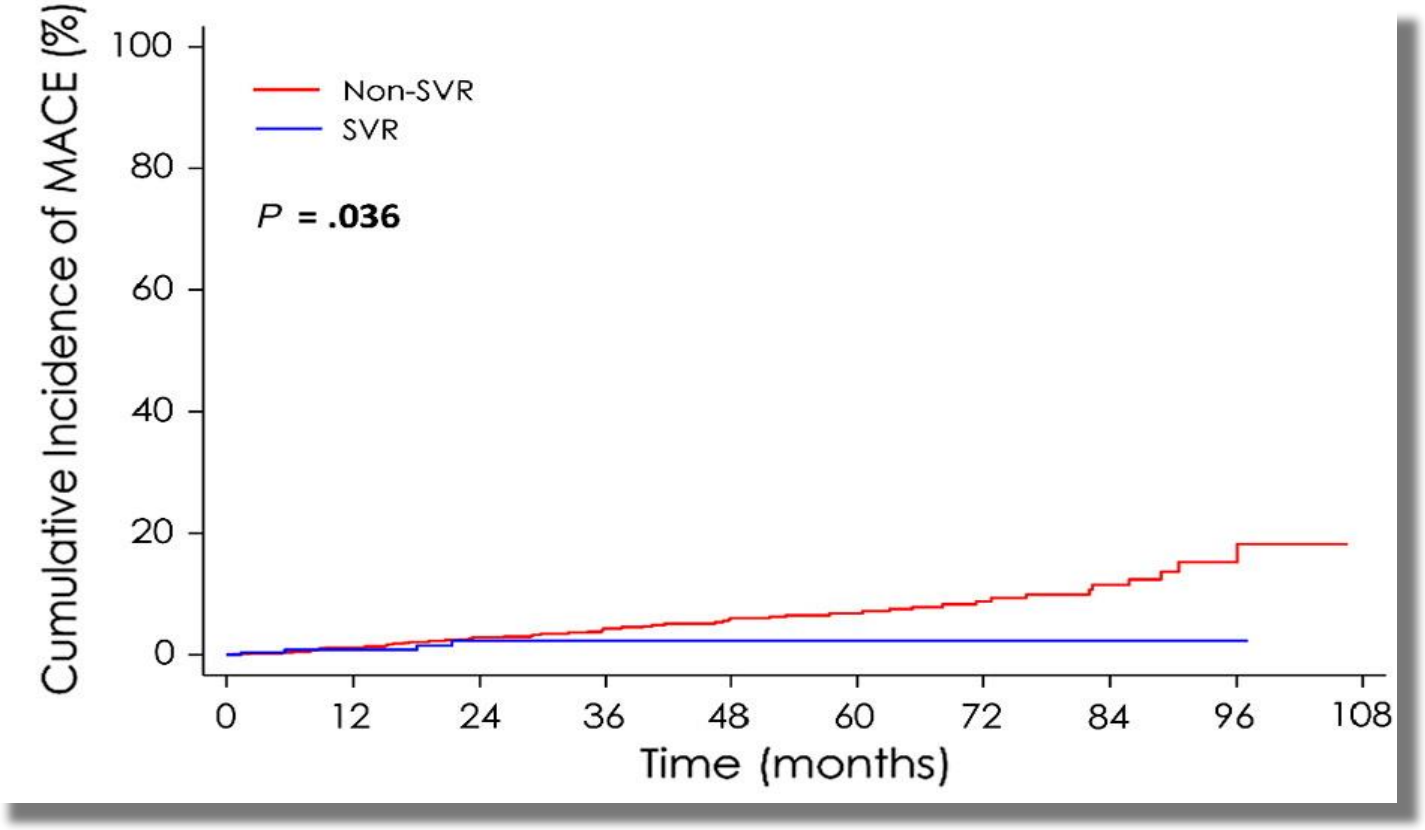




Petta S et al J Hepatol 2018

HCV & Malattie Cardio-Vascolari

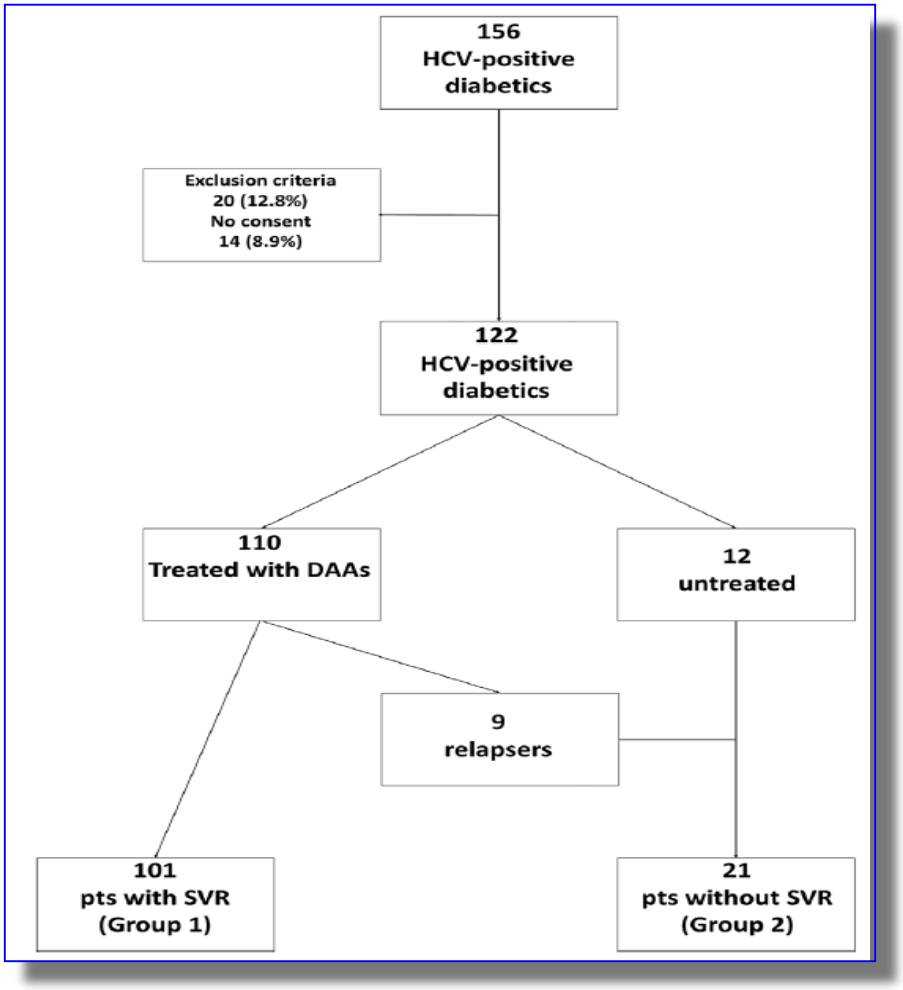
Impatto della guarigione su eventi cardiovascolari



Cacoub P et al, Am Heart J 2018

HCV & DM Tipo II

Impatto della guarigione: popolazione



Ciancio A. et al., J Med Virol 2018

HCV & DM Tipo II

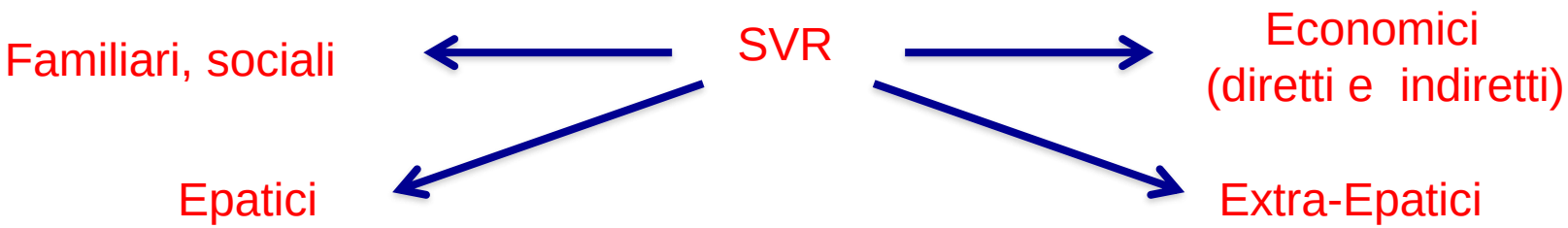
Impatto della guarigione: risultati

TABLE 4 Anthropometric, biochemical, and metabolic variations in sustained responders and relapsing/untreated patients

	Group 1 (101 patients)			Group 2 (21 patients)		
	Baseline	End of study	*P*	Baseline	End of study	*P*
AST (IU/mL)[a]	42.3 ± 37.6	28.2 ± 11.0	0.02	40.3 ± 38.4	42.2 ± 39.8	0.85
ALT (IU/mL)[a]	81.2 ± 77.2	36.0 ± 12.0	<0.001	78.7 ± 67.3	82.2 ± 71.6	0.74
GGT (IU/mL)[a]	87.8 ± 81.0	62.5 ± 73.2	0.02	65.2 ± 64.0	67.0 ± 68.1	0.43
Bilirubin (mg/dL)[b]	1.0 (0.6-1.8)	0.8 (0.7-1.1)	0.12	0.9 (0.6-1.3)	1.0 (0.7-1.4)	0.52
Albumin (g/L)[b]	42 (31-48)	44 (33-49)	0.09	43 (34-47)	42 (33-48)	0.78
INR[b]	1.3 (1.0-1.8)	1.0 (1.0-1.5)	0.08	1.2 (1.0-1.7)	1.3 (1.0-2.1)	0.33
Leukocytes ($x10^3$/μL cells)[b]	4.2 (2.2-7.8)	5.4 (3.3-8.2)	0.07	4.4(2.8-6.2)	4.1 (2.3-7.3)	0.64
Platelets ($x10^3$/μL cells)[b]	155 (62-287)	173 (52-274)	0.08	164 (73-245)	162 (68-274)	0.35
Glucose (mg/dL)[a]	152.4 ± 56.4	134.3 ± 41.3	0.002	145.3 ± 30.2	140.0 ± 47.9	0.71
HbA1c (mmoL/moL)[a]	52.2 ± 15.4	46.5 ± 16.2	<0.001	53.4 ± 9.5	55.3 ± 20.6	0.78
HOMA-IR[a]	5.2 ± 2.5	3.1 ± 1.6	<0.001	4.9 ± 2.6	4.6 ± 2.3	0.29
Body weight (kg)[a]	75.3 ± 13.7	77.9 ± 19.8	0.02	76.6 ± 19.3	76.9 ± 20.7	0.56

Ciancio A. et al., J Med Virol 2018

I benefici potenziali della SVR



Riduzione
- Infiammazione
- Fibrosi
- Cirrosi
- Ipertensione portale: sanguinamemto da varici
- Scompenso: Ascite ecefalopatia
- Epatocarcinoma

Potenziale riduzione
- Crioglobulinemia
- Linfoma B cellulare Non H
- Insufficienza renale
- Linchen Planus, sd Sjogren
- Resistenza insulinica e diabete tipo 2
- Rischio di Ictus e ichemia miocardica
- Fatica e depressione
- Miglioramento funzione neurocognitiva
- Miglioramento del HRQoL e della produzione lavorativa

Riduzione della morbilità e mortalità epatica

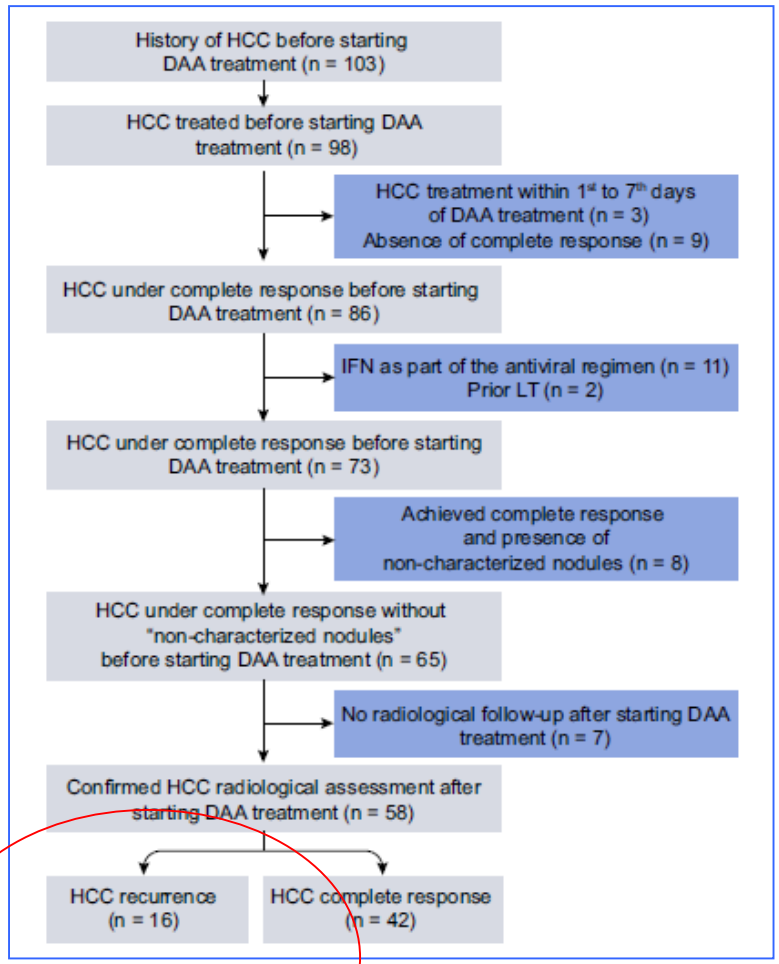
Riduzione della morbilità e mortalità extraepatica

Riduzione di tutte le cause di morte

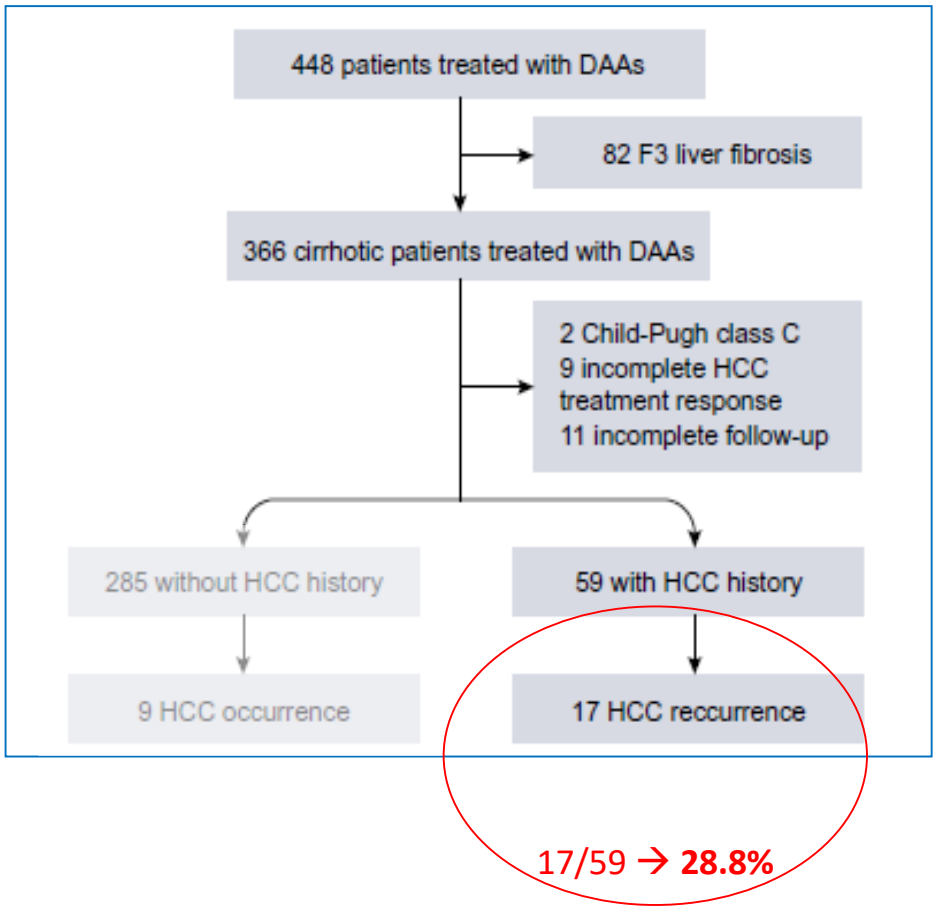
Metwally MA, et al. Gastroenterology 2003; van der Meer AJ, et al. JAMA 2012; Arase Y, et al. Hepatology 2009; Ware JJ, et al. Hepatology 1999

HCV treatment and HCC

HCC recurrence after DAAs-based antiviral therapy



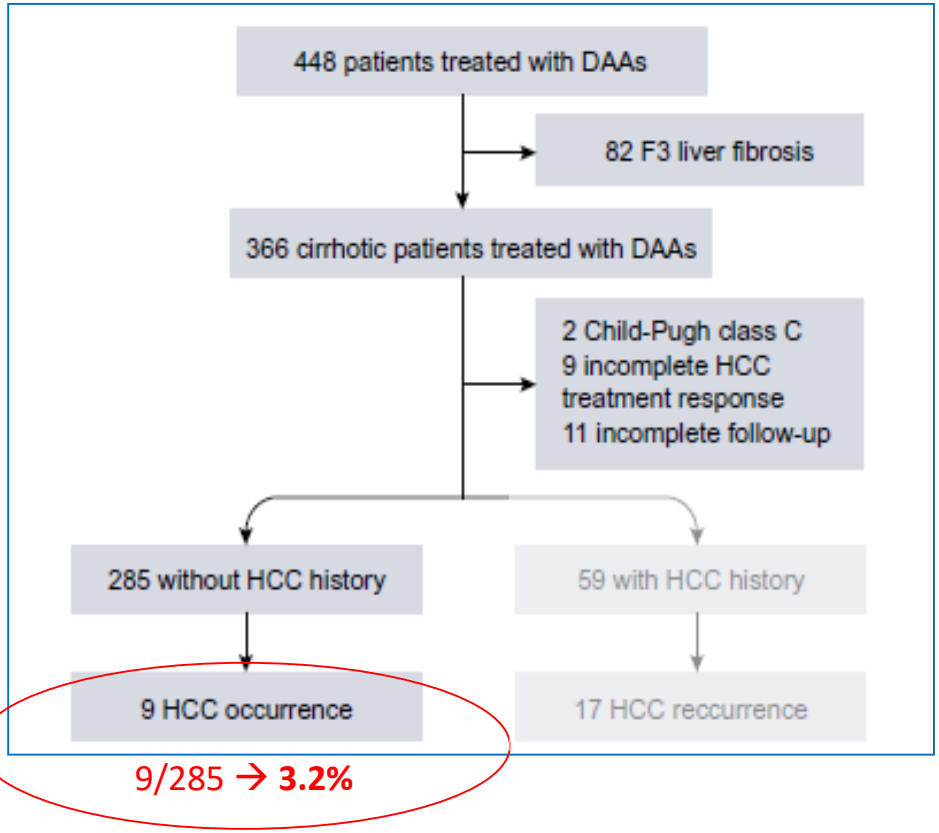
16/58 → **27.6%**



17/59 → **28.8%**

Reig *J Hepatol* 2016 , Conti *J Hepatol* 2016

HCC first ocurrence after DAAs-based antiviral therapy



	Without HCC after DAAs (n = 318)	With HCC after DAAs (n = 26)	*p* value
Males, n. (%)	189 (59.4)	18 (69.2)	0.40
Age, yr (median, range)	64 (37-86)	57.5 (47-81)	0.32
Diabetes, n. (%)	62 (19.5)	6 (23.1)	0.61
BMI, median (range)	25.6 (17-40)	25.2 (21-30)	0.37
Child-Pugh class B, n. (%)	32 (10.1)	7 (26.9)	0.02
Liver stiffness, kPa (mean, SEM)	23.1 (0.8)	28.1 (2.5)	0.01
Liver stiffness, kPa			
<21.3	134	5	0.005
>21.3	101	16	
HCV genotype			
1	224	13	
2	35	5	0.15
3	34	4	
4	25	4	
SOF + SMV	135	7	
3D	54	2	
SOF + RBV	52	10	0.22
SOF + DCV	51	6	
SOF + LDV	23	1	
DCV + SMV	1	0	
SVR12			
Yes	292	22	0.26
No	26	4	
Previous antiviral treatment			
Naive	146	7	0.07
Experienced	172	19	
History of previous HCC			
Yes	42	17	0.0001
No	276	9	
Albumin, g/dl (mean, SEM)	3.86 (0.03)	3.76 (0.09)	0.11
Bilirubin, mg/dl (mean, SEM)	1.03 (0.07)	1.20 (0.14)	0.07
Platelets, x1000/mm³ (mean, SEM)	124.4 (3.9)	102.3 (13.7)	0.02

Conti *J Hepatol* 2016

DAAs are responsible for a higher incidence or recurrence HCC after Curative treatment: a note of caution

Author (site)	Population	Mean follow-up post DAAs	Occurrence (DAAs)	Recurrence (DAAs)	Transplant Setting
Reig M (Spain)	58	5.7	NA	27.6%	NA
Conti F (Italy)	344	6	3.2%	28%	NA
Cardoso H (portugal)	54	12	7.4%	NA	NA
Yang JO (USA)	81	-	NA	NA	YES
Pol S ANRS (France)	267	20-70	NA	0.7-1.1/100 pts/month	NA
Cheurg MG (UK)	406	6-15	5.2%	11.1%	NA
Torres HA (USA)	8	12	NA	0	NA
Zavaglia c (Italy)	31	8	NA	3.2	NA
Kobayasghi (Japan)	77	48	2.6%	NA	NA
Petta S ITALICA (Italy)	58	18	28%	NA	NA

Imaging features of Microvascular Invasion in HCC in HCV-related cirrhosis after DAA therapy

Radiologic criteria for MVI were used to assess:

1) internal arteries+noncontinuous hypodense halos as two-trait predictor of venous invasion (TTPVI)
2) peritumoral enhancement (PTE)
3) non-smooth tumor margins (NSTM)

9/10 patients *without* previous HCC and **10/18** patients *with* history of HCC developed nodules with at least 2 imaging features predictive of MVI

HCC before and after DAA: paired comparison in the same patients (data available in 16/18 patients)

	HCC pre-DAA	HCC post-DAA
Single nodule / multinodular (n.)	12 / 4	10 / 6
Nodule max size (mm, median)	21.5 (15-65)	15 (10-42)
Radiologic features of MVI (%)*	13	56 (* p= 0.02)

Imaging features of MVI in 41 nodules after DAA

Size & n.	TTPVI	PTE	NSTM	≥ 2 features
10-20 mm (n= 29)	19	19	21	19 (66%)
20-50 mm (n= 11)	10	8	11	10 (91%)
> 50 mm (n= 1)	1	1	1	1 (100%)

Renzulli *AASLD* 2016, Renzulli *Radiology* 2016

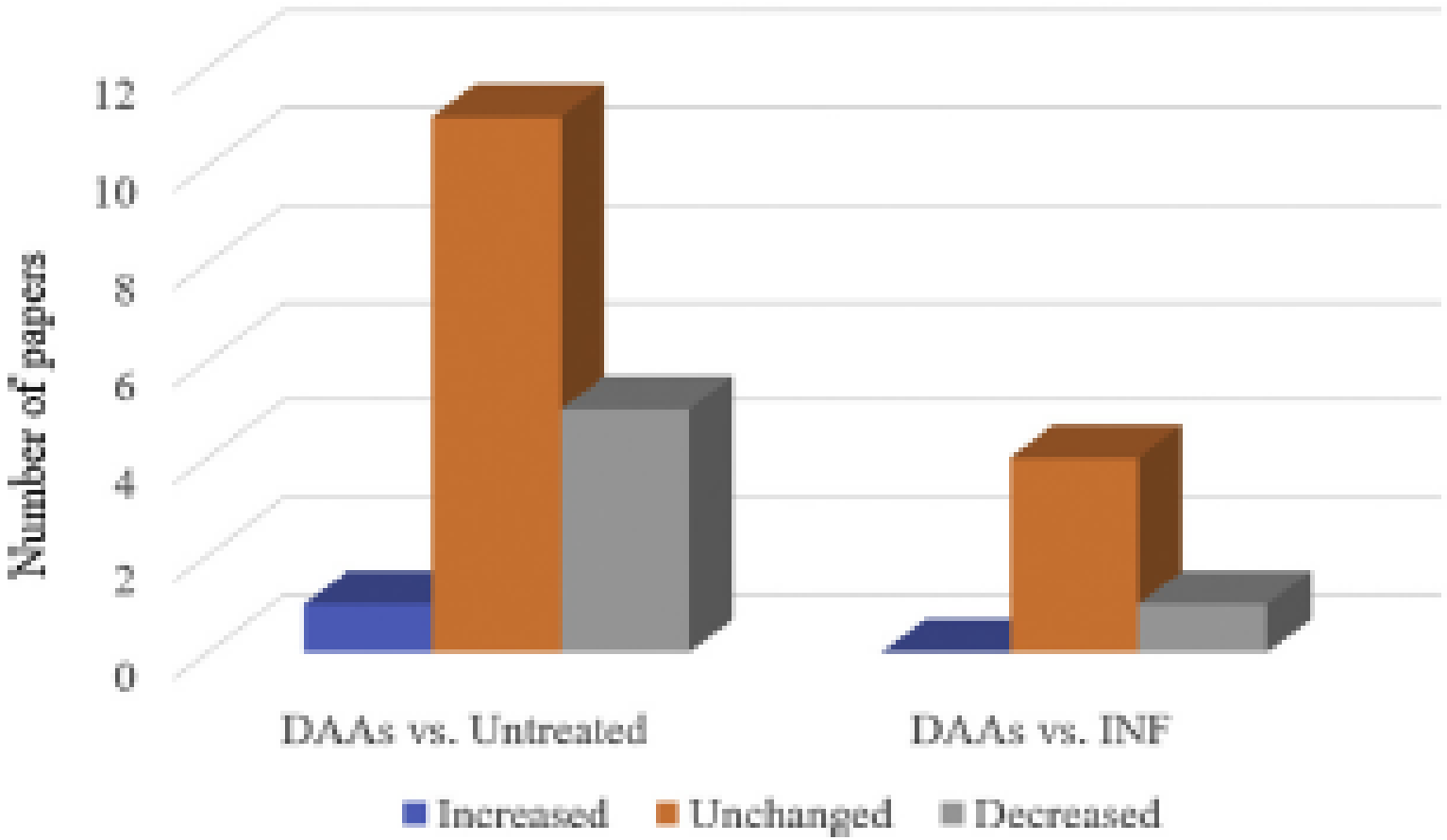
Immune inflammation indicators and ALBI score to predict liver cancer in HCV-patients treated with direct-acting antivirals

Andrea Casadei Gardini, Francesco Giuseppe Foschi, Fabio Conti, and the member of the Bologna DAA group

Conclusion: ALBI score, platelet count and ALRI are promising, easy to perform and inexpensive tools for identifying patients with higher risk of HCC after treatment with DAAs.

Digestive and Liver Disease in press

Risk of Recurrence HCC



Guarino M et al Special Interest Group on “Hepatocellular carcinoma and new anti-HCV therapies” Digestive and Liver Disease in press

Predictors for recurrence

- Non curative treatment
- Prior Recurrence
- Tumor size
- Liver Cirrhosis
- Liverr stiffness
- Alpha fetoprotein
- Anti HBc status
- Des gamma Carboxy Prothrombin (DCP)
- HCC treatment and antiviral Therapy

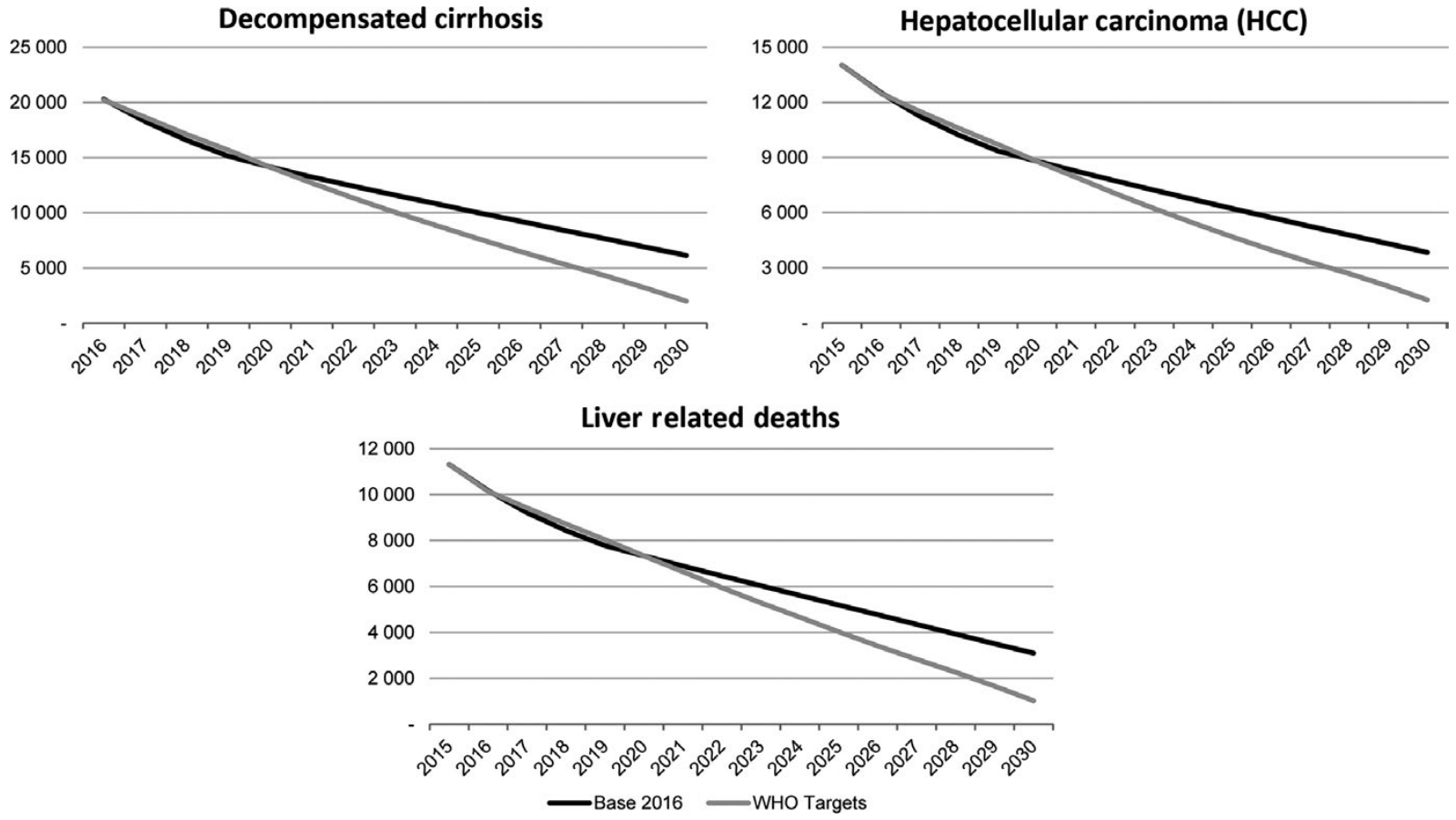
Guarino M et al Special Interest Group on "Hepatocellular carcinoma and new anti-HCV therapies" Digestive and Liver Disease in press

Conclusion

"The available data about the risk of HCC recurrence after DAAstreatment in HCV patients cannot be considered definitive, but the initial alarmist data indicating an increased risk of recurrence havenot been confirmed by most subsequent studies. Nonetheless, since there are no clear evidences of a detrimental effect of DAAs on HCC recurrence, we believe that DAAs should not be denied to these patients, as well as, it is mandatory to maintain an active surveil-lance for HCC".

Guarino M et al Special Interest Group on "Hepatocellular carcinoma and new anti-HCV therapies" Digestive and Liver Disease in press

Liver-related morbidity and mortality by scenario, 2015-2030. The forecasted liver-related outcomes by Base 2016 and WHO Targets scenarios were compared. By 2030, all HCV-related outcomes are expected to decline due to the higher treatment rate in Italy.



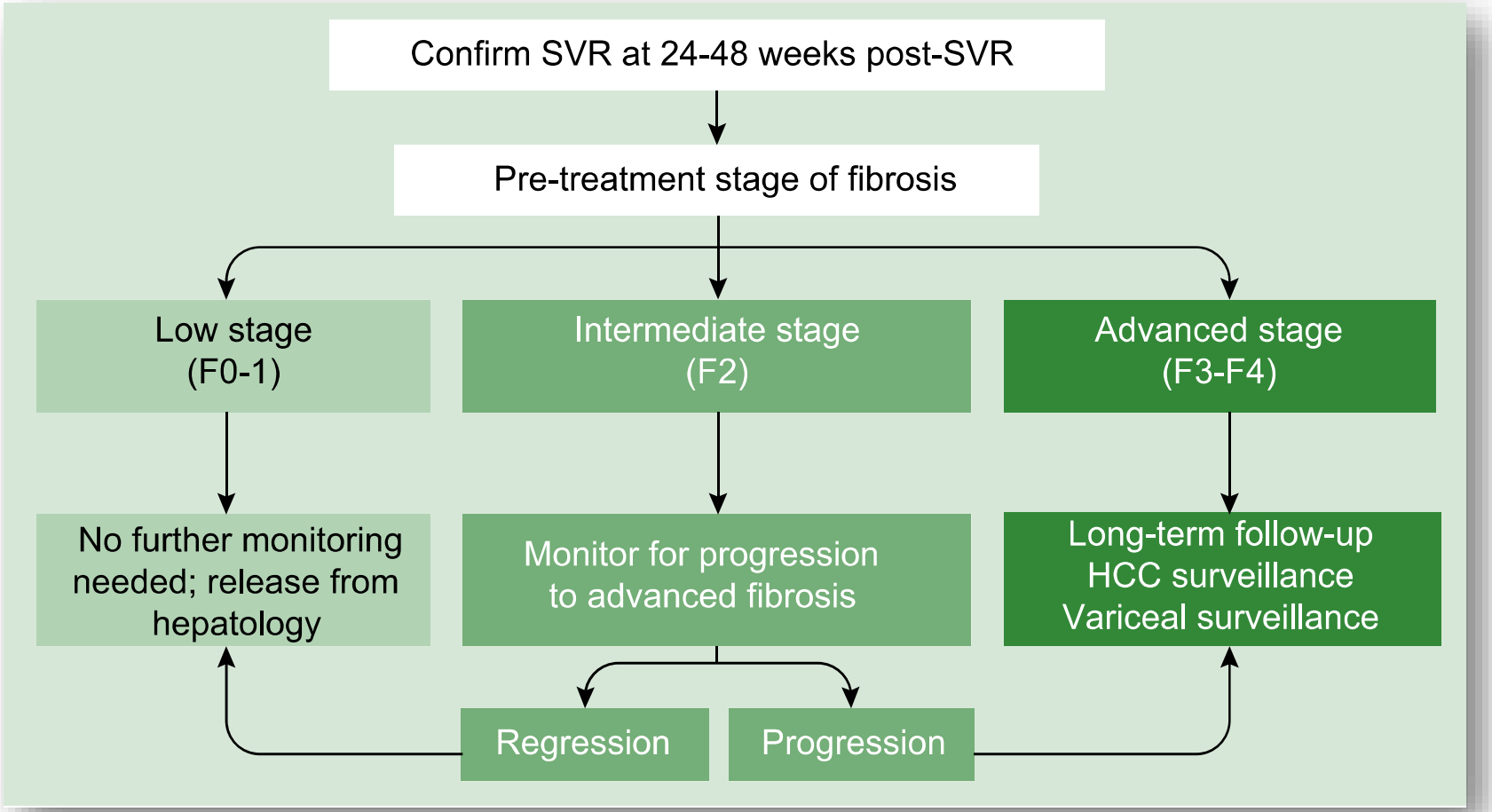
Kondili LA et al Liver International 2018

Dopo la guarigione

Dopo l'Infezione ?

- Il management del paziente dopo SVR
  - senza fibrosi avanzata
  - con cirrosi compensata
  - con cirrosi scompensata
- La sorveglianza e il monitoraggio dopo SVR
- Lo stile di vita e abitudini sociali
- Le indicazioni dell'EASL

Algoritmo per il monitoraggio dopo SVR



Terrault NA, et al. J Hepatol 2016

Guida per il monitoraggio dopo SVR

Monitoraggio di routine:

- F0/F1: non specifico
- F2: visite specialistiche ogni 1 o 2 anni in base ai fattori di rischio di progressione
- F3/F4 compensati: ogni 6 mesi
- F4 scompensati: ogni 3 mesi o meno se necessario

Terrault NA, et al. J Hepatol 2016

Sorveglianza dopo SVR

- **VARICI ESOFAGEE (F4):** ogni 1-3 anni in base al grado iniziale
- **EPATOCARCINOMA (F3/F4):** ecografia ogni 6 mesi ± AFP
- **FIBROSI:** ogni 1-2 anni con elastografia o markers sierologici
- **REINFEZIONE:** HCV-RNA ogni anno nei soggetti con comportamenti a rischio

Terrault NA, et al. J Hepatol 2016

Fattori associati con rischio di complicanze

- **Fattori con evidenza chiara**
  - Cirrosi
  - Ipertensione portale (piastrinopenia)
- **Fattori frequentemente associati**
  - Diabete
  - Alcol
  - Età avanzata
- **Fattori possibilmente importanti**
  - Obesità
  - Genotipo 3
  - ALT elevate
  - Coinfezioni virali
  - Sesso maschile

Terrault NA, et al. J Hepatol 2016

Stili di vita e abitudini sociali

- **Peso corporeo**: raggiungere/mantenere quello ideale
- **Esercizio fisico** regolare sia per ridurre il peso sia per l'efficienza dell'apparato muscolo-scheletrico → evitare sarcopenia e osteoporosi
- **Nutrizione** adeguata (dieta mediterranea) ottimizzata in base alle alterazioni metaboliche. *No schemi dietetici per epatopatici*!
- Supplementi di vitamine e parafarmaci solo se necessari. *Counseling per evitare l'autoprescrizione … soprattutto delle erbe medicinali*!
- **Astensione dall'alcol** nei pazienti con fibrosi significativa/cirrosi **(?)**
- **Astensione dal fumo** di tabacco soprattutto nei cirrotici
- **Evitare l'uso di marijuana**: nei pazienti con fibrosi significativa/cirrosi
- **Caffè**: nessuna proibizione

Vandenbulcke H, et al. J Hepatol 2016; Nishikawa H, et al. Mediators Inflamm 2015; Smart NA, et al. Br J Sports Med 2016; Bemeur C, et al. J Clin Exp Hepatol 2015; Guerra TS, et al. Arq Gastroenterol 2016; Chen ZM, et al. Int J Cancer 2003; Franceschi S, et al. Cancer Epidemiol Biomarkers Prev 2006; Ishida JH, et al. Clin Gastroenterol Hepatol 2008; Hézode C, et al. Hepatology 2005; Freedman ND, et al. Gastroenterology 2011;

Grazie per l’attenzione

HCV & DM Tipo II

Impatto della guarigione su eventi renali e c-vascolari

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Antiviral Treatment for Hepatitis C Virus Infection Is Associated With Improved Renal and Cardiovascular Outcomes in Diabetic Patients

Yao-Chun Hsu,[1,2] Jaw-Town Lin,[2,3,4] Hsiu J. Ho,[3] Yu-Hsi Kao,[5] Yen-Tsung Huang,[6] Nai-Wan Hsiao,[7] Ming-Shiang Wu,[8] Yi-Ya Liu,[9] and Chun-Ying Wu[1,9,10,11,12]

Hepatology 2014