

# **AGORÀ PENITENZIARIA 2018**

## **XIX CONGRESSO NAZIONALE SIMSPE-ONLUS**



*Sessione 3: Microeradicazione di HCV in sezioni detentive: obiettivo perseguibile?*

**Resistenze ai DAA, reinfezioni e inconsapevoli:  
come HCV resiste all'eradicazione**

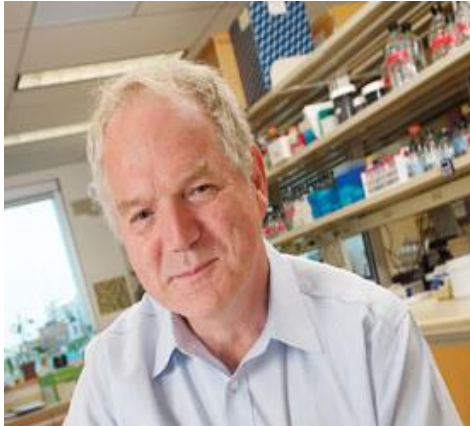
**Francesca Ceccherini-Silberstein**

Università degli Studi di Roma  
“Tor Vergata”

Cattedra di Virologia

**Roma 4 ottobre 2018**

# HCV discovery: one of the most significant biomedical breakthroughs in the last 25 years



Michael Houghton

SCIENCE, VOL. 244

21 APRIL 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

21 APRIL 1989

SCIENCE, VOL. 244

## An Assay for Circulating Antibodies to a Major Etiologic Virus of Human Non-A, Non-B Hepatitis

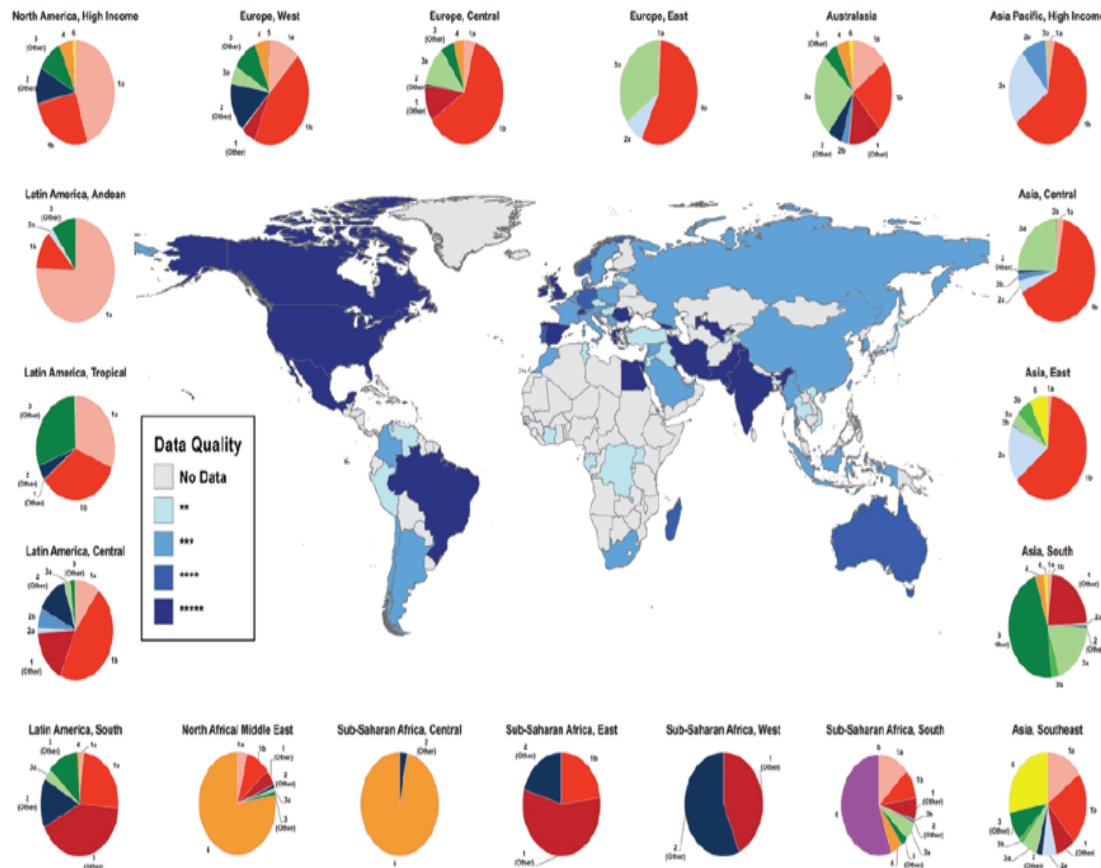
G. KUO, Q.-L. CHOO, H. J. ALTER, G. L. GITNICK, A. G. REDEKER,  
R. H. PURCELL, T. MIYAMURA, J. L. DIENSTAG, M. J. ALTER, C. E. STEVENS,  
G. E. TEGTMEIER, F. BONINO, M. COLOMBO, W.-S. LEE, C. KUO, K. BERGER,  
J. R. SHUSTER, L. R. OVERBY, D. W. BRADLEY, M. HOUGHTON

**This discovery has facilitated the development of effective diagnostics, blood screening tests and the elucidation of promising drug and vaccine targets to control this global pathogen and save the lives of millions of people around the world....**

# Hepatitis C is one of the most pressing health emergencies worldwide

The global prevalence of viremic HCV infection has been estimated at 1\*-3%, which equates to 62\*-170 million people

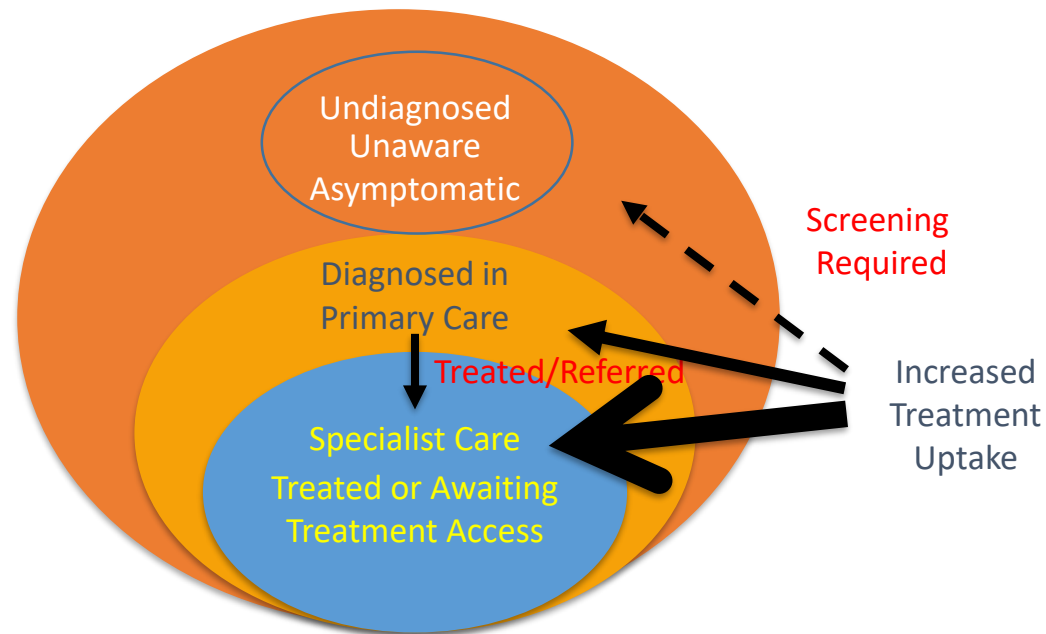
>350,000 mortality cases each year for HCV chronic disease related



# HCV Population

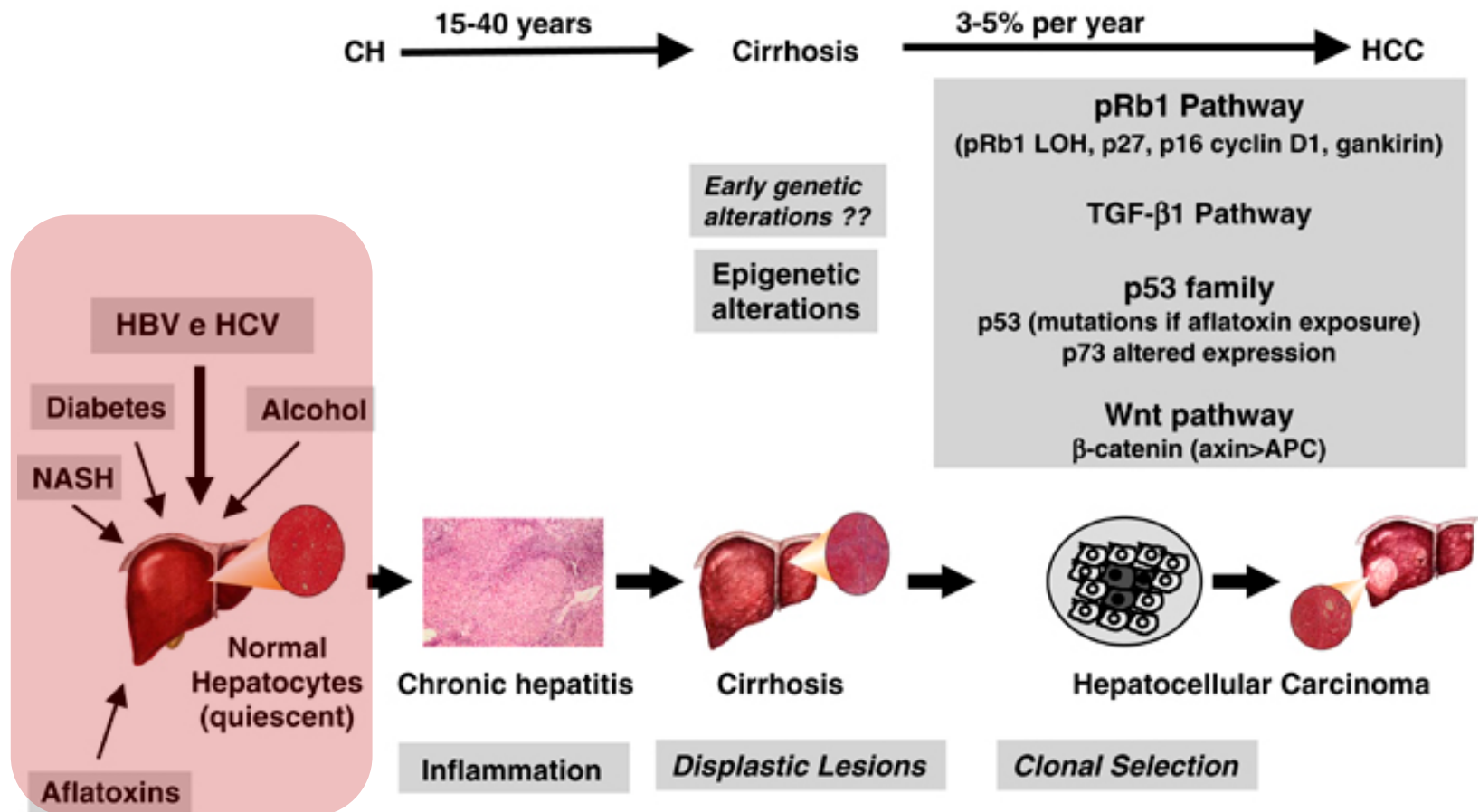
The number of chronically infected persons worldwide is estimated to be about 62-170 million, but most are unaware of their infection.

HCV prevalence and incidence data are needed to analyse the magnitude of the pandemic in different regions and to design public health interventions.

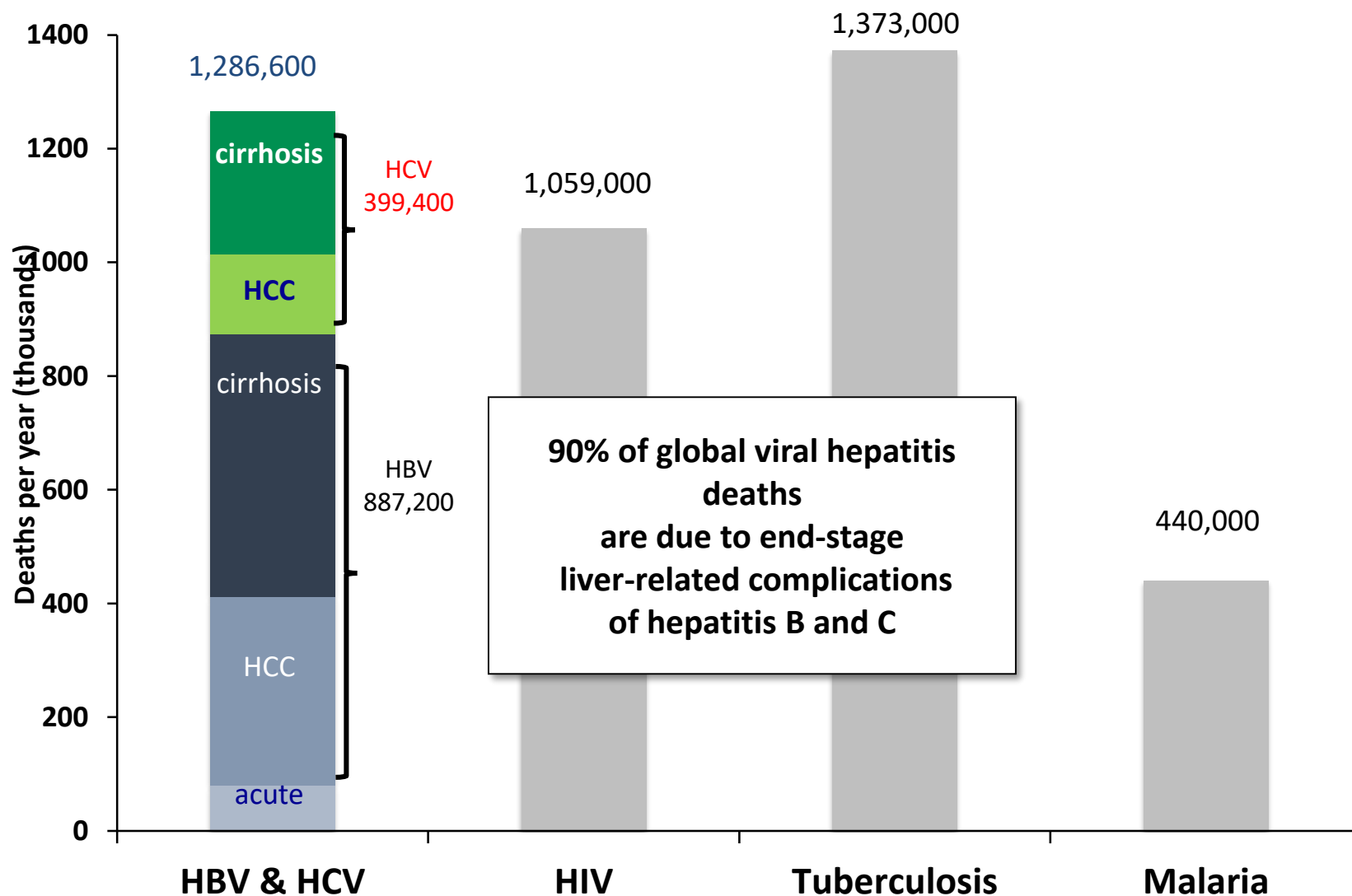




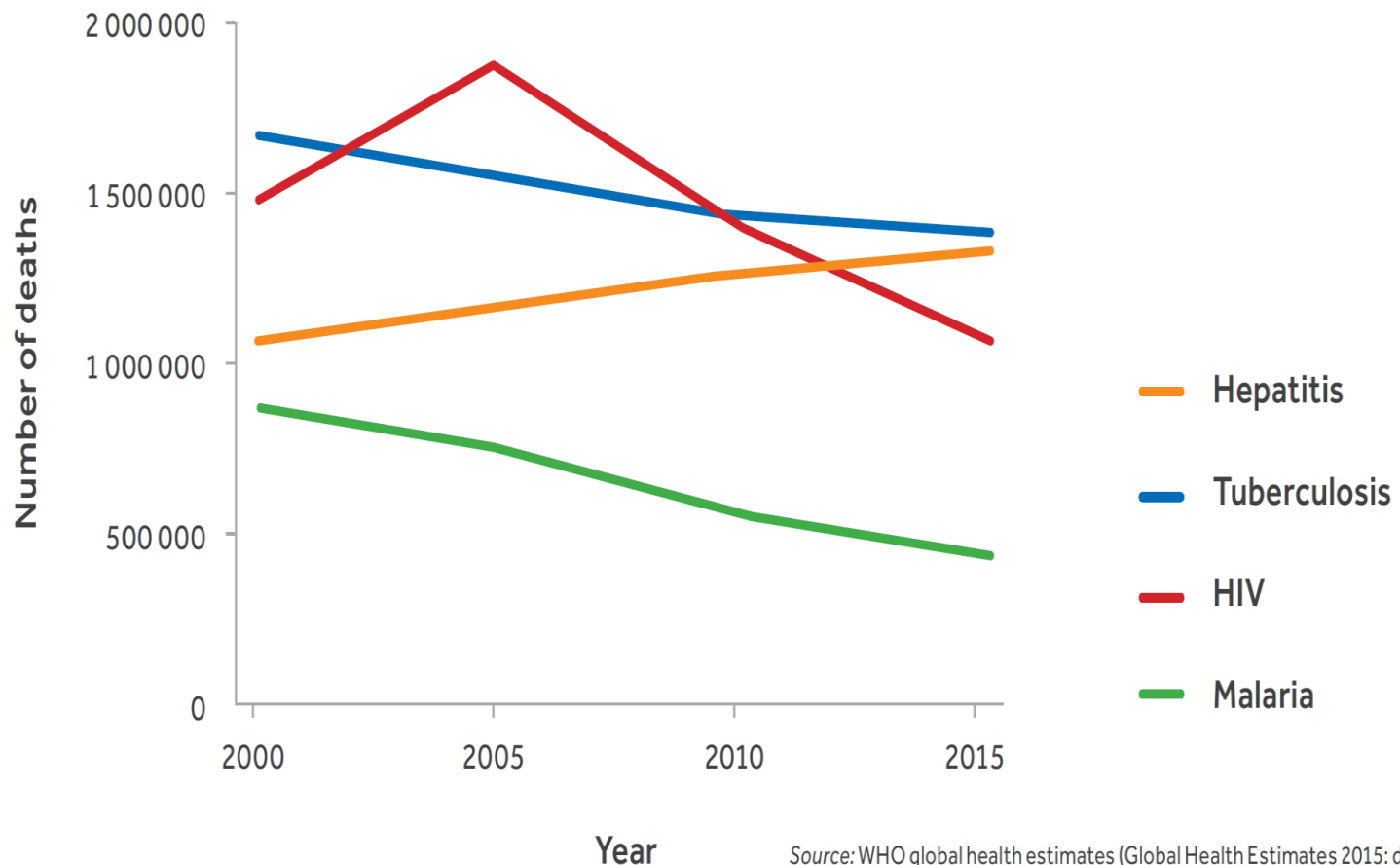
**Chronic hepatitis associated with HBV and HCV infection is the major risk factor for the development of HCC, being involved in more than 80% of cases of HCC worldwide**



# The burden of viral liver disease



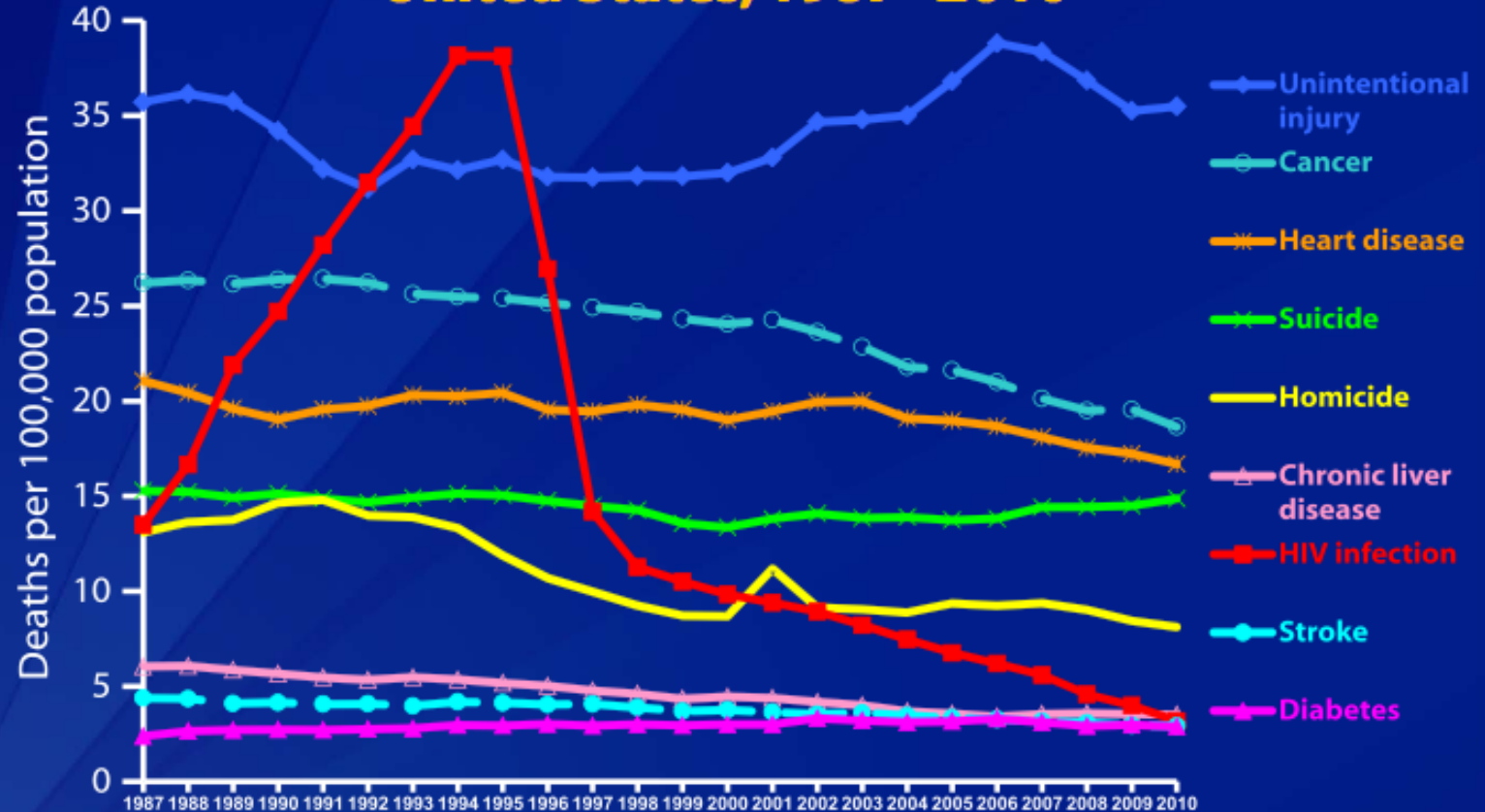
# Global annual mortality from hepatitis, HIV, tuberculosis and malaria, 2000–2015: unlike HIV, tuberculosis and malaria, the trend in mortality from viral hepatitis is increasing



Source: WHO global health estimates (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000-2015. Geneva: World Health Organization; 2016.)

# HIV and AIDS

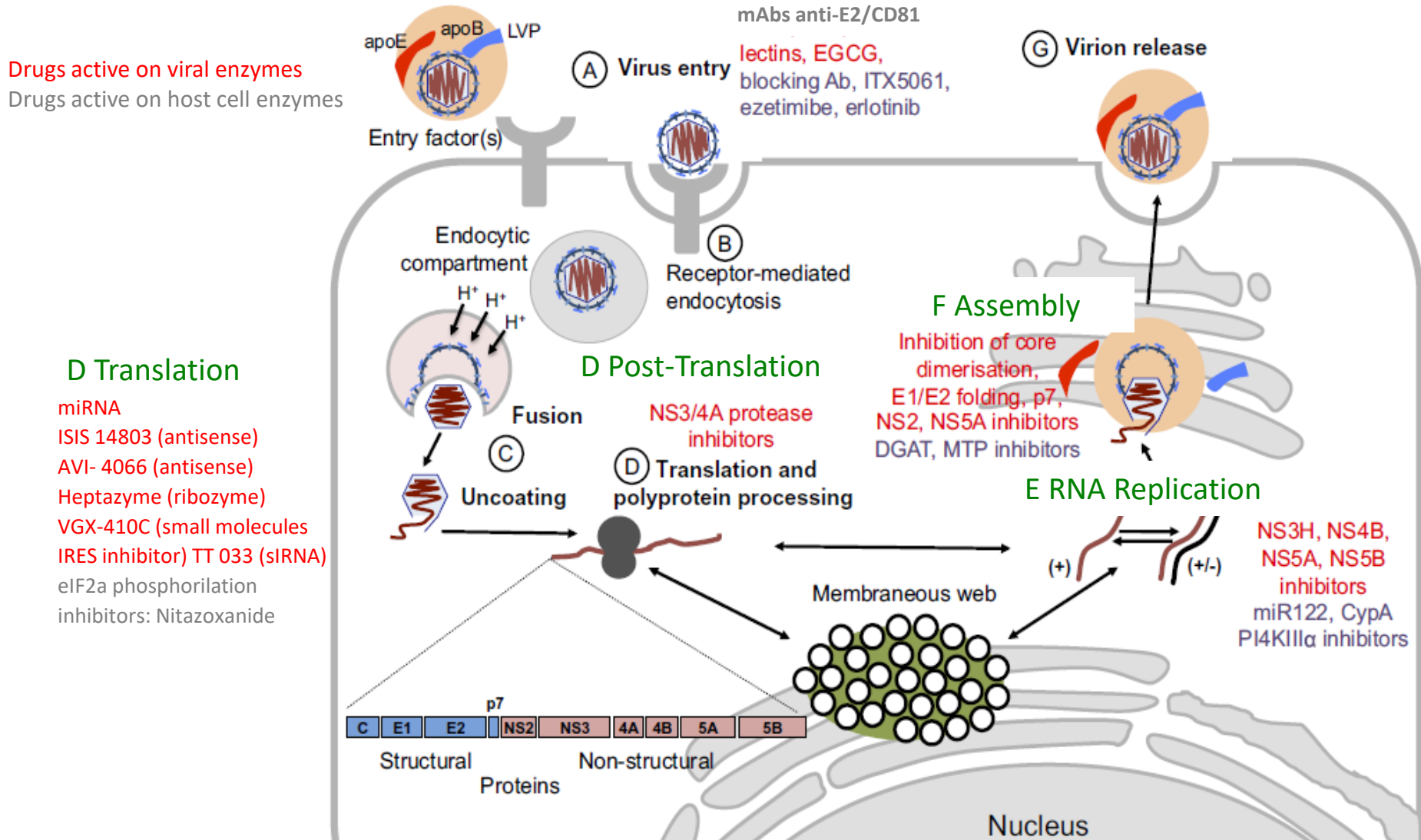
## Trends in Annual Rates of Death due to the 9 Leading Causes among Persons 25–44 Years Old, United States, 1987–2010



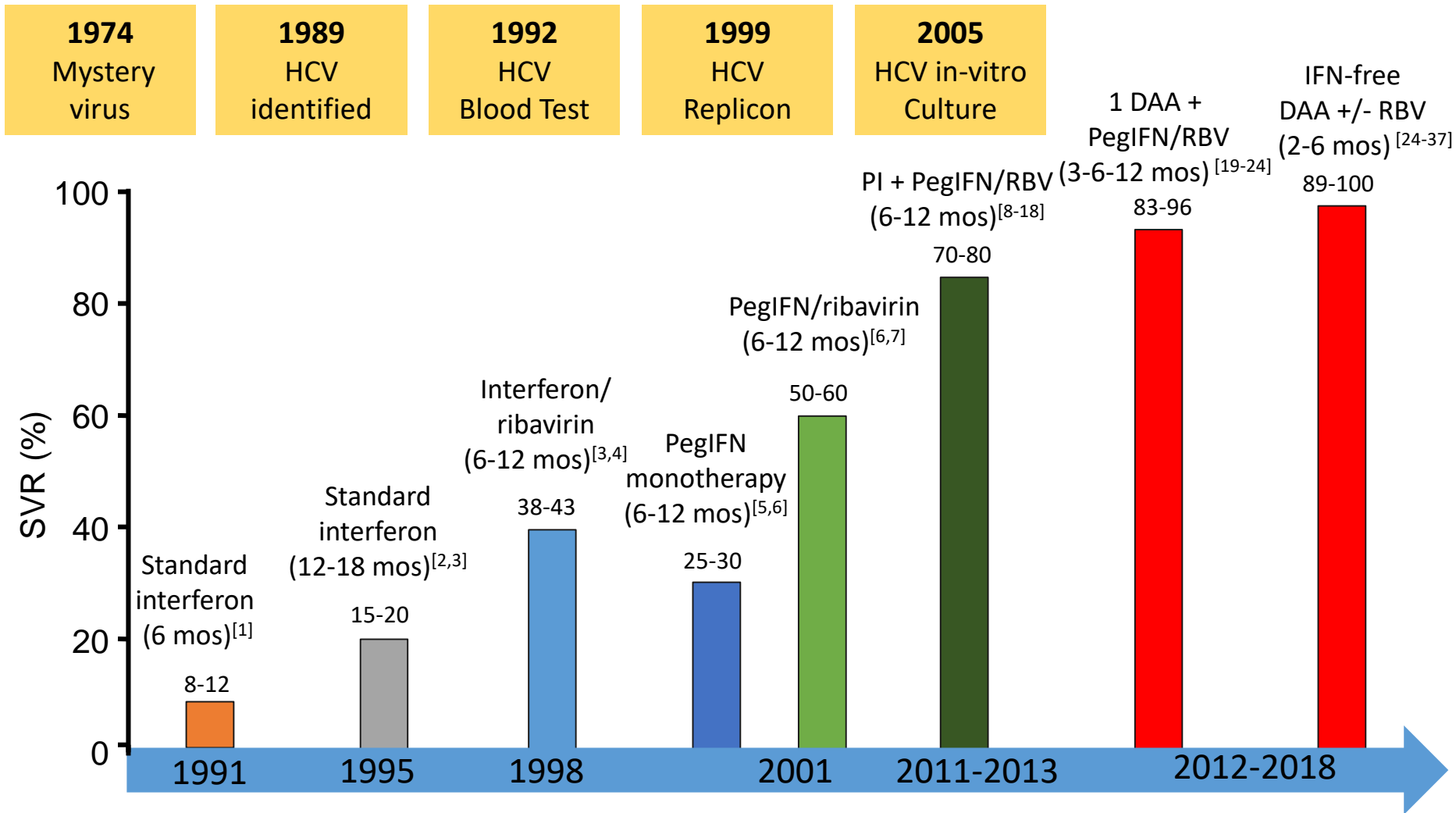
Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.



# The better knowledge of HCV replication cycle allowed the identification of several targeted drugs



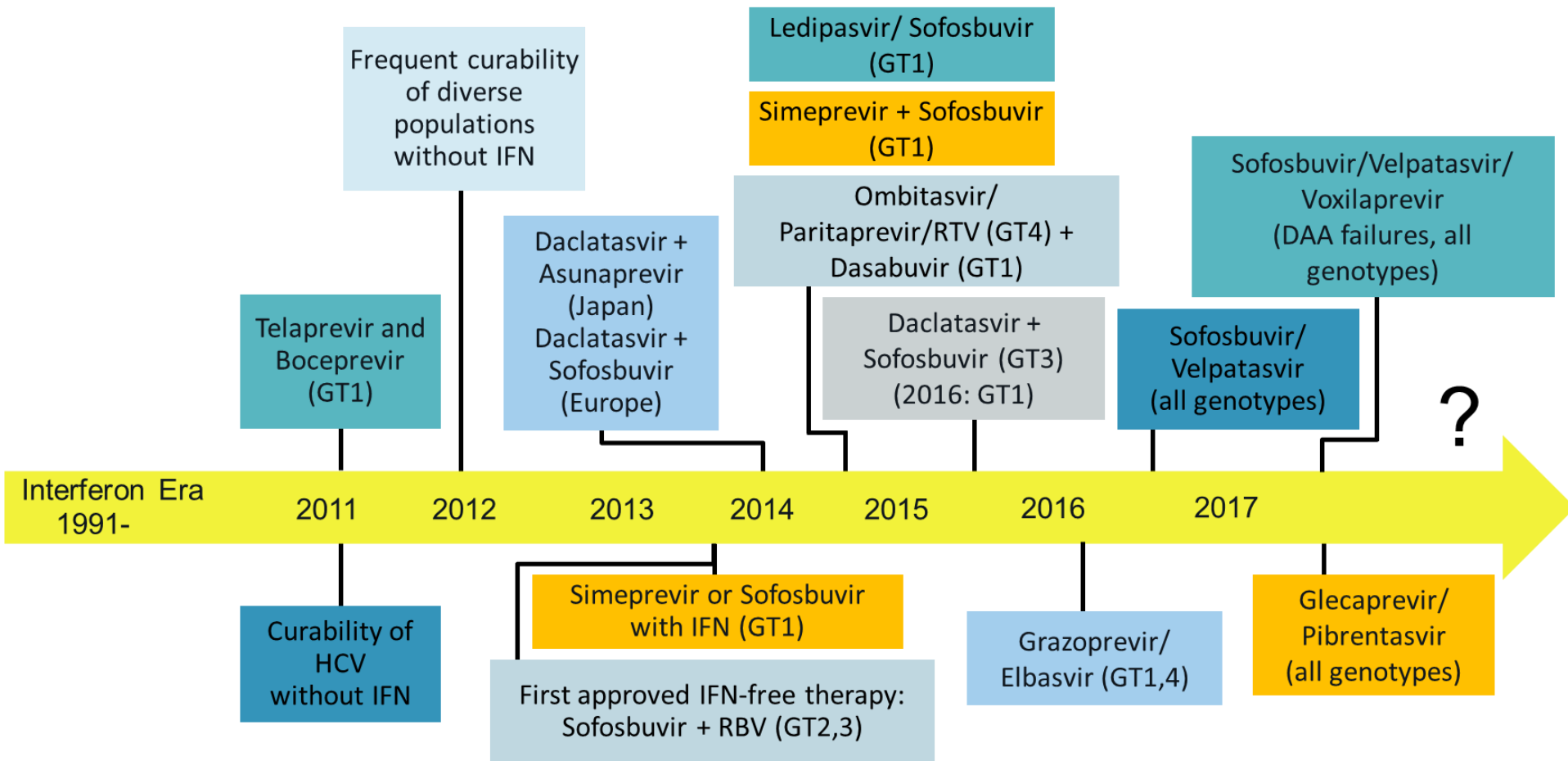
# The standard of care for HCV patients has greatly improved



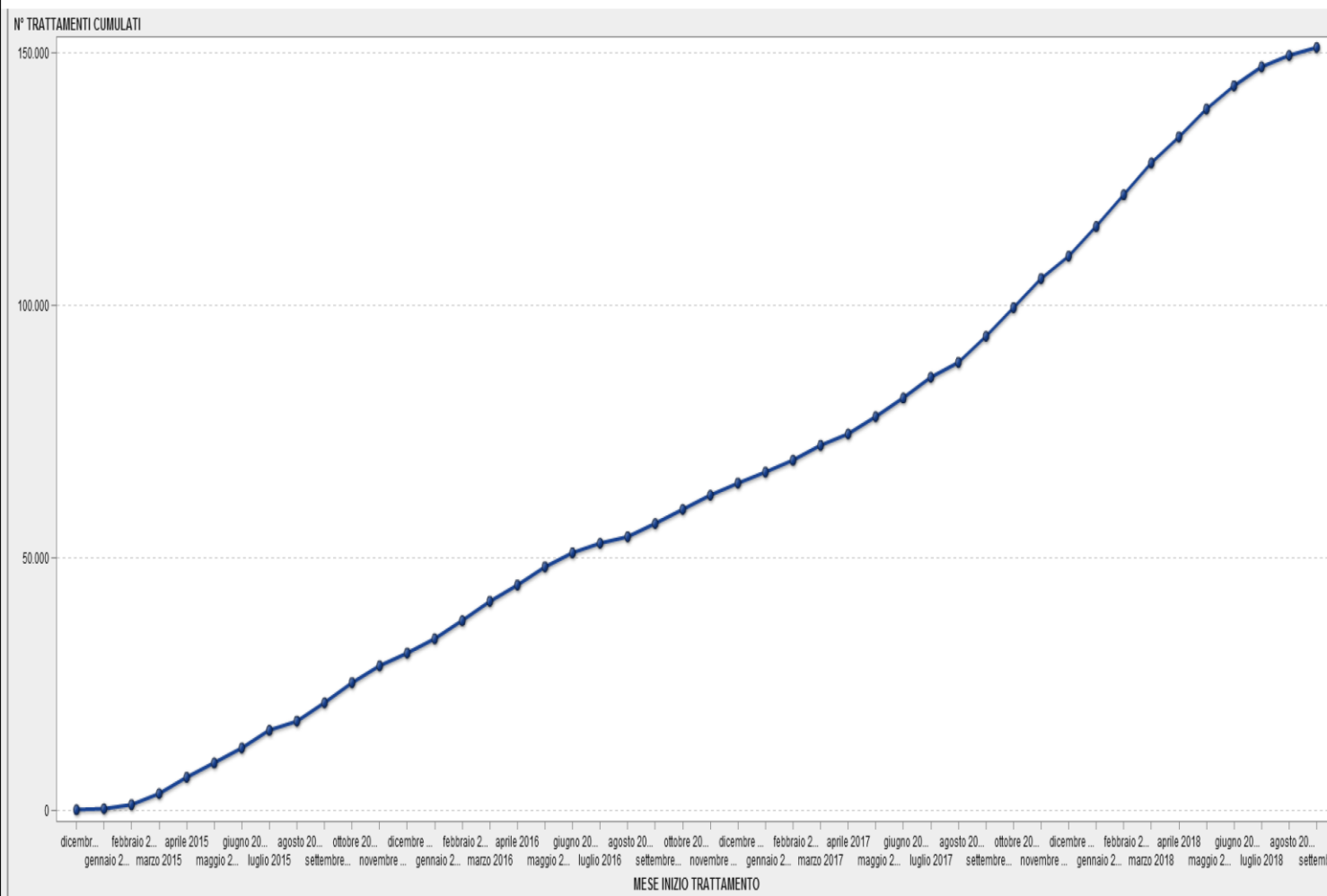
1. Carithers RL Jr., et al. *Hepatology*. 1997;26(3 suppl 1):83S-88S. 2. Zeuzem S, et al. *N Engl J Med*. 2000;343:1666-1672. 3. Poynard T, et al. *Lancet*. 1998;352:1426-1432. 4. McHutchison JG, et al. *N Engl J Med*. 1998;339:1485-1492. 5. Lindsay KL, et al. *Hepatology*. 2001;34:395-403. 6. Fried MW, et al. *N Engl J Med*. 2002;347:975-982. 7. Manns MP, et al. *Lancet*. 2001;358:958-965. 8. Poordad F, et al. *N Engl J Med*. 2011;364:1195-1206. 9. Jacobson IM, et al. *N Engl J Med*. 2011;364:2405-2416. 10. Sherman KE, et al. *N Engl J Med*. 2011;365:1014-1024. 11. Jacobson IM, et al. 64th Annual Meeting of the American Association for the Study of Liver Diseases, 1-5 November 2013, Washington, DC. 12. Zeuzem S, et al. *Gastroenterology* 2014;146:430-41. 13. Lawitz E, et al. *Gastroenterology* 2013;144:S-151. 14. Jensen D, et al. 64th Annual Meeting of the American Association for the Study of Liver Diseases, 1-5 November 2013, Washington, DC. 15. Jacobson I, et al. 64th Annual Meeting of the American Association for the Study of Liver Diseases, 1-5 November 2013, Washington, DC. 16. Marcellin P, et al. *Gastroenterology* 2013;145:790-800e3. 17. Bronowicki JP, et al. *Antiviral Ther* 2013;18:885-93. 18. Manns MP, et al. *Hepatology* 2012;56:884-93. 19. Hezode C, et al. *Hepatology* 2012;56:553A-4A. 20. Dore G, et al. *J Hepatol* 2013;58:S570-1. 21. Lawitz E, et al. *Lancet Infect Dis* 2013;13:401-8. 22. Kowdley KV, et al. *Lancet* 2013;381:2100-7. 23. Lawitz E, et al. 64th Annual Meeting of the American Association for the Study of Liver Diseases. Washington, DC, 1-5 November 2013. 24. Lawitz E, et al. *N Engl J Med* 2013;368:1878-87. 25. Jacobson IM, et al. *N Engl J Med* 2013;368:1867-77. 26. Zeuzem S, et al. *N Engl J Med* 2014;370:1993-2001. 27. Osinusi A, et al. *JAMA* 2013;310:804-11. 28. Jacobson IM, et al. 64th Annual Meeting of the American Association for the Study of Liver Diseases. Washington, DC, 1-5 November 2013. 29. Sulkowski MS, et al. *N Engl J Med* 2014;370:211-21. 30. Zeuzem S, et al. *N Engl J Med* 2014;370:1889-9. 31. Afdhal N, et al. *N Engl J Med* 2014;370:1483-9. 32. Feld JJ, et al. *N Engl J Med* 2014;370:1594-603. 33. Zeuzem S, et al. *N Engl J Med* 2014;370:1604-14. 34. Ferenci P, et al. *N Engl J Med* 2014;370:1983-9. 35. Poordad F, et al. *N Engl J Med* 2014;370:1973-82. 36. Lawitz E, et al. 64th Annual Meeting of the American Association for the Study of Liver Diseases, Washington, DC, 1-5 November 2013. 37. Gane EJ, et al. *Gastroenterology* 2014;146:736-43e1.



# The evolution of HCV therapy



## Trend cumulativo dei trattamenti avviati



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

# Overall efficacy of different anti-HCV treatments in Italian real-life practice is 95-98%

Failure rate following the first DAA regimen in patients with advanced disease is similar to or lower than that reported in clinical trials (3.6%), although the majority of patients were treated with suboptimal regimens.

**Table 3. Failure rates following the first DAA regimen, by HCV genotype and treatment regimen in patients who completed the 12 weeks post treatment evaluation (n = 3,830 patients).**

DAA regimen	Overall	HCV genotype					
	N. of failures/N. of treated patients (%)	N. of failures/N. of treated patients (%)					
	139/3830 (3.6)	1a	1b	2	3	4	5
SOF+RBV	68/710 (9.6)	5/15 (33.3)	20/56 (35.7)	8/499 (1.6)	32/132 (24.2)	3/8 (37.5)	-
SOF+SIM±RBV	38/683 (5.6)	8/99 (8)	24/520 (4.6)	1/2 (50)	1/1 (100)	3/60 (5)	1/1 (100)
SOF+LDV±RBV	16/1002 (1.6)	3/200 (1.5)	10/752 (1.3)	-	0/1 (0)	3/44 (6.8)	0/5 (0)
3D±RBV	9/894 (1)	3/86 (3.5)	6/806 (0.7)	-	-	0/2 0	-
2D+RBV	2/64 (3.1)	-	-	-	-	2/59 3.4%	0/5 (0)
SOF+DCV±RBV	6/471 (1.3)	0/47 0	1/115 (0.9)	0/55 (0)	5/244 (2)	0/10 (0)	
SIM+DCV	0/6 (0)	-	0/6 (0)	-	-	-	-

<https://doi.org/10.1371/journal.pone.0185728.t003>

Data on HCV genotype, liver disease severity, and first and second line DAA regimens were prospectively collected in consecutive patients who reached the 12-week post-treatment and retreatment evaluations from January 2015 to December 2016 in 23 of the PITER network centers.

# **Considerations in DAA Treatment Failure**

- **Re-infection as a cause of recurrent viremia?**
- **Was initial therapy sub-optimal?**
  - Drug combo
  - Duration
  - RBV use
- **Indications of other problems on treatment?**
  - Adherence?
  - Significant drug interactions?
- **Are there other baseline host/disease factors that may have contributed?**
  - Cirrhosis, especially decompensation
  - IL28B, age, treatment experience, high viral load, baseline RASs

# Treatment of chronic Hepatitis C: changing the horizon

**High anti-viral effect: 90-95%**

**Great possibility to use DAAs across all spectrum of the disease**

**Mild-to-moderate-advanced decompensated-pre / post-transplant**

## **Aim at individual level**

Abolishing liver disease progression

Regression of the hepatic damage

Reducing liver and non-liver complications

*At individual level:  
treat infection/ liver  
disease*

## **Aim at community level**

Reduce (abolish) the spread of HCV infection

Reduce disease burden

Elimination of HCV infection

*At community level:  
treating infection;  
those with high  
potential  
for transmission*

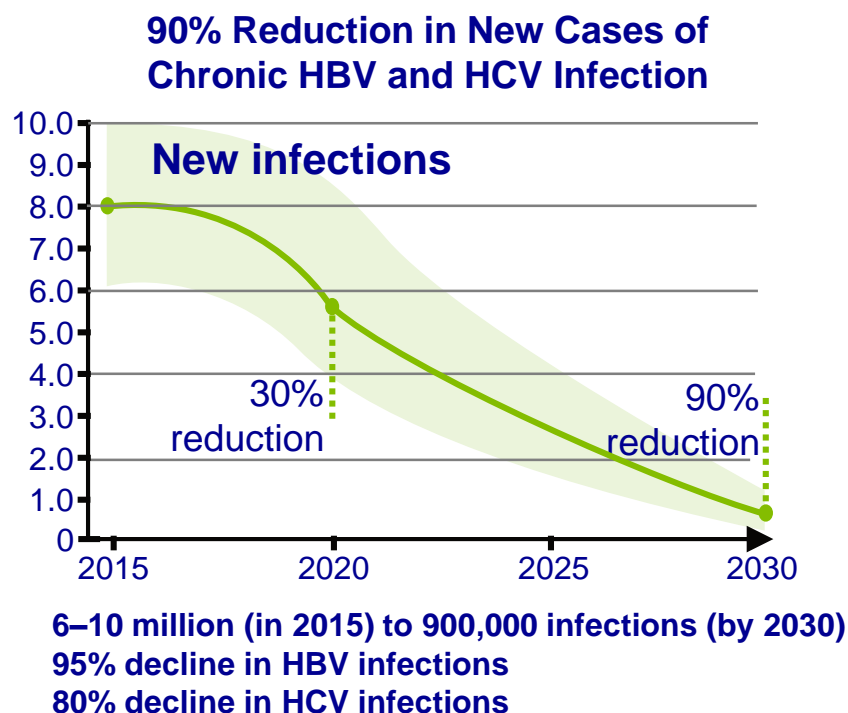
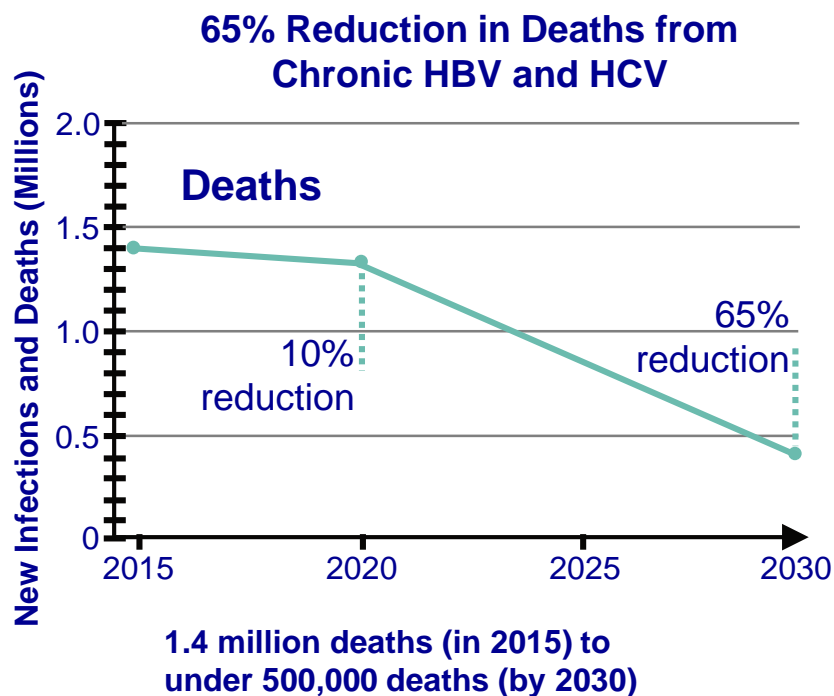
# Disease Eradication vs Elimination vs Control

.....*From individual health to community health perspective*.....

- **Control:** reduction in the incidence, prevalence, morbidity, or mortality of an infectious disease to a locally acceptable levels; continued intervention measures required
- **Elimination:** reduction to zero of incidence in a defined geographical area as a result of deliberate efforts; continued intervention measures required
- **Eradication:** permanent reduction to zero of the worldwide incidence of infection; intervention measures no longer needed
  - Only 1 example: smallpox



# Proposed WHO targets for reducing new infections and stopping deaths



**Elimination:** reduction to zero of incidence in a defined geographical area as a result of deliberate efforts; continued intervention measures required.

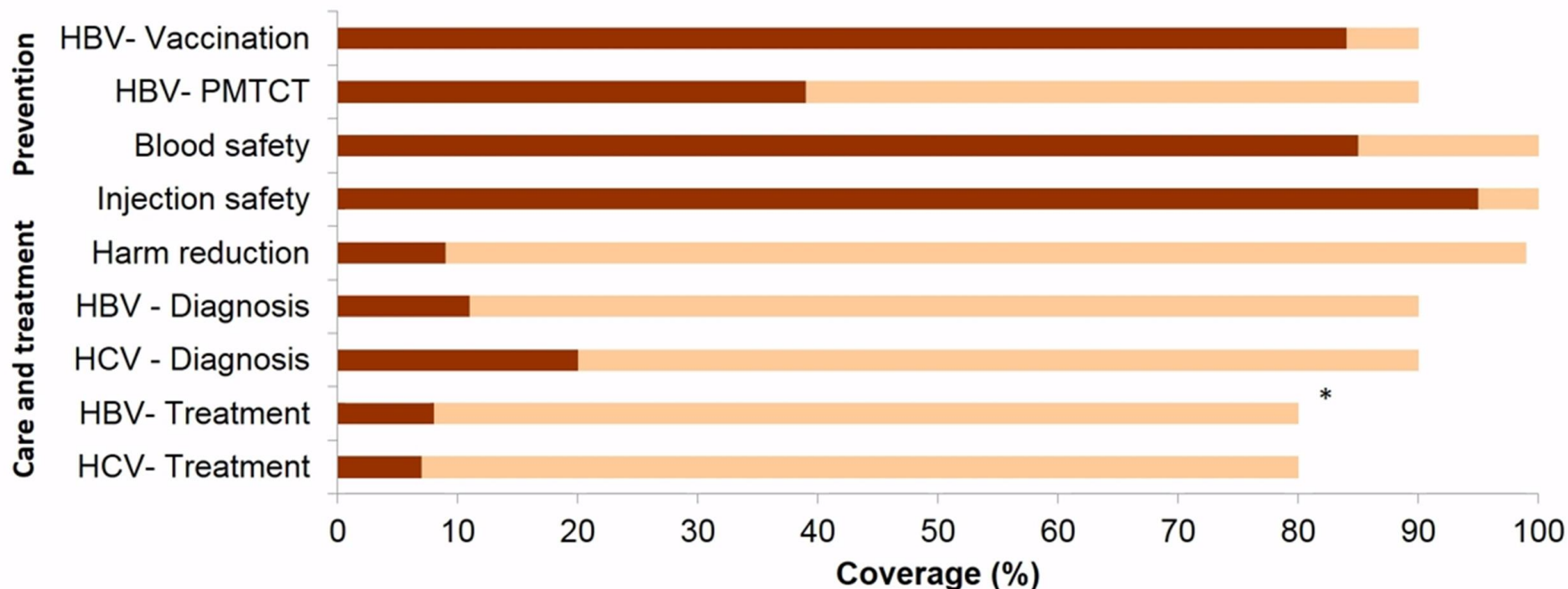
WHO global health sector strategy on viral hepatitis 2016–2021.

Available at: <http://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/> (accessed March 2018).

# GLOBAL ELIMINATION STRATEGY:

2015 BASELINE

TOWARDS 2030 TARGETS



# Evolution of Treatment Guidelines: Treatment Is Now Indicated for All Patients

EASL<sup>1</sup>  
Last updated April 2018

WHO<sup>2</sup>  
Last updated April 2017

AASLD<sup>3</sup>  
Last updated September 2017

Treatment is indicated for:

All treatment-naïve and treatment-experienced patients with HCV infection who have no contraindications for treatment\*

All adults and children with chronic HCV infection, including PWID

All patients with chronic HCV infection, except those with short life expectancies that cannot be remediated

*\* Treatment is generally not recommended in patients with limited life expectancy because of non-liver-related comorbidities.*

EASL recommendations on the treatment of hepatitis C 2018. *J Hepatol* 2018; E-pub ahead of print (doi: 10.1016/j.jhep.2018.03.026).

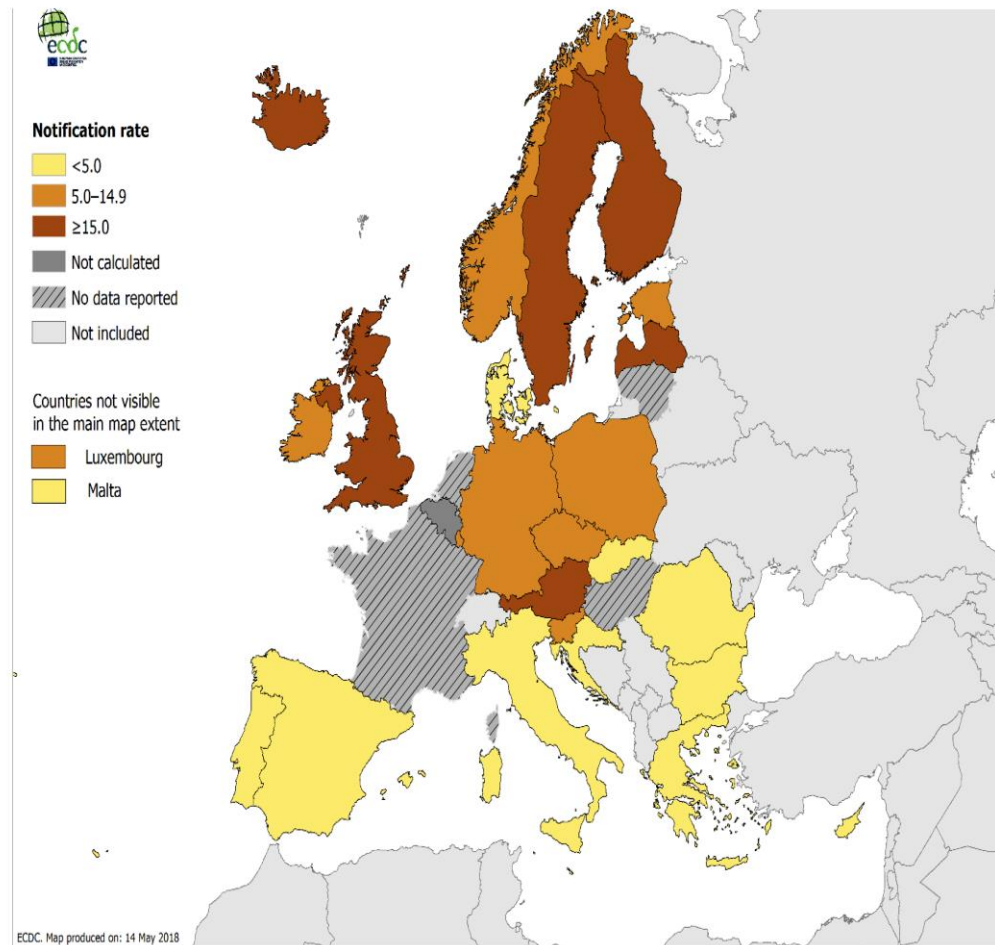
WHO guidelines for the screening, care and treatment of persons with chronic HCV infection.

Available at: [http://apps.who.int/iris/bitstream/10665/205035/1/9789241549615\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/205035/1/9789241549615_eng.pdf?ua=1) (accessed March 2018);

AASLD recommendations for testing, managing and treating hepatitis C.

Available at: <http://www.hcvguidelines.org/full-report-view> (accessed March 2018).

# Rate of newly diagnosed hepatitis C cases per 100000 population by country\*, EU/EEA, 2016

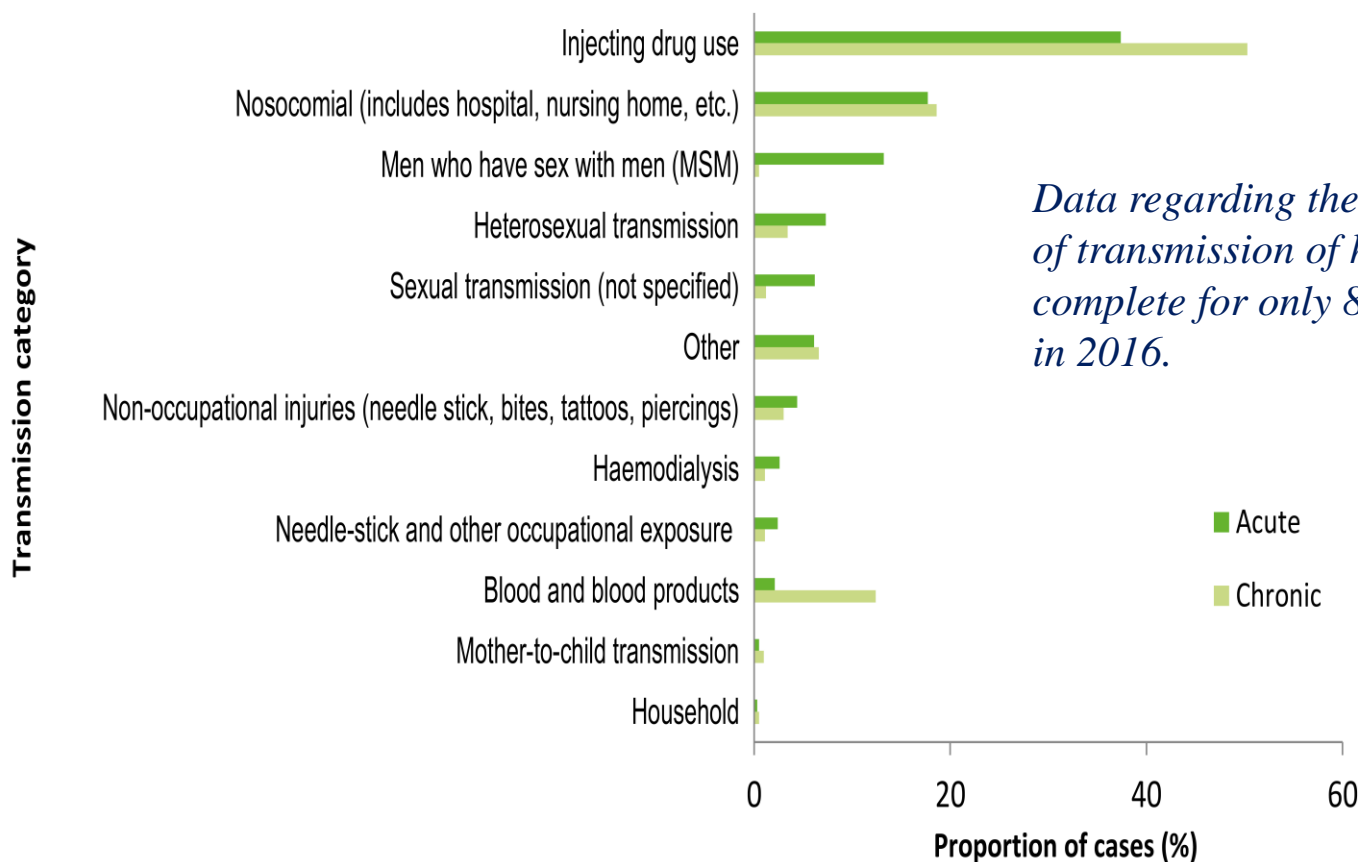


Source: Country reports from Austria, Bulgaria, Croatia, Czech Republic, Cyprus, Denmark, Estonia, Finland, Germany, Greece, Iceland, Ireland, Italy, Latvia, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

\* Countries not reporting or only reporting data on acute cases are excluded.

# The most commonly reported route of transmission across all disease categories was injecting drug use, which accounted for 45.5% of cases with complete information

**Figure 4. Transmission category of hepatitis C cases by acute and chronic disease status, EU/EEA, 2016**

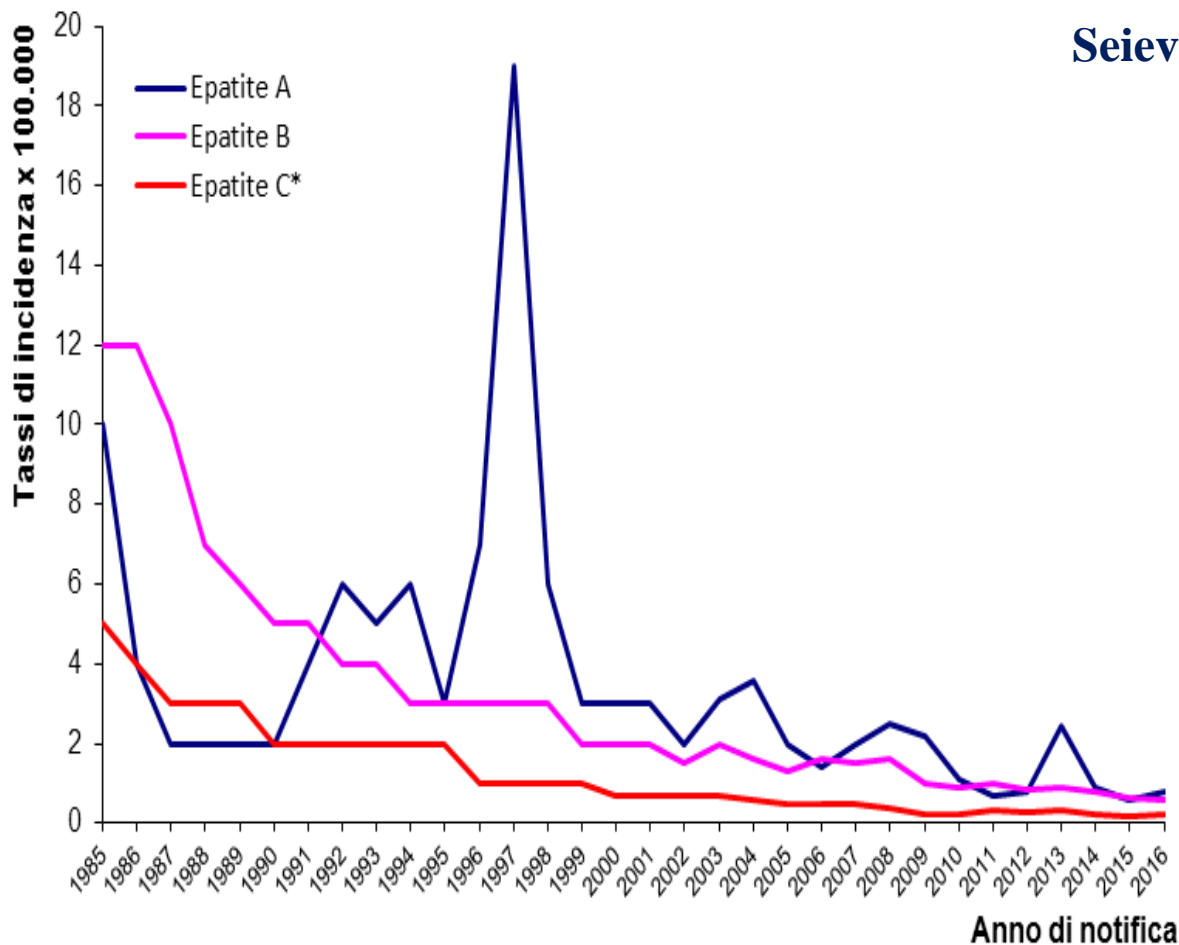


*Data regarding the most likely route of transmission of hepatitis C were complete for only 8 952 (26.4%) cases in 2016.*

Source: Country reports from Austria, Denmark, Estonia, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

Dopo una decisa flessione registrata dal Seieva nei primi dieci anni di sorveglianza, l'incidenza di epatite C acuta ha continuato a decrescere, stabilizzandosi su tassi tra 0,2 e 0,3 casi per 100.000 abitanti, a partire dal 2009. Nel 2016 l'incidenza è stata pari a 0,2 per 100.000 (non sono stati osservati casi nella fascia d'età 0-14 anni; mentre l'incidenza maggiore si ha nella classe di età 25-34 anni: 0,3 x 100.000 abitanti)

### Tassi di incidenza per 100.000 abitanti delle epatiti virali acute, per anno





# I maggiori fattori di rischio riportati sono: i rapporti sessuali non protetti, l'uso di droghe per via endovenosa, gli interventi chirurgici e l'esposizione percutanea in corso di trattamenti cosmetici.

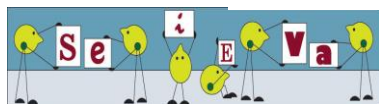
Casi\* notificati di Epatite C con fattore di rischio identificato. SEIEVA 2016.

Fattore di rischio		Fascia di età										TOTALE	
		0-14		15-24		25-34		35-54		55+			
		N.	%	N.	%	N.	%	N.	%	N.	%	N.	%
Parenterale o sessuale	Trasfusione sangue	0	0,0	2	22,2	9	45,0	4	16,7	1	4,0	16	20,5
	Interventi chirurgici	0	0,0	0	0,0	1	6,3	1	4,6	6	23,1	8	11,0
	Ospedalizzazione	0	0,0	1	11,1	4	20,0	3	13,0	6	23,1	14	17,9
	Altre esposizioni parenterali**	0	0,0	3	33,3	3	18,8	5	22,7	5	19,2	16	21,9
	Terapia odontoiatrica	0	0,0	3	37,5	2	12,5	5	22,7	3	12,0	13	18,3
	Uso di droghe E.V.	0	0,0	7	70,0	6	35,3	5	21,7	2	7,7	20	26,3
	Convivente tossicodipendente	0	0,0	3	42,9	1	7,1	0	0,0	0	0,0	4	7,1
	Contatto con itterico nei 6 mesi	0	0,0	4	57,1	1	8,3	1	7,7	0	0,0	6	11,8
	Partner sessuali (>1 nell'ultimo anno)	0	0,0	2	33,3	3	33,3	11	61,1	2	22,2	18	42,9
	Convivente di soggetto HCV+	0	0,0	1	14,3	0	0,0	2	15,4	1	5,6	4	8,5
TOTALE CASI***		0		10		20		25		26		81	

\* I casi possono avere più di un fattore di rischio

\*\* Piercing, tatuaggi, agopuntura, manicure/pedicure, rasatura dal barbiere

\*\*\* Per alcuni casi l'informazione relativa ad alcuni fattori di rischio non è disponibile



**Available epidemiological data on HCV Ab seroprevalence are affected by several limitations; data from available epidemiological studies estimated that seroprevalence of HCV in Italy is the highest in Central Europe likely ranging between 3 and 4.5 %, with different distribution in different age ranks and with a north–south gradient**

Authors	Site of study	Population	<i>n</i>	Year(s) of study	Age	Overall prevalence of anti-HCV (%)
Bellentani et al. [28]	Campogalliano (Modena) and Cormons (Gorizia)	All the citizens aged 12–65 year were contacted by letter	6917	1991–1993	12–65	3.2
Guadagnino et al. [19]	Sersale (Catanzaro)	The sample was selected from the census by a systematic 1:4 sampling procedure	1352	1996	>18	12.6
Guadagnino et al. [17]	Sersale (Catanzaro)	The sample was selected from the census by a systematic 1:4 sampling procedure	1012	2010	>18	5.7
Maio et al. [18]	Buonalbergo (Napoli)	The sample was selected from the census by a random cluster sampling procedure	488	1997	>5	16.2
Di Stafano et al. [20]	Camporeale (Palermo)	A random 1:4 sampling from the census of the general population was performed	721	1999–2000	10–90	10.4
Pendino et al. [21]	Cittanova (Reggio Calabria)	A sample of the general population was selected from the census list using a systematic random 1 in 5 sampling procedure	1645	2002–2003	>12	6.5
Fabris et al. [22]	Vicenza	Tests were offered to inhabitants of a district of the city	965	2002	>0	2.6
Raffaele et al. [24]	Gioia dei Marsi and Lecce dei Marsi (L'Aquila)	Subjects were selected by random sampling among people living in Gioia dei Marsi and Lecce dei Marsi	250	1997	>16	22.4
Cozzolongo et al. [23]	Putignano (Bari)	Using a systematic random 1-in-5 sampling procedure, a sample of the general population >18 years of age was drawn from the general practitioner's list of records	2195	2005–2007	>18	2.6
Mazzeo et al. [25]	Loiano and Monghidoro (Bologna)	All subjects aged 18–69 years who were resident in Loiano and Monghidoro were called	1646	1986–1996	18–69	3.5
Campello et al. [26]	The area of study corresponds to the administrative boundary of the former "USL 22" (Local Health Unit) in the Lombardia Region.	Subjects employed in the processing and/or trade of food and beverages were invited to participate	2154	1994–1995	17–67	3.3
Ansaldi et al. [27]	18 Italian Regions	Tests were performed from residual serum of European Serum Epidemiology Network	3577	1996–1997	0–90	2.7



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## European Journal of Internal Medicine

journal homepage: [www.elsevier.com/locate/ejim](http://www.elsevier.com/locate/ejim)

## Original Article

## Declining prevalence and increasing awareness of HCV infection in Italy: A population-based survey in five metropolitan areas



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 Christian Coco<sup>f</sup>, Maurizio Russello<sup>f</sup>, Antonina Smedile<sup>g</sup>, Elisa Petrini<sup>g</sup>, Silvia Martini<sup>g</sup>,  
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## ARTICLE INFO

## Keywords:

HCV

HCV infection

Epidemiology

Risk factors

## ABSTRACT

**Background:** Data on the prevalence of hepatitis C virus (HCV) infection in Italy are outdated and usually derived from studying residents in small towns.

**Methods:** To assess prevalence of and risk factors for HCV infection among Italian residents in 5 metropolitan areas, subjects  $\geq 20$  years of age were randomly selected from the list of the general practitioners' registers in 2015. Anti-HCV was tested by a salivary test; HCV-RNA, HCV genotypes, and ALT were determined in positive individuals. Logistic regression analysis evaluated independent risk factors for HCV.

**Results:** Of the 4907 enrolled subjects, 112 (2.3%) tested anti-HCV positive. The prevalence of HCV increased with age, from 0.2% in subjects born after the year 1984, to 4.2% in those born before the year 1935 ( $P < 0.01$ ). The birth-cohort prevalence peaked (7.0%) in elderly. Serum HCV-RNA was detected in 1.7% of the whole population. Nearly 80% of anti-HCV subjects were aware of their status. Age  $> 70$  years, low education level, past use of glass syringes, blood transfusion, intravenous drug use, and cohabitation with an anti-HCV positive subject predicted the HCV positivity.

**Interpretation:** In metropolitan areas in Italy, HCV is prevalent in elderly, reflecting a cohort effect determined by modalities of viral transmission no longer operative. The impact of the infection will further diminish in the years to come due to the natural depletion of the reservoir of the virus. This age pattern and the high proportion of subjects aware of their status do not warrant a policy of screening.

	HCV-antibody positive		HCV-antibody negative		Crude Odds Ratios
	n = 112		n = 4795		(95% CI)
	n	%	n	%	
Age (years)					
≤70	64	57	4045	84	1
> 70	48	43	750	16	4,0 (2,8-5,9)
Gender					
Female	51	46	2656	55	1
Male	61	54	2139	45	1,5 (1,0-2,2)
Years of school					
> 8	31	28	2320	48	1
≤8	81	72	2475	52	2,5 (1,6-3,7)
History of IDU					
Never	100	89	4758	99,5	1
Yes	12	1	23	0,5	24,8 (12,0-51,3)
Past use of glass syringes					
No	31	29	2346	52	1
Yes	75	71	2126	48	2,7 (1,8-4,1)
Blood transfusion					
No	84	76	4387	92	1
Yes	27	24	362	8	3,9 (2,5-6,1)
Previous surgery					
No	30	27	1819	38	1
Yes	82	73	2972	62	1,7 (1,1-2,6)
Household contact with a HCV+ subject					
No	88	81	4250	94	1
Yes	21	19	272	6	3,7 (2,3-6,1)
Past hospitalization					
No	53	47	2592	54	
Yes	59	53	2194	46	-
Tattoo/piercing					
No	96	86	4045	84	
Yes	16	14	749	16	-
Area of residency					
North/center	42	37	1955	41	
South/insular	70	63	2840	59	-

# Of the 4907 enrolled subjects, 112 (2.3%) were anti-HCV positive

Serum HCV-RNA was detected in 1.7% of the whole population. **Nearly 80% of anti-HCV subjects were aware of their status**

Age > 70 years, low education level, past use of glass syringes, blood transfusion, intravenous drug use, and cohabitation with an anti-HCV positive subject predicted the HCV positivity.

**The prevalence of HCV increased with age, from 0.2% in subjects born after the year 1984, to 4.2% in those born before the year 1935**

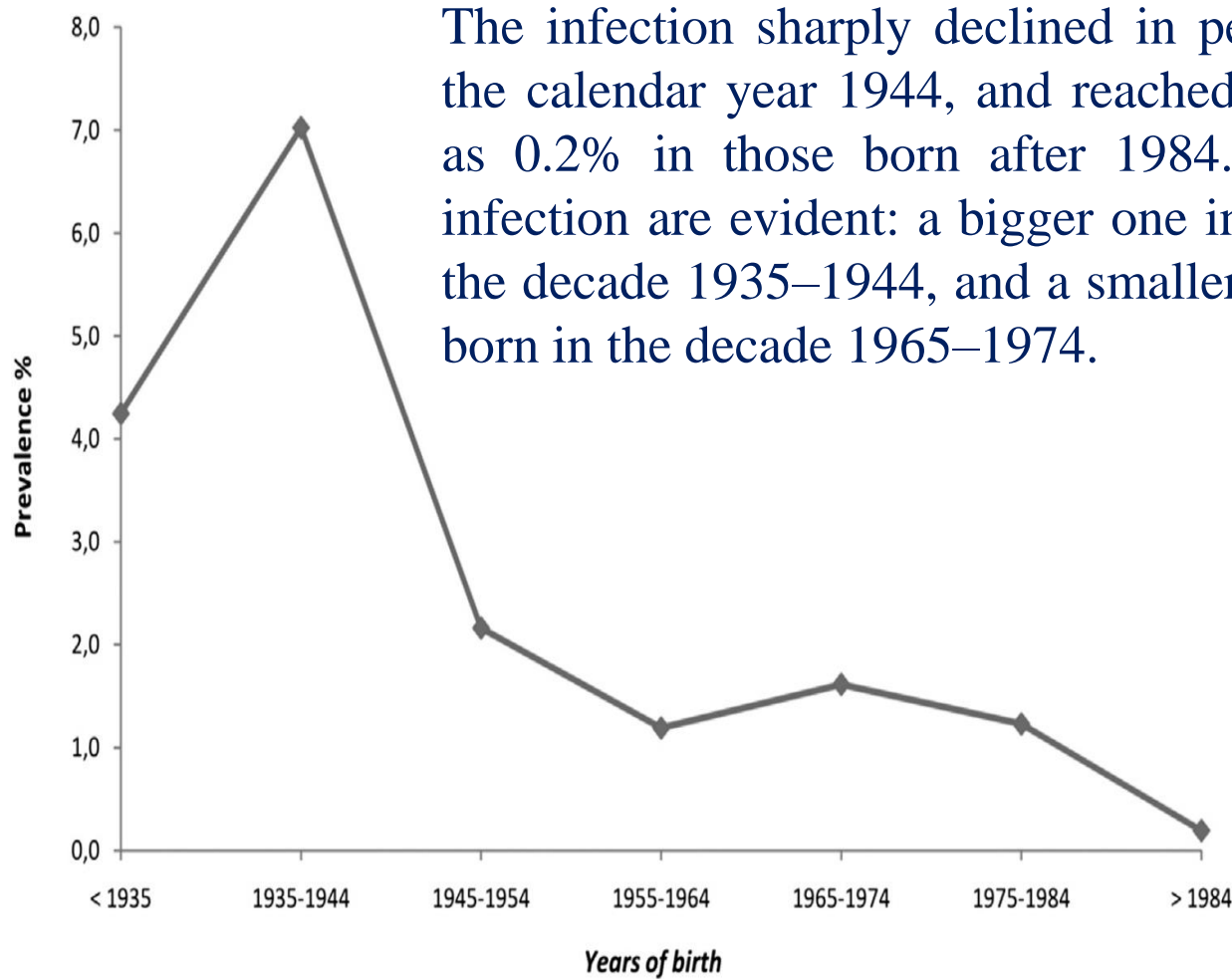


Fig. 1. Prevalence of anti-HCV positivity by cohort of birth in 5 Italian metropolitan areas, 2015.

For residents in North, Central and South Italy, the overall prevalence was 1.6%, 2.6%, and 2.4%, respectively

**Table 2**

Birth-cohort prevalence of anti-HCV by geographical area in five Italian Metropolitan area 2015.

Year of birth	North	Centrum	South
	No. positive/no. tested (%)	No. positive/no. tested (%)	No. positive/no. tested (%)
> 1984	0/160 (0.0)	1/100 (1.0)	0/264 (0,0)
1975–1984	1/165 (0.6)	4/153 (2.6)	3/334 (0.9)
1965–1974	2/180 (1.1)	3/170 (1.8)	9/518 (1.7)
1955–1964	5/172 (2.9)	2/161 (1.2)	5/677 (0.7)
1945–1954	4/151 (2.6)	2/182 (1.1)	15/639 (2.3)
1935–1944	4/124 (3.2)	11/171 (6.4)	32/374 (8.6)
< 1935	0/45 (0.0)	3/63 (4.8)	6/104 (5.8)
Total	16/997 (1.6)	26/1000 (2.6)	70/2910 (2.4)



# Where Are the Undiagnosed and Untreated?



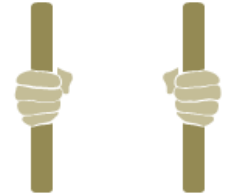
PWID  
(people who  
inject drugs)<sup>1</sup>



MSM  
(men who have  
sex with men)<sup>1</sup>



Ethnic  
Minorities/Migrants<sup>1</sup>



Prisoners<sup>1</sup>



Certain birth cohorts<sup>2</sup>



People living in  
countries with  
restricted access to  
treatment<sup>1</sup>



Patients who are  
lost to follow-up



Patients with chronic  
kidney disease<sup>3</sup>

1. Global Hepatitis Report 2017. Geneva: World Health Organization; 2017. License: CC BY-NC-SA 3.0 IGO. 2. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; 2017. License: CC BY-NC-SA 3.0 IGO. 3. Ladino M et al. *J Am Soc Nephrol.* 2016;27:2238-2246.

## **Incidence of HCV infection amongst HIV positive men who had sex with men and prevalence data from patients followed at the Infectious Diseases Clinic of Modena, Italy.**

[Cuomo G](#)<sup>1</sup>, [Digaetano M](#)<sup>2</sup>, [Menozzi M](#)<sup>3</sup>, [Tagliazucchi S](#)<sup>4</sup>, [Guaraldi G](#)<sup>5</sup>, [Borghi V](#)<sup>6</sup>, [Mussini C](#)<sup>7</sup>.

### Author information

### **Abstract**

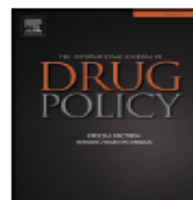
**BACKGROUND:** Men who had sex with men (MSM) living with HIV are at higher risk of developing sexual transmitted diseases. This study reports two years incidence rate and prevalence of HCV in a cohort of HIV positive MSM.

**METHODS:** MSM HIV-positive outpatients negative to HCV-Ab at first observation entered a Kaplan-Meier model in order to assess the HCV infection incidence rate. Prevalence analysis was performed with MSM HIV-positive that were on follow-up at 2016. An MSM population HIV-negative served as control.

**RESULTS:** 421 patients entered the incidence analysis. The incidence rate of HCV infection among MSM-HIV people was 0.44 per 100 patients-years (19 events). 40 out of 442 (9%) patients were HCV-positive (prevalence analysis); they were mostly genotype 1a and 3 with APRI score <0.7 (87.5%). Univariate analysis between MSM HIV-positive patients and MSM HIV-negative showed significant differences in the prevalence rate (9.0% vs 0.6%,  $P < 0.001$ ) and median age (39 vs 47,  $P < 0.001$ ).

**CONCLUSION:** Incidence and prevalence rate of HCV amongst MSM HIV-positive patients is higher than in other settings. Annual HCV-Ab screening for MSM HIV-positive patients should be enforced and early treatment of HCV recommended.

**The development of HCV infection was observed in 19 patients, resulting in a cumulative incidence of 4.5%.**



## Short Report

# Treatment with direct-acting antivirals in a multicenter cohort of HCV-infected inmates in Italy



Emanuele Pontali<sup>a</sup>, Vito Fiore<sup>b</sup>, Anna Maria Ialungo<sup>c</sup>, Roberto Ranieri<sup>d</sup>, Oscar Mollaretti<sup>e</sup>, Giorgio Barbarini<sup>f</sup>, Daniele Marri<sup>g</sup>, Tullio Prestileo<sup>h</sup>, Serena Dell'Isola<sup>c</sup>, Elena Rastrelli<sup>c</sup>, Guido Leo<sup>e</sup>, Giulio Starnini<sup>c</sup>, Sergio Babudieri<sup>b,\*</sup>, Giordano Madeddu<sup>b</sup>, Gruppo Infettivologi Penitenziari

## ABSTRACT

**Background:** People who are incarcerated have a significantly higher prevalence of HCV infection than the general population. Given their high-risk behavior, they represent a reservoir of HCV infection for the whole community.

**Methods:** We evaluated all HCV-infected people who were incarcerated in 25 Italian prisons starting direct-acting antivirals (DAAs) treatment between May 2015 and October 2016. We collected information on demographic characteristics, liver disease, HCV-related aspects, anti-HCV treatment, HIV or HBV co-infection.

**Results:** We enrolled 142 incarcerated people treated with DAAs. They were mostly Italians (93.7%) and males (98.6%). Median age was 50 years and 108/142 (76.1%) were cirrhotic patients. Prevalent genotypes were 1a (35.9%) and 3 (35.9%). Two patients were HBV co-infected, twenty-one patients (14.8%) were HIV co-infected and almost all (95.2%) received antiretroviral therapy. 118/142 (83.1%) DAAs-based regimens included sofosbuvir. Treatment completion rate was 94.4%. There were eight (5.6%) discontinuations, one (0.7%) due to an adverse reaction, one due to death (0.7%) and six (5.6%) due to release from prison. SVR12 was achieved in 90.8%. Four patients relapsed but no breakthrough occurred.

**Conclusions:** Our study shows that in Italian penitentiary settings DAAs treatment is feasible and effective. This intervention is crucial for reducing HCV circulation with possible benefits to the general population.

**Table 1**

Demographic, clinical and virological features, anti-HCV regimens and treatment outcome among 142 inmates from twenty-five Italian prisons receiving direct-acting antivirals.

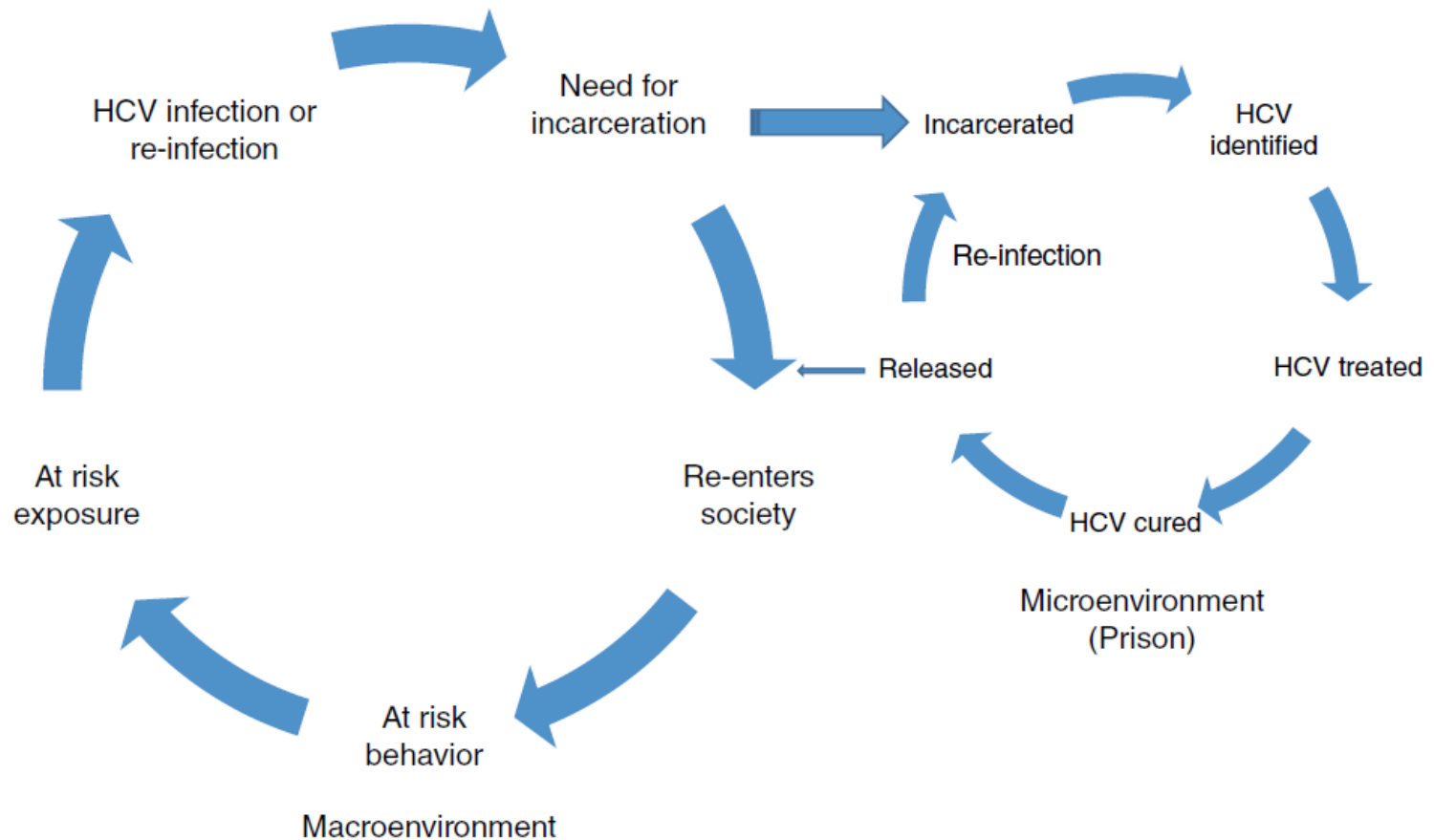
Variable	
Italian nationality	133/142 (93.7%)
Age	50 ± 7.5
Male gender	140/142 (98.6%)
Co-infections	
HIV co-infection	21/142 (14.8%)
HBV co-infection	2/142 (1.4%)
Laboratory abnormalities	
Thrombocytopenia	67/142 (47.2%)
Hepatic transaminase increase	135/142 (95.1%)
Stage of liver disease	
Liver cirrhosis	108/142 (76.1%)
Child-Pugh A	98/142 (90.7%)
Child-Pugh B	10/142 (9.3%)
Previous HCC diagnosis	4/142 (2.8%)
Liver fibrosis F3 according to METAVIR	24/142 (16.9%)
Liver fibrosis F2 according to METAVIR	7/142 (4.9%)
Liver fibrosis F0-F1 according to METAVIR	3/142 (2.1%)
HCV genotype	
1a	51/142 (35.9%)
1b	21/142 (14.8%)
2	8/142 (6.1%)
3	51/142 (35.9%)
4	11/142 (7.3%)
HCV-RNA baseline	2,293,374 UI/ml (IQR = 1,474,225 UI/ml)
DAA regimens	
sofosbuvir + ledipasvir ± ribavirin	50/142 (35.2%)
sofosbuvir + daclatasvir ± ribavirin	47/142 (33.1%)
sofosbuvir + simeprevir ± ribavirin	14/142 (9.9%)
sofosbuvir + ribavirin	7/142 (4.9%)
ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin	14/142 (9.9%)
simeprevir + pegylated interferon alpha 2a + ribavirin	10/142 (7.0%)
Treatment outcome	
SVR12 at ITT	129/142 (90.8%)
SVR12 at mITT	129/134 (96.2%)
Virologic response at EOT	135/142 (95.1%)
Virologic failures	5/142 (3.5%)
Lost after EOT	8/142 (5.6%)

Data expressed as mean ± standard deviation, mean (IQR) or number/total (percentage).

DAA: direct-acting antivirals; SVR: sustained virological response; ITT: intention-to-treat.

mITT: modified intention-to-treat; EOT: end of treatment.

# High-risk behavior increases the risk of acquiring HCV



Many exposed patients spend time incarcerated in the prison microenvironment, providing opportunity for detection and treatment of HCV. Upon release, patients re-enter society and are once again at risk for further re-exposure; however, they now presumably put others at less risk after prison-based HCV treatment

Many lessons learnt from HIV can be helpful for designing adequate treatment strategies against viral hepatitis such as HCV....



# The personalized medicine

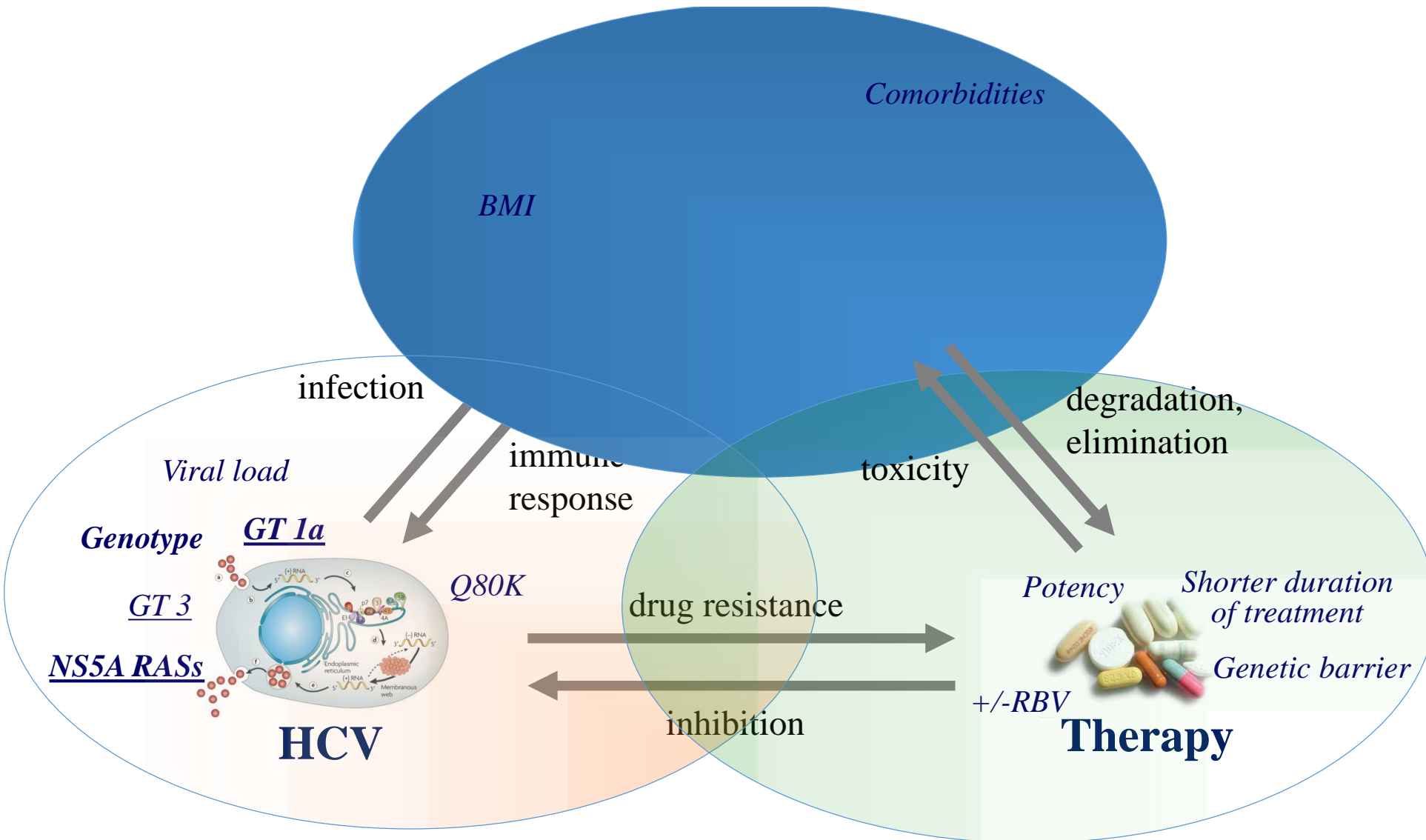
All international guidelines focus on the importance of **tailoring antiretroviral therapy** to the individual patient, on the basis of **HIV-1 genetic data**, integrated with clinical, laboratory and therapeutic information.



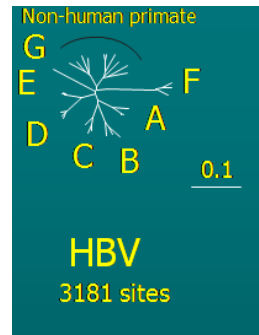
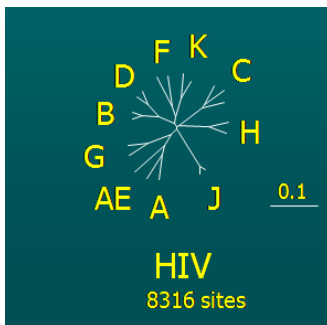
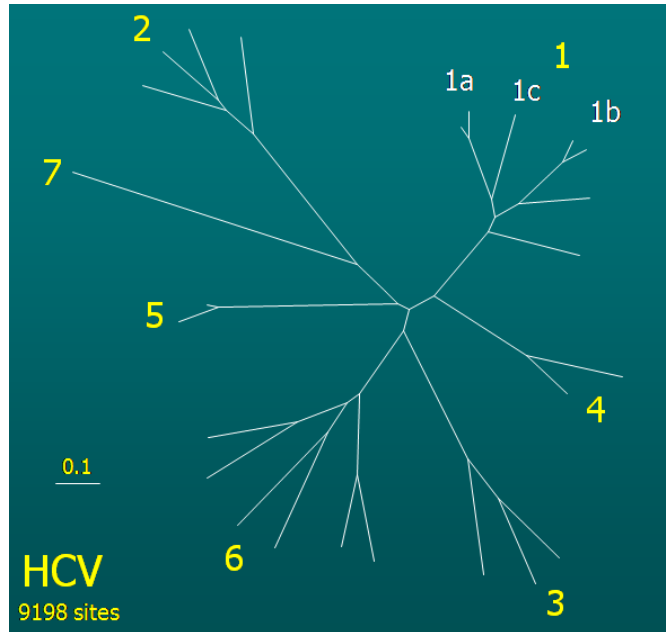
*Profilo di volti  
Ernesto Treccani*



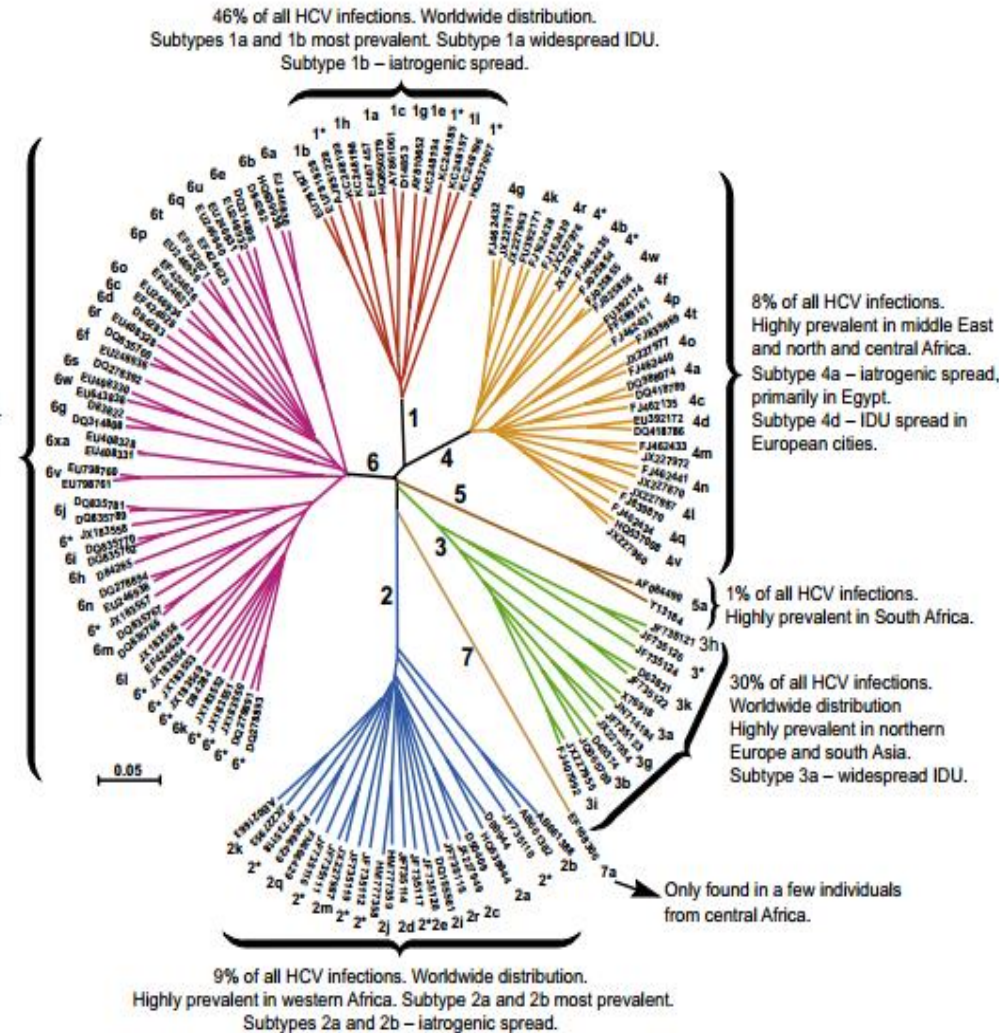
# Many factors contribute to viral response to DAA-treatment



# HCV genetic variability is higher than HIV's and HBV's



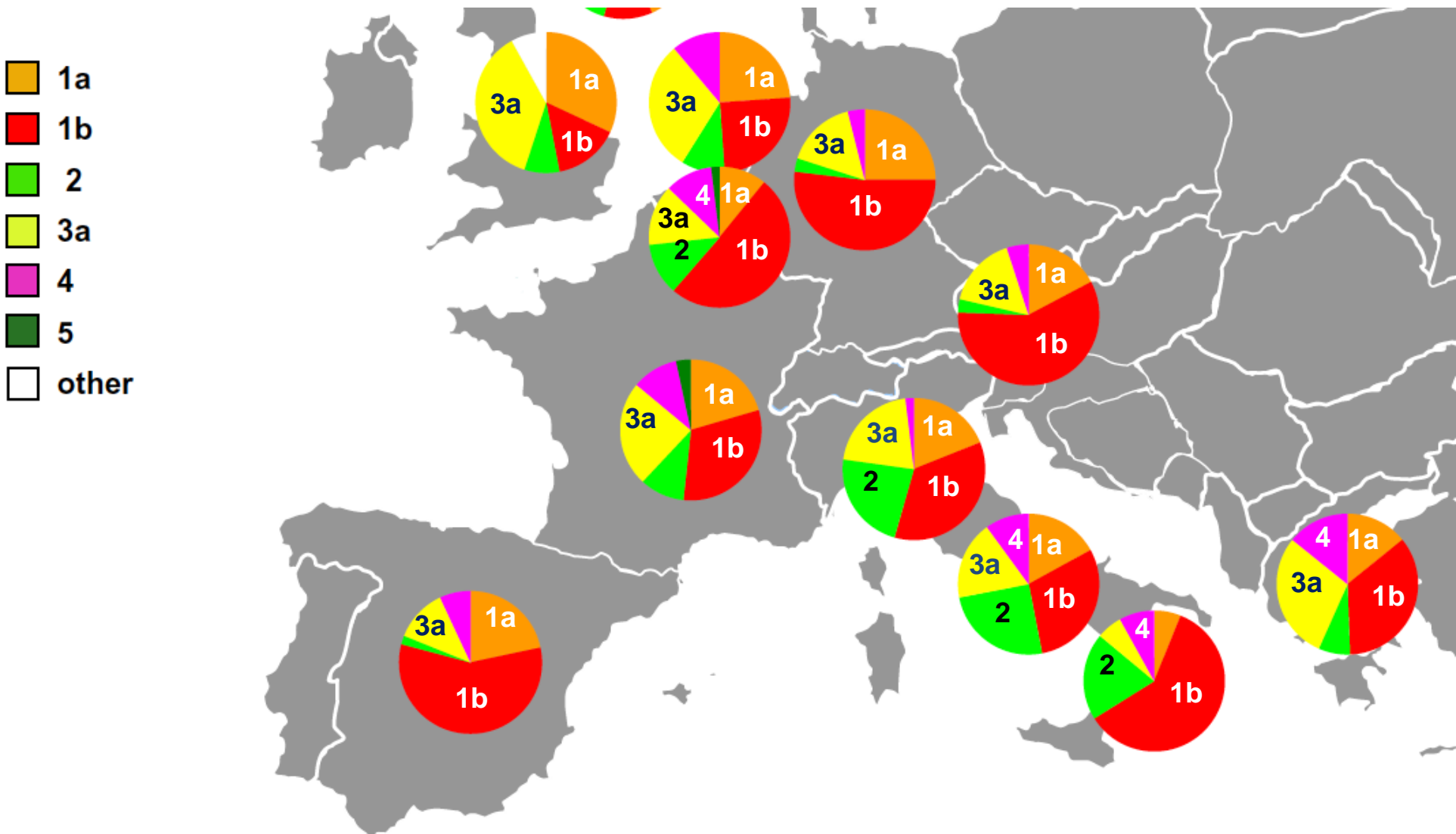
6% of all HCV infections. Prevalent in southeast Asia. Subtype 6a – IDU spread in Hong Kong and Vietnam.



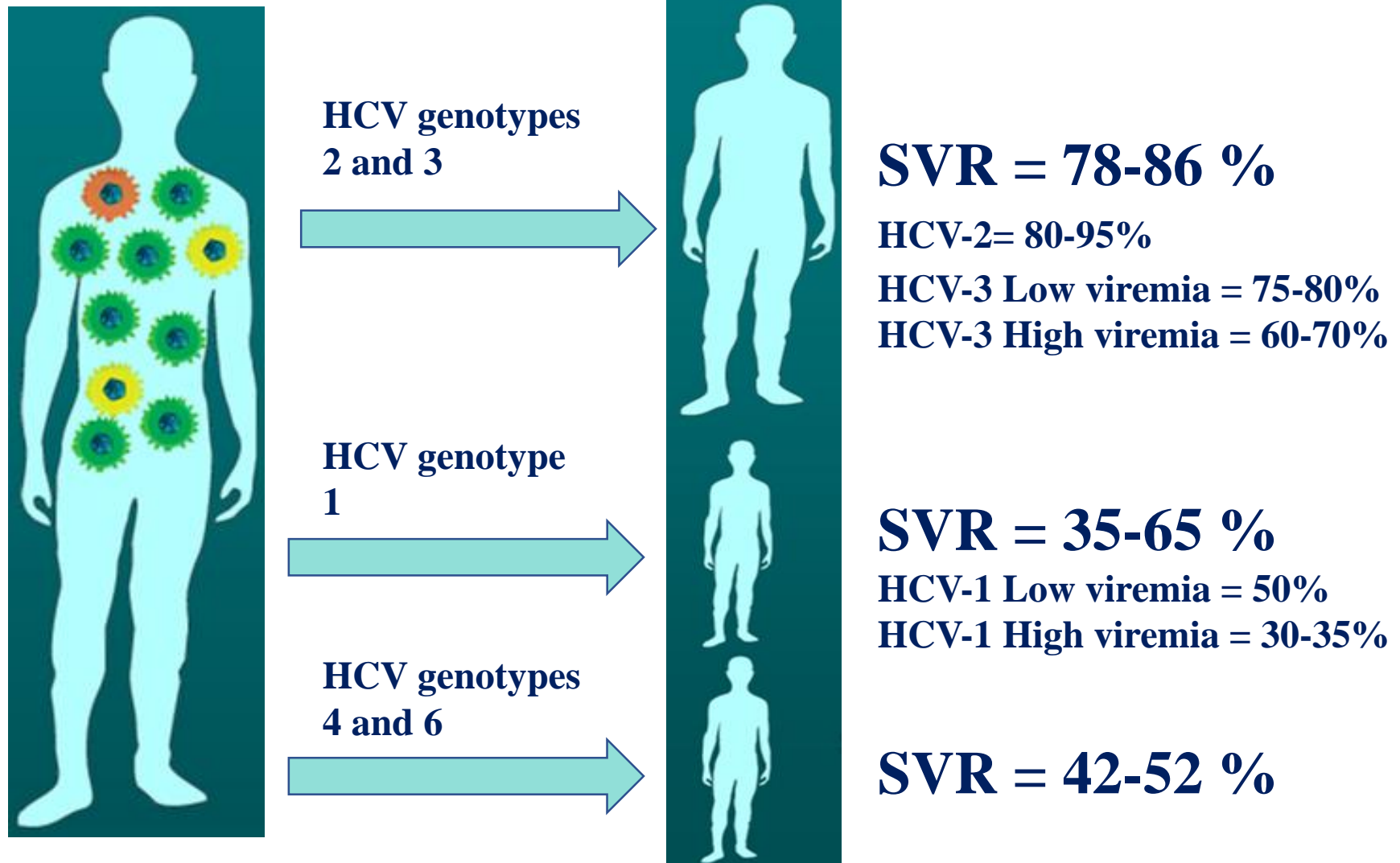
Jens Bukh 2016 *J Hepatol*

31%–33% nucleotide difference among the 7 known HCV genotypes and 20%–25% among the nearly 67 HCV subtypes (Smith et al., 2014).

# Genotype 1 is by far the most frequent genotype in chronically infected patients worldwide as well as in Europe



# HCV genotype was the most important baseline predictor for response to Peg-IFN + Ribavirin combination therapy



*Manns, Lancet 2001; Fried, N Engl J Med 2002; Hadziyannis, Ann Intern Med 2004; Alfaleh, Liver Int 2004*

The underlying functional mechanisms for lower SVR rates of the different HCV genotypes were unknown

*The Journal of Infectious Diseases*

MAJOR ARTICLE



# Identification of a Novel Hepatitis C Virus Genotype From Punjab, India: Expanding Classification of Hepatitis C Virus Into 8 Genotypes

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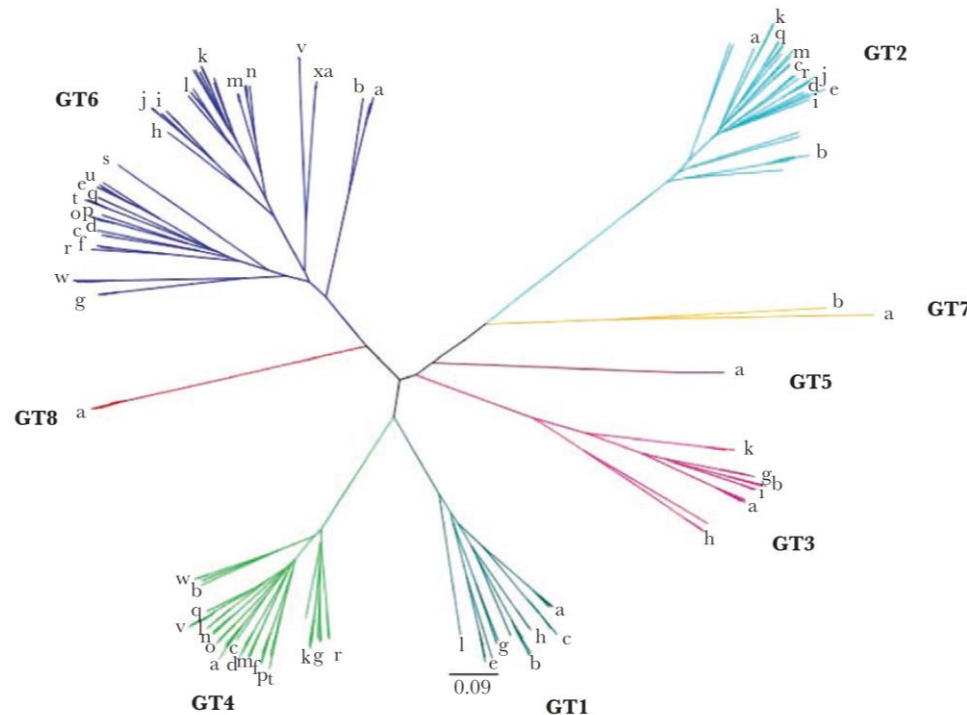
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Received 14 February 2018; editorial decision 25 June 2018; accepted 27 June 2018; published online June 30, 2018.



# A novel HCV GT was recently identified in 4 patients originating from Punjab, India

This novel HCV GT, **GT8**, is genetically distinct from previously identified HCV GT1–7 with >30% nucleotide sequence divergence to the established HCV subtypes.



**Figure 2.** Punjabi districts from which patients with hepatitis C virus genotype 8 originated. Two patients were from the Ludhiana district, 1 from the Barnala district and 1 from the Sangur district. Insert, Punjab State in red.

The estimated prevalence of HCV infection in India is approximately 0.5%–2.0%, with GT3 being most common. Despite the low prevalence of HCV, India with its large population accounts for a significant proportion of the global HCV burden with approximately 12–18 million people infected

# The four patients were previously identified to be infected with GT5 by LiPA or Abbott RealTime polymerase chain reaction assays

Despite presence of baseline resistance-associated substitutions within the GT8 virus of all 4 patients, all patients achieved a sustained virologic response; 2 treated with sofosbuvir/velpatasvir/voxilaprevir for 8 weeks, 1 with sofosbuvir/ledipasvir plus ribavirin for 24 weeks and 1 with sofosbuvir plus daclatasvir for 12 weeks.

**Table 1. Characteristics of Patients with GT8 HCV Infection**

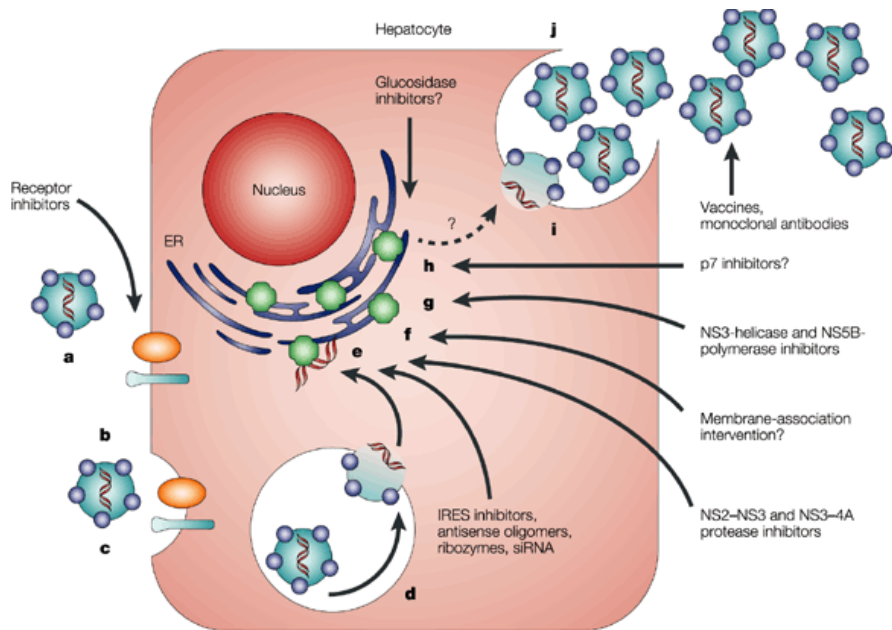
Patient	HCV VL (IU/mL)	Country (Origin)	Race	Age	Sex	GT by Abbott or LiPA	GT by Phylo Analyses	Resistance-Associated Substitutions <sup>a</sup>			Treatment	SVR12
								NS3 RASs	NS5A RASs	NS5B RASs		
1	20 100 000	CAN (Kalala village, Barnala District, Punjab, India)	Asian	28	Male	GT5	GT8	V36L Q80K	Q30S Y93S	None	SOF/VEL/VOX 8 wks	Yes
2	8 710 000	CAN (Rampura village, Sangrur District, Punjab State, India)	Asian	31	Male	GT5	GT8	V36L Q80R	Q30S Y93S	None	SOF/VEL/VOX 8 wks	Yes
3	4 735 001	CAN (Ludhiana City, Ludhiana District, Punjab, India)	Asian	40	Male	GT5	GT8	V36L Q80R	Q30S Y93S	None	SOF + DCV 12 wks	Yes
4	4 200 000	CAN (Raikot City, Ludhiana District, Punjab State, India)	Asian	66	Female	GT5	GT8	V36L Q80K	Q30S Y93S	None	LDV/SOF + RBV 24 wks	Yes

Abbreviations: CAN, Canada; DAA, direct-acting antiviral; DCV, daclatasvir; GT, genotype; HCV, hepatitis C virus; LVD, ledipasvir; RAS, resistance-associated substitution; RBV, ribavirin; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SVR, sustained virologic response; VL, viral load.

<sup>a</sup>RASs are defined as substitutions that confer reduced susceptibility to any approved DAA inhibitor with >2.5-fold change compared with GT1a reference (HCV1a H77 NC AF009606).



# Mutations occur frequently during the replication of HCV



It has been predicted that every nucleoside of the 3.2 kb HBV genome or the 10 kb HIV and HCV genomes theoretically can be substituted every day within a given infected patient

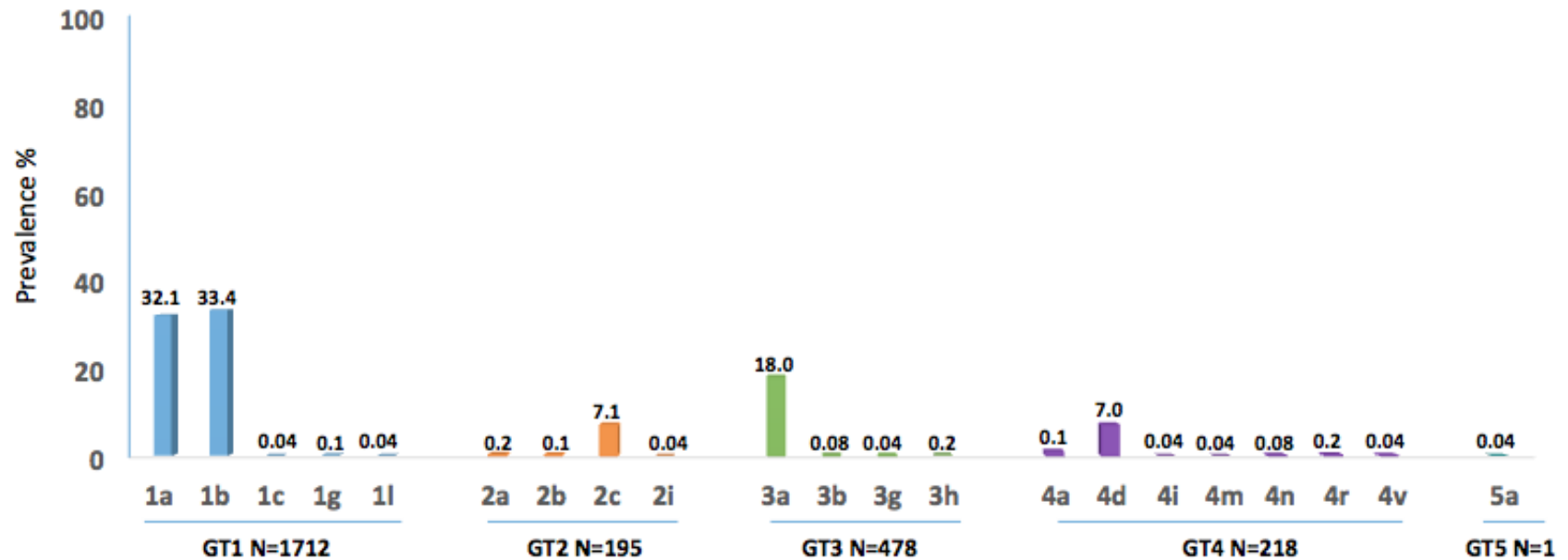
**Table 1.** Probabilities and rates of generation of various HCV mutants.

Time	Number of nucleotide changes	Probability	Number of virions generated per day	Number of all possible mutants	Fraction of all possible mutants created per day
Before therapy	0	0.91	$9.1 \times 10^{11}$		
	1	0.087	$8.7 \times 10^{10}$	$2.9 \times 10^4$	1
	2	0.0042	$4.2 \times 10^9$	$4.1 \times 10^8$	1
	3	0.00013	$1.3 \times 10^8$	$4.0 \times 10^{12}$	$3.4 \times 10^{-5}$
End of first day of therapy*	0	0.91	$9.1 \times 10^6$		
	1	0.087	$8.7 \times 10^5$	$2.9 \times 10^4$	1
	2	0.0042	$4.2 \times 10^4$	$4.1 \times 10^8$	$1.0 \times 10^{-4}$
	3	0.00013	$1.3 \times 10^3$	$4.0 \times 10^{12}$	$3.4 \times 10^{-10}$

\*Additional drug-resistant or compensatory mutation after a 5-log<sub>10</sub> decrease in the HCV RNA production during treatment



# Distribution of HCV genotypes/subtypes within the Italian resistance database Vironet C (N=2604 patients)



OPEN

## Prevalence of Single and Multiple Natural NS3, NS5A and NS5B Resistance-Associated Substitutions in Hepatitis C Virus Genotypes 1–4 in Italy

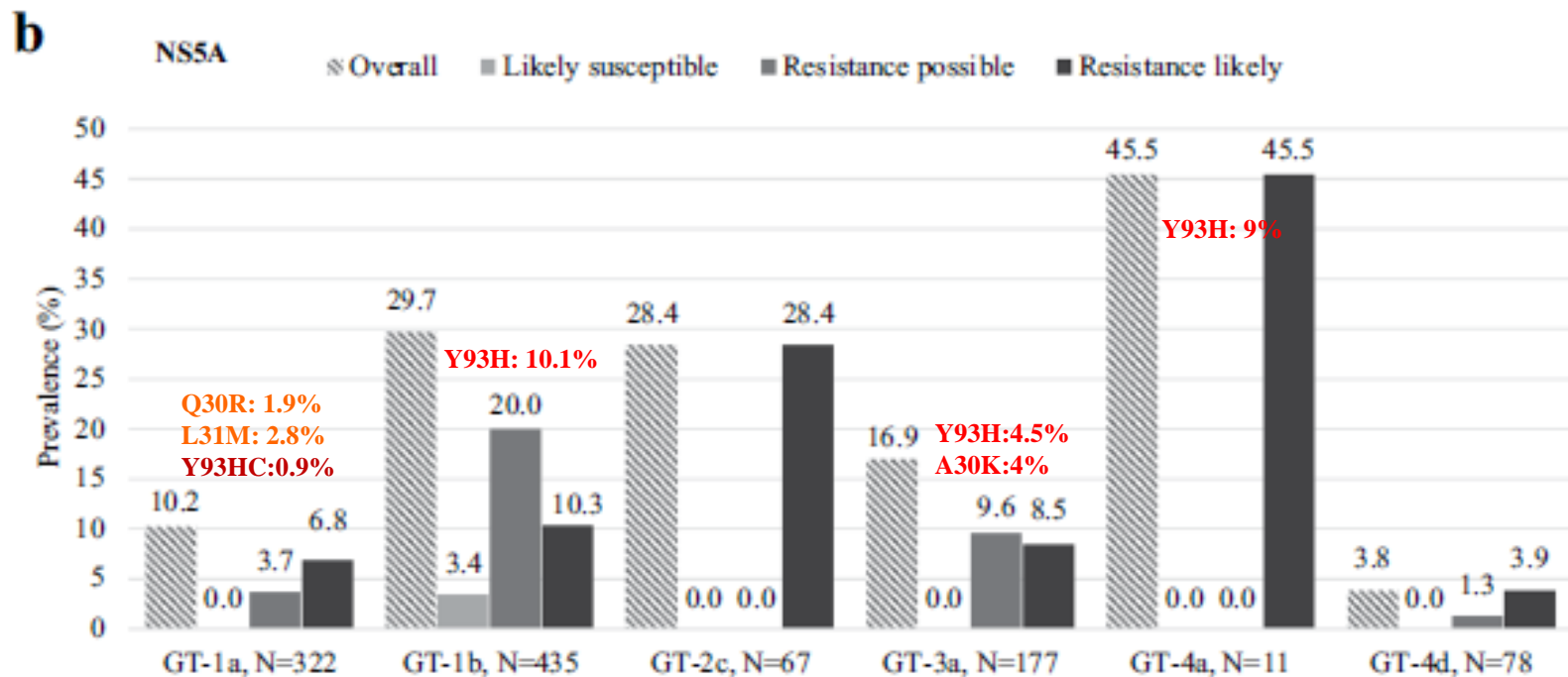
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Ada Bertoli<sup>1</sup>, Maria Chiara Sorbo<sup>1</sup>, Marianna Aragri<sup>1</sup>, Ilaria Lenci<sup>2</sup>, Elisabetta Teti<sup>3</sup>, Ennio Polilli<sup>4</sup>, Velia Chiara Di Maio<sup>1</sup>, Laura Gianserra<sup>5</sup>, Elisa Biliotti<sup>6</sup>, Chiara Masetti<sup>2</sup>, Carlo F. Magni<sup>7</sup>, Sergio Babudieri<sup>8</sup>, Laura A. Nicolini<sup>9</sup>, Martina Milana<sup>2</sup>, Pierluigi Cacciatore<sup>4</sup>, Loredana Sarmati<sup>3</sup>, Adriano Pellicelli<sup>10</sup>, Stefania Paolucci<sup>11</sup>, Antonio Craxi<sup>12</sup>, Filomena Morisco<sup>13</sup>, Valeria Pace Palitti<sup>14</sup>, Massimo Siciliano<sup>15</sup>, Nicola Coppola<sup>16</sup>, Nerio Iapadre<sup>17</sup>, Massimo Puoti<sup>18</sup>, Giuliano Rizzardini<sup>7</sup>, Gloria Taliani<sup>6</sup>, Caterina Pasquazzi<sup>5</sup>, Massimo Andreoni<sup>3</sup>, Giustino Parruti<sup>4</sup>, Mario Angelico<sup>2</sup>, Carlo Federico Perno<sup>19</sup>, Valeria Cento<sup>1</sup>, Francesca Ceccherini-Silberstein<sup>1</sup> & HCV Virology Italian Resistance Network (VIRONET-C)\*

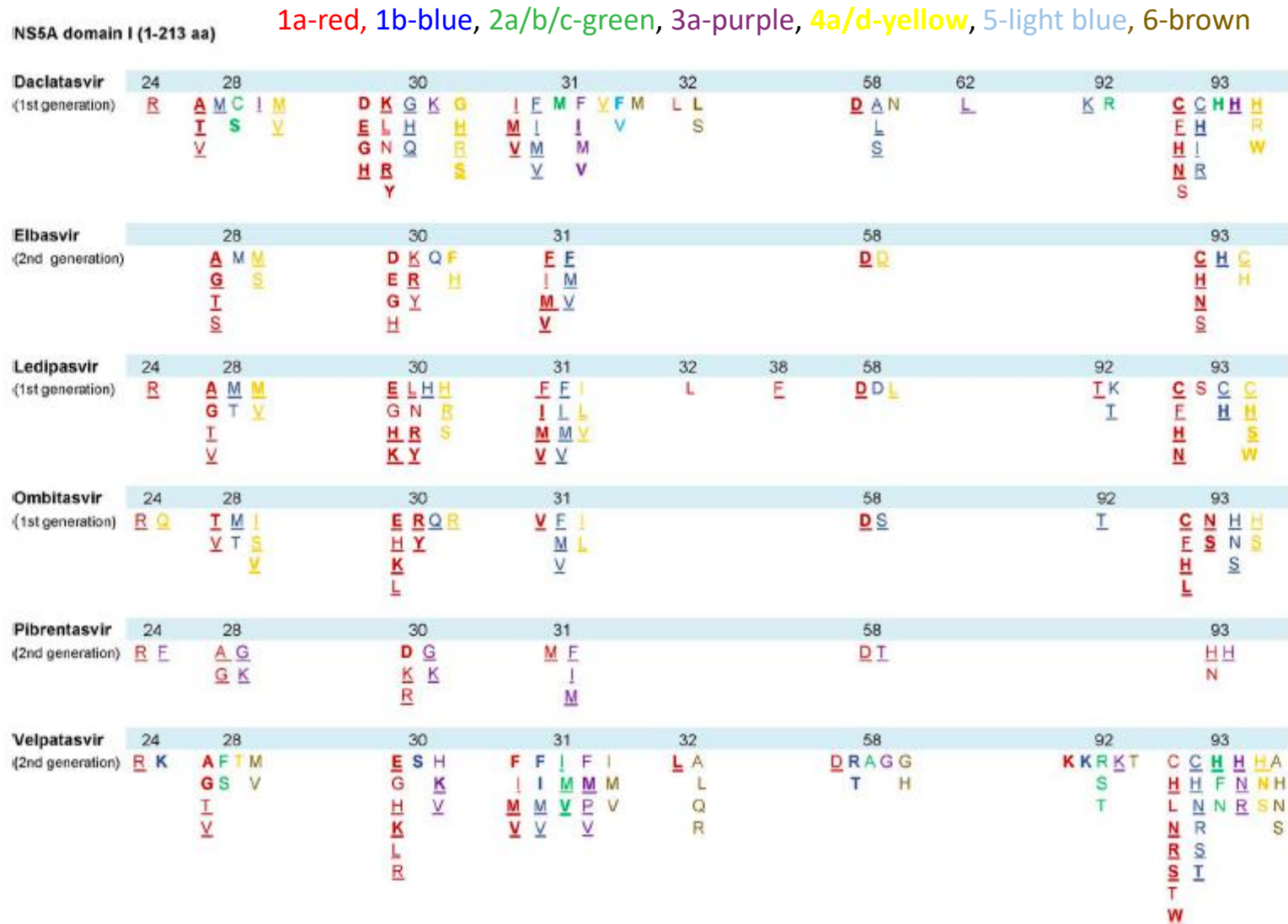
Natural resistance-associated substitutions (RASs) are reported with highly variable prevalence across different HCV genotypes (GTs). Frequency of natural RASs in a large Italian real-life cohort of patients infected with the 4 main HCV-GTs was investigated. NS3, NS5A and NS5B sequences were analysed in 1445 HCV-infected DAA-naïve patients. Sanger-sequencing was performed by home-made protocols on 464 GT1a, 585 GT1b, 92 GT2c, 199 GT3a, 16 GT4a and 99 GT4d samples. Overall, 20.7% (301/1455) of patients showed natural RASs, and the prevalence of multiclass-resistance was 7.3% (29/372 patients analysed). NS3-RASs were particularly common in GT1a and GT1b (45.2–10.8%, respectively), mainly due to 80K presence in GT1a (17%). Almost all GTs showed high prevalence of NS5A-RASs (range: 10.2–45.4%), and especially of 93H (5.1%). NS5A-RASs with fold-change >100x were detected in 6.8% GT1a (30H/R-31M-93C/H), 10.3% GT1b (31V-93H), 28.4% GT2c (28C-31M-93H), 8.5% GT3a (30K-93H), 45.5% GT4a (28M-30R-93H) and 3.8% GT4d (28V-30S-93H). Sofosbuvir RAS 282T was never detected, while the 159F and 316N RASs were found in GT1b (13.4–19.1%, respectively). Natural RASs are common in Italian patients infected with HCV-GTs 1–4. High prevalence of clinically-relevant RASs (such as Y93H) supports the appropriateness of HCV resistance-test to properly guide DAA-based therapy.

The prevalence of pre-treatment NS5A RASs in GT-1 is different across different countries, ranging from 6% to 25%, and different according to subtype.....

*The Italian experience: different NS5A RASs prevalence according to genotype and subtype in DAA naive patients*



# Not all NS5A RASs are equally clinical relevant



**Summary of NS5A substitutions associated with resistance to NS5A inhibitors.** HCV genotypes and subtypes are represented by different colors: 1a-red, 1b-blue, 2a/b/c-green, 3a-purple, 4a/d-yellow, 5-light blue, 6-brown. Amino acid substitutions detected *in vivo* in DAA failing patients are underlined, independently of *in vitro* data information. In addition, NS5A RASs detected only *in vitro* but associated with fold-change in drug activity compared to the wild-type replicons  $\geq 100$  (1<sup>st</sup> generation NS5A-inhibitors,) or  $\geq 3$  (2<sup>nd</sup> generation NS5A-inhibitors) are also included in the figures. For 1<sup>st</sup> generation NS5A-inhibitors, *in vivo* substitutions with fold-change  $\geq 100$ , and *in vitro* substitutions with fold-change  $> 000$  are represented in bold. For 2<sup>nd</sup> generation NS5A-inhibitors, *in vivo* and/or *in vitro* substitutions with fold-change  $> 10$  are represented in bold.



Format: Abstract ▾

Send to ▾

Hepatology. 2018 Aug 19. doi: 10.1002/hep.30225. [Epub ahead of print]

## Frequent antiviral treatment failures in patients infected with hepatitis C virus genotype 4, subtype 4r.

Fourati S<sup>1,2</sup>, Rodriguez C<sup>1,2</sup>, Hézode C<sup>2,3</sup>, Soulier A<sup>1,2</sup>, Ruiz I<sup>2,3</sup>, Poiteau L<sup>1,2</sup>, Chevaliez S<sup>1,2</sup>, Pawlotsky JM<sup>1,2</sup>.

⊕ Author information

### Abstract

Hepatitis C virus (HCV) genotype 4 is highly heterogeneous. HCV subtype 4r has been suggested to be less responsive to direct-acting antiviral (DAA) drug treatment than other genotype 4 subtypes. Among 537 DAA-treated patients who experienced a virological failure in France between 2015 and 2018, 121 (22.5%) were infected with genotype 4 and 27 of them (22.3%) with subtype 4r; subtype 4r was thus over-represented as compared to its prevalence in the French general population. Population sequencing of the NS3, NS5A and NS5B genes was performed in all subtype 4r patients at treatment failure and in 6 of them at baseline, while full-length HCV genome sequencing was performed in 2 baseline and 3 treatment failure samples by means of an original shotgun metagenomics method based on deep sequencing. At treatment failure, all subtype 4r patients harbored 2 to 3 dominant NS5A resistance-associated substitutions (RASs), including at least L28A/C/I/M/V and L30R. Among 13 patients exposed to sofosbuvir and an NS5A inhibitor (daclatasvir, ledipasvir or velpatasvir), 5 (38.5%) also harbored NS5B S282C/T RASs at treatment failure. An additional patient harbored S282C/T RASs at treatment failure by deep sequencing. The prevalence of S282C/T RASs at treatment failure was significantly higher in patients infected with genotype 4r than with other genotypes, including other subtypes of genotype 4.

**CONCLUSION:** The lower rates of SVR in patients infected with subtype 4r are related to the frequent preexistence at treatment baseline and subsequent selection by DAA treatment of both NS5A and NS5B S282 RASs. Our study suggests that these patients should be identified and receive a triple DAA combination regimen as first-line treatment. This article is protected by copyright. All rights reserved.

This article is protected by copyright. All rights reserved.

**KEYWORDS:** HCV ; direct-antiviral agents; genotype 4; resistance

# HCV genotype still dictates the choice of anti-HCV drugs and can modulate the duration of treatment in infected patients with chronic hepatitis C

The HCV genotype, including genotype 1 subtype (1a or 1b), should be assessed prior to treatment initiation.

## EASL Recommendations on Treatment of Hepatitis C 2018

Genotype	Pangenotypic regimens			Genotype-specific regimens		
	SOF/VEL	GLE/PIB	SOF/VEL/VOX	SOF/LDV	GZR/EBR	OBV/PTV/r + DSV
Genotype 1a	Yes	Yes	No*	Yes <sup>a</sup>	Yes <sup>b</sup>	No
Genotype 1b	Yes	Yes	No*	Yes	Yes	Yes
Genotype 2	Yes	Yes	No*	No	No	No
Genotype 3	Yes <sup>c</sup>	Yes	Yes <sup>d</sup>	No	No	No
Genotype 4	Yes	Yes	No*	Yes <sup>a</sup>	Yes <sup>e</sup>	No
Genotype 5	Yes	Yes	No*	Yes <sup>a</sup>	No	No
Genotype 6	Yes	Yes	No*	Yes <sup>a</sup>	No	No

DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; IFN, interferon; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

\* Triple combination therapy efficacious but not useful due to the efficacy of double combination regimens.

<sup>a</sup> Treatment-naïve patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis.

<sup>b</sup> Treatment-naïve and treatment-experienced patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis with an HCV RNA level  $\leq 800,000$  IU/ml ( $5.9 \log_{10}$  IU/ml).

<sup>c</sup> Treatment-naïve and treatment-experienced patients without cirrhosis.

<sup>d</sup> Treatment-naïve and treatment-experienced patients with compensated (Child-Pugh A) cirrhosis.

<sup>e</sup> Treatment-naïve patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis with an HCV RNA level  $\leq 800,000$  IU/ml ( $5.9 \log_{10}$  IU/ml).

Rating: Class I, Level A

Testing for HCV genotype is recommended to guide selection of the most appropriate antiviral regimen.



HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

Update 21 Sept 2017



HCV GT	Regimen	Duration, Wks	
		No Cirrhosis	Compensated Cirrhosis
1	GLE/PIB	8	12
	GZR/EBR	12	12
	SOF/LDV	8 or 12	12
	SOF/VEL	12	12
2 or 3	GLE/PIB	8	12
	SOF/VEL	12	12
4	GLE/PIB	8	12
	SOF/VEL	12	12
	GZR/EBR	12	12
	SOF/LDV	12	12
5 or 6	GLE/PIB	8	12
	SOF/LDV	12	12
	SOF/VEL	12	12



# Issues in HCV genotyping



# HCV Sanger sequencing confirmed the previous genotype by commercial-assays in 89.7% of cases analysed

	Patients (N)	Patients (%)
Genotype/subtype confirmed	1627	89.7

**Overall, 95 out of 1813 (5.2%) HCV infected patients candidate to start a treatment containing a DAA showed a discordant genotype or subtype according to the sequencing**

## Discordant cases

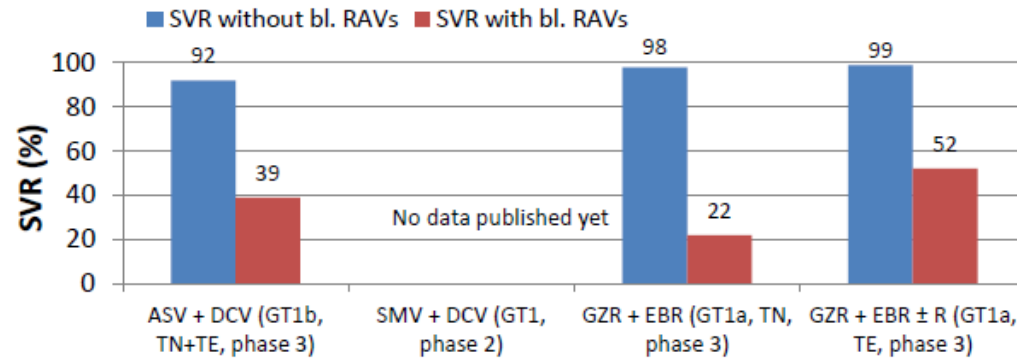
Discordant genotypes	37	2.0
Genotype 1 with discordant subtype	58	3.2
Total	1813	100

# HCV sequencing is useful for identifying RASs but also the “correct” genotype: 15/310 (4.8%) patients were found infected with a different HCV genotype at failure

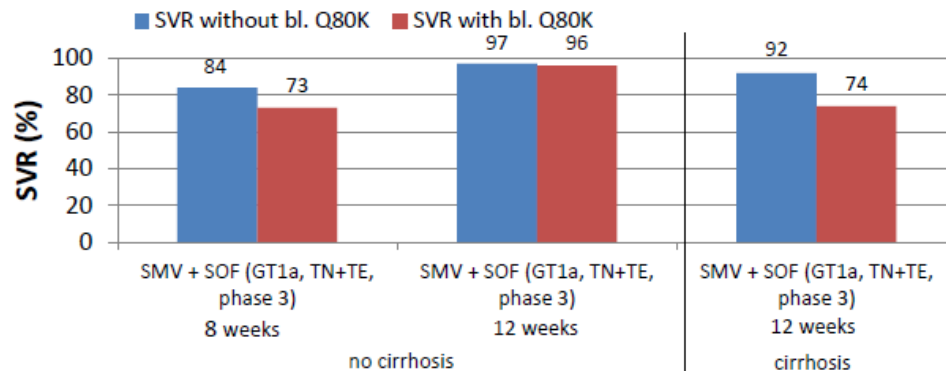
Notably, 10 patients previously classified as infected with HCV-1 were actually infected with HCV-2 and HCV-3, 9/10 failed a 3D+RBV regimen and all presented RASs at failure

ID Patient	Pre-therapy genotype by commercial assay	Genotype by sequencing at failure	DAA regimen	DAA response	Failure RASs		
					NS3	NS5A	NS5B
1497	1a	3a	3D+RBV	Non-responder		Y93H	
2150	1a	3a	3D+RBV	Breakthrough	Q80K	Y93H	
2068	1b	3a	3D	Non-responder	Q80K	Y93H	
1424	1b	3a	3D+RBV	Non-responder		Y93H	
2140	1b	3a	3D+RBV	Non-responder		A30K	
2353	1	3a	3D	Non-responder		Y93H	
1823	1b	2c	3D+RBV	Non-responder	D168V		
2020	1b	2c	3D	Non-responder	D168V	F28C	
2623	1b	2c	3D	Relapse		F28C	
2890	1b	2c	SMV+SOF	Relapse		L31M	
2204	2	1b	LDV+SOF+RBV	Relapse		R30Q+L31I+Y93H	C316N
2886	2	1b	SOF+RBV	Relapse	Y56F		C316N
2153	2	3a	SOF+RBV	Relapse		A30K+L31F	
1111	4	1a	2D+RBV	Breakthrough	V36M+Y56H	M28T	
45	4	3a	SMV+SOF	Relapse	D168K		

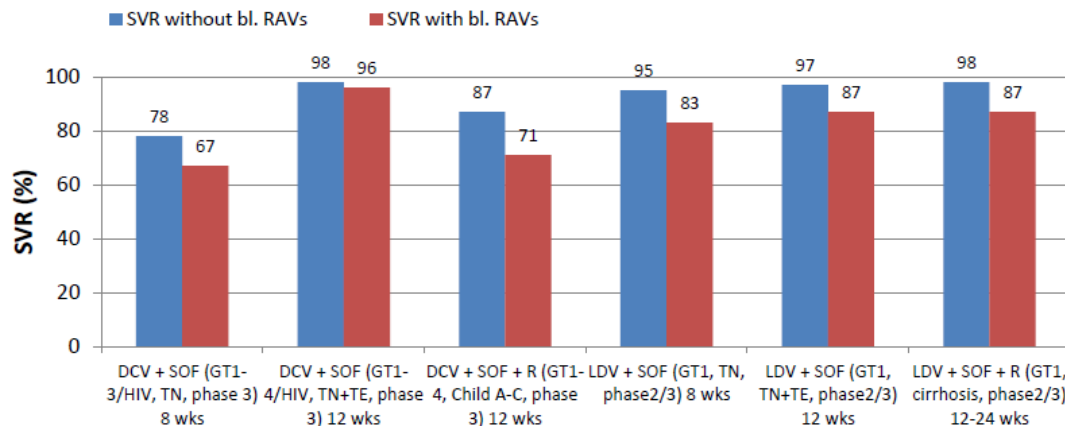
# Should we be worried about baseline RAVs?



SVR rates to **NS3** protease inhibitor plus **NS5A** inhibitor combination regimens in HCV genotype 1 infected patients according to the presence of baseline RAVs.



SVR rates for **NS3** protease inhibitor plus nucleos(t)ide **NS5B** inhibitor combination regimens in HCV genotype 1 infected patients according to the presence of baseline RAVs.



SVR rates **NS5A** inhibitor plus nucleos(t)ide **NS5B** inhibitor DAA combination regimens in HCV genotype 1 infected patients according to the presence of baseline RAVs.

# HCV Resistance Testing Prior to (First-Line) DAA Therapy

Available, reliable,  
Interpretable,  
understandable\*



Presence of NS5As RASs  
conferring high-level  
resistance (pop seq or >15%)



Add ribavirin and/or increase  
treatment duration

Not available



Optimize therapy to avoid  
treatment failure



- ✓ Add RBV in TE patients with SOF/LDV, SOF/DCV, SOF/SMV
- ✓ With 3D, use RBV in GT1a, treat NR cirrhotics 24 weeks
- ✓ Use GZR/EBR 16 weeks with RBV in GT1a patients

*\*Recommended for GZR/EBR for patients with GT1a  
but also for LDV/SOF for patients with GT1a  
and DCV/SOF and VPV/SOF patients with GT3*

*Pawlotsky et al, Gastroenterology 2016  
NEW EASL Guidelines Sept 2016*

# HCV Resistance Testing Prior to (First-Line) DAA Therapy

Available, reliable,  
Interpretable

Not available

**THERE'S THE NEED TO STANDARDIZE  
HCV RESISTANCE EVALUATION AND  
INTERPRETATION ... ONLY AFTER THAT,  
HCV RESISTANCE TESTING CAN BE  
EFFICIENTLY APPLIED INTO CLINICAL  
PRACTICE**

**.....VIRONET C.....**

**RBV in GT1a patients**

*\*Recommended for GZR/EBR for patients with GT1a  
but also for LDV/SOF for patients with GT1a  
and DCV/SOF and VPV/SOF patients with GT3*

*Pawlotsky et al, Gastroenterology 2016  
NEW EASL Guidelines Sept 2016*



## National Quality Control and Validation of Hepatitis C NS3, NS5A and NS5B Genotypic Resistance Testing

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# Despite the excellent efficacy of DAA containing regimens, virological failures can occur, often associated with development of resistance and with differences according to the type of regimen and HCV genotype

	GT1a			GT1b			GT2		GT3		GT4		
	NS3	NS5A	NS5B	NS3	NS5A	NS5B	NS5A	NS5B	NS5A	NS5B	NS3	NS5A	NS5B
<b>simeprevir/ sofosbuvir</b>	R155K D168E	n.d.	no RASs	D168V	n.d.	L159F C316N	not applicable		not applicable		Q80R D168E	n.d.	no RASs
<b>daclatasvir/ sofosbuvir</b>	n.d.	Q30H/R L31M	no RASs	n.d.	L31M Y93H	L159F C316N	no patients		Y93H	S282T*	n.d.	L28M	S282T
<b>ledipasvir/ sofosbuvir</b>	n.d.	Q30H/R L31M Y93H	S282T*	n.d.	L31M Y93H	L159F S282T* C316N	not applicable		no RASs	no RASs	n.d.	L28M Y93C/H	S282T
<b>3D/2D</b>	R155K D168V	M28T/V Q30R	S556G	Y56H D168V	Y93H	L159F C316N S556G	not applicable		not applicable		Y56H D168V	L28V Y93H	n.d.
<b>sofosbuvir/ribavirin± pegylated-interferon</b>	n.d.	n.d.	no RASs	n.d.	n.d.	L159F C316N	n.d.	no RASs	n.d.	L159F*	not applicable		

**Table 1:** Summary of the most frequent treatment-selected RASs according to the HCV genotype and treatment regimen. These characteristic RASs were defined to have a more than 10% increased prevalence after treatment failure compared to DAA-naïve patients (exceptions are marked with asterisks). The color refers the level of resistance conferred by the respective RAS.

**Despite the excellent efficacy of DAA containing regimens, virological failures can occur, often associated with development of resistance and with differences according to the type of regimen and HCV genotype**

	GT1a			GT1b			GT2		GT3		GT4		
	NS3	NS5A	NS5B	NS3	NS5A	NS5B	NS5A	NS5B	NS5A	NS5B	NS3	NS5A	NS5B

**Understanding more about RASs may help us learn why the patients failed, *and may allow optimization of treatment to other new patients & retreatment choices.***

**Table 1.** Summary of the most frequent treatment selected RASs according to the HCV genotype and treatment regimen. These characteristic RASs were defined to have a more than 10% increased prevalence after treatment failure compared to DAA-naïve patients (exceptions are marked with asterisks). The color refers the level of resistance conferred by the respective RAS.

# Also virological failures to new DAAs occur with resistance

20 out of 1,778 patients (1.1%) treated **Sofosbuvir/Velpatasvir** with for 12 weeks experienced virologic failure: 7 infected with GT1, 12 infected with GT3, and 1 infected with GT4 HCV

Number of patients	GT	NS5A RASs				NS5B NI RASs	
		Baseline (%)	Ref FC VEL at baseline	Virologic failure (%)	Ref FC VEL <sup>a</sup> at virologic failure	Baseline (%)	Virologic failure (%)
n = 2	1a	None	0.8 <sup>a</sup>	Y93N (>99%) or Y93N (91.9%)	805 <sup>a</sup>	None	None
n = 1	1a	None	NA	Y93H (>99%)	609 <sup>b</sup>	None	None
n = 2	1a	None	NA	None	NA	None	None
n = 1	1b	L31M (>99%) Y93H (>99%)	44 <sup>b</sup>	L31M (>99%) Y93H (>99%)	ND	V321I (94.1%)	V321I (>99%)
n = 1	1c/1h	Q30R (98.7%) L31M (>99%)	1.4 <sup>a</sup>	Q30R (>99%) L31M (88.4%) Y93H (72.3%)	763 <sup>a</sup>	None	None
n = 2	3a	Y93H (>99%)	347–1,073 <sup>a</sup>	Y93H (>99%)	302–1,221 <sup>a</sup>	None	None
n = 1	3a	Y93H (15.2%)	724 <sup>b</sup>	Y93H (>99%)	724 <sup>b</sup>	None	None
n = 1	3a	A30K (>99%)	30 <sup>a</sup> , 50 <sup>b</sup>	A30K (>99%) Y93H (97.2%)	35154 <sup>a</sup>	None	None
n = 8	3a	None	0.2–1.3 <sup>a</sup>	Y93H (>99%)	74–1,138 <sup>a</sup>	None	None
n = 1	4a	None	ND	None	ND	None	None

Ref FC VEL = VEL half-maximal effective concentration fold change from reference; NA, not applicable.

GT, genotype; HCV, hepatitis C virus; RAS, resistance-associated substitution; SVR12, sustained virologic response at 12 weeks; VEL, velpatasvir.

<sup>a</sup> Susceptibility to velpatasvir was evaluated using patient isolates.

<sup>b</sup> Susceptibility to velpatasvir was evaluated using site-directed mutant and compared to wild-type replicon.

The overall prevalence of Y93H/N across all genotypes was 2.8% (49/1773) at baseline and 84% (16/20) at virologic failure, respectively. Only one patient with a GT1b infection had V321I NS5B NI RAS at baseline and virologic failure. No sofosbuvir NS5B RASs were observed at baseline or virologic failure in these 20 patients

# Also virological failures to new DAAs occur with resistance

High SVR12 with 8/12-week **Glecaprevir/Pibrentasvir**: Integrated analysis of HCV Genotype 1-6 2041 patients without cirrhosis. In the ITT population, 943/965 (98%) and 1060/1076 (99%) of patients achieved SVR12 when treated for 8 and 12 weeks, respectively

**eTable 3. Patients with Virologic Failure: NS3 and NS5A Polymorphisms/Substitutions at Baseline and Time of Failure**

Treatment Duration	HCV Subtype	Failure	NS3 Variants		NS5A Variants	
			Baseline	At Failure	Baseline	At Failure
ENDURANCE-1						
8 weeks	1a	Failed to Suppress	None	A156V	None	Q30R + L31M + H58D
SURVEYOR-II						
8 weeks	2a	Relapse	None	None	L31M	L31M
8 weeks	2a	Relapse	None	None	L31M	L31M
ENDURANCE-3						
8 weeks	3a	Relapse	T54S	T54S	None	None
8 weeks	3a	Relapse	None	Q168L	A30K	A30K + Y93H
8 weeks	3a	Relapse	A166S	Y56H, Q168L	A30K	A30K + Y93H
8 weeks	3a	Failed to Suppress	A166S, Q168R	Q80R, A156G	A30K	A30K + Y93H
8 weeks	3a	Relapse	A166S	A166S	None	Y93H
8 weeks	3a	Relapse	None	Y56H	A30K	A30K + Y93H
12 weeks	3a	Relapse	None	Reinfection	None	Reinfection
12 weeks	3a	Breakthrough	Q168R	Y56H+Q168R	A30K/V, Y93H	A30K + Y93H
12 weeks	3a	Relapse	None	None	None	A30G, Y93H
12 weeks	3b	Relapse	None	Q80K	V31M	V31M + Y93H

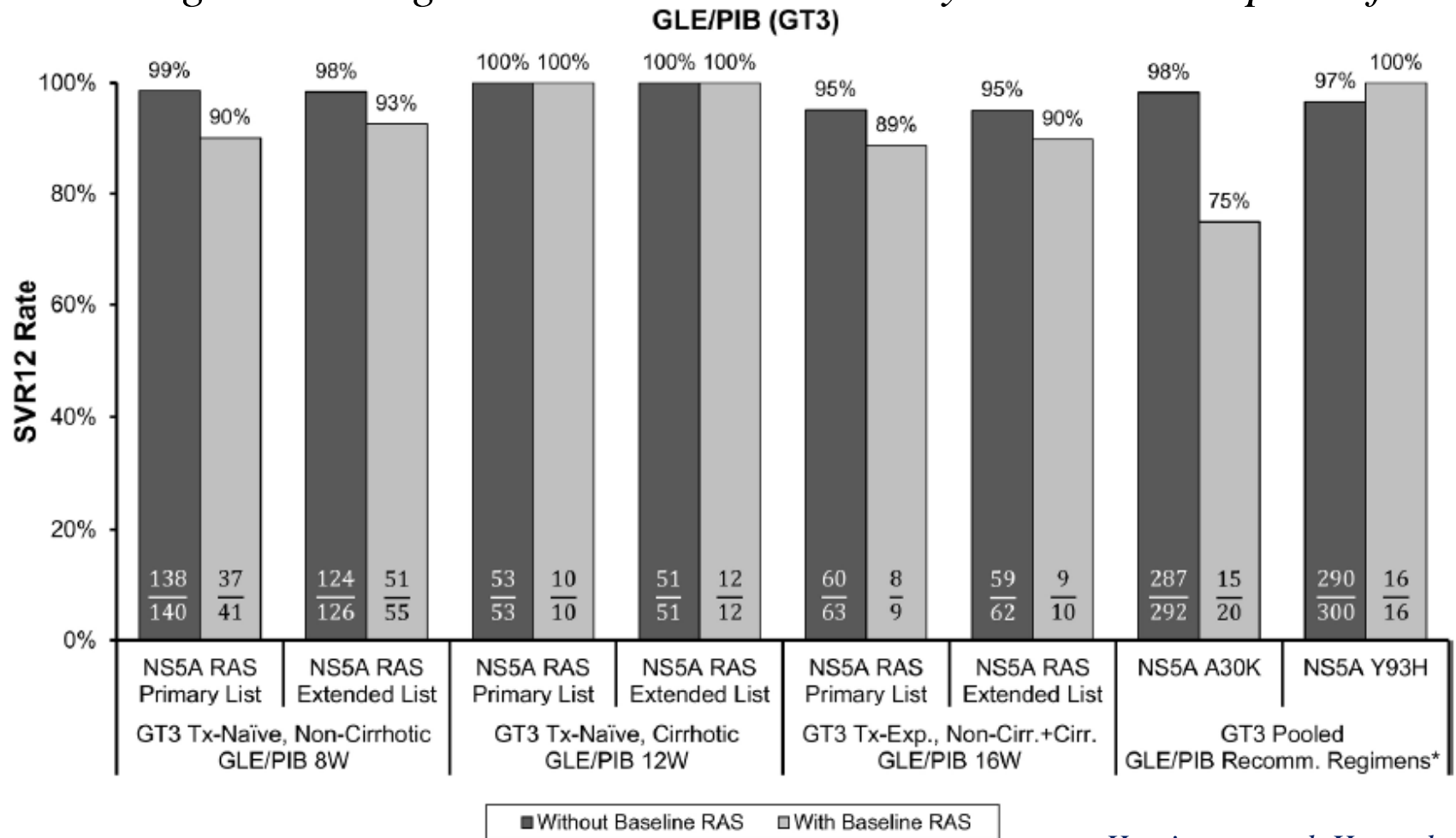
Detection of baseline polymorphisms and treatment-emergent substitutions was done with next-generation sequencing using a 15% detection threshold. For samples with multiple variants (polymorphisms/substitutions) within a target, if individual variants were detected at ≥90% prevalence, they are considered to be linked and denoted by "+", whereas if one or more of the variants was detected at <90% prevalence, the variants are separated by a comma

Amino acid positions included in analysis of patients with GT1: 36, 43, 54, 55, 56, 80, 155, 156, 168 in NS3; 24, 28, 29, 30, 31, 32, 58, 62, 92, 93 in NS5A

Amino acid positions included in analysis of patients with GT2 or GT3: 36, 43, 54, 55, 56, 80, 155, 156, 166, 168 in NS3; 24, 28, 29, 30, 31, 32, 58, 92, 93 in NS5A

No BL GRT recommendations are included in U.S. labeling for GLE/PIB, although available data on the impact of the GT3 NS5A A30K BL RAS are described for consideration by clinicians on a case-by-case basis

*Indicating that a longer treatment duration may reduce the impact of A30K*





# Y93H fold change for approved NS5A-inhibitors across genotypes 1a, 1b, 2, 3, 4

NS5A-inhibitors	Fold-change <i>in vitro</i> <sup>a</sup>				
	GT-1a	GT-1b	GT-2	GT-3	GT-4
<b>Daclatasvir</b>	1400-5432	19-145	749-1750	2154	45-169
<b>Elbasvir</b>	220-600	12-67	-	157	-
<b>Ledipasvir</b>	1677-3309	1319	-	30 <sup>b</sup>	1000
<b>Ombitasvir</b>	41383	77	4710	6728	20-100
<b>Pibrentasvir</b>	7	0.6	-	2-3	-
<b>Velpatasvir</b>	609	3	46	724	3

<sup>a</sup>Y93H fold change value in comparison with wild type strains; maximum and minimum values are reported [26, 27, 39, 42, 57, 65, 71, 96, 105, 125, 132, 134, 144, 146, 157, 161]. For 1<sup>st</sup> generation NS5A-inhibitors, RASs with fold-change >100x are reported in red (resistance likely); RASs with fold-change 20-100 are reported in yellow (resistance possible); RASs with fold-change 3-20x are reported in green (likely susceptible); only *in-vivo* RAS, with no fold-change available are reported in violet (resistance possible). For 2<sup>nd</sup> generation NS5A-inhibitors elbasvir and velpatasvir, RASs with fold-change ≥10x are reported in red (resistance likely); RASs with fold-change 2.5-9 are reported in yellow (resistance possible); RASs with fold-change ≤2.5x are reported in green (likely susceptible); only *in-vivo* RAS, with no fold-change available are reported in violet (resistance possible). <sup>b</sup>Ledipasvir exhibited an EC<sub>50</sub> value of 141 nM, affording a >670-fold reduction in potency when compared to daclatasvir [134]. GT, genotype. “-” indicates no data available.



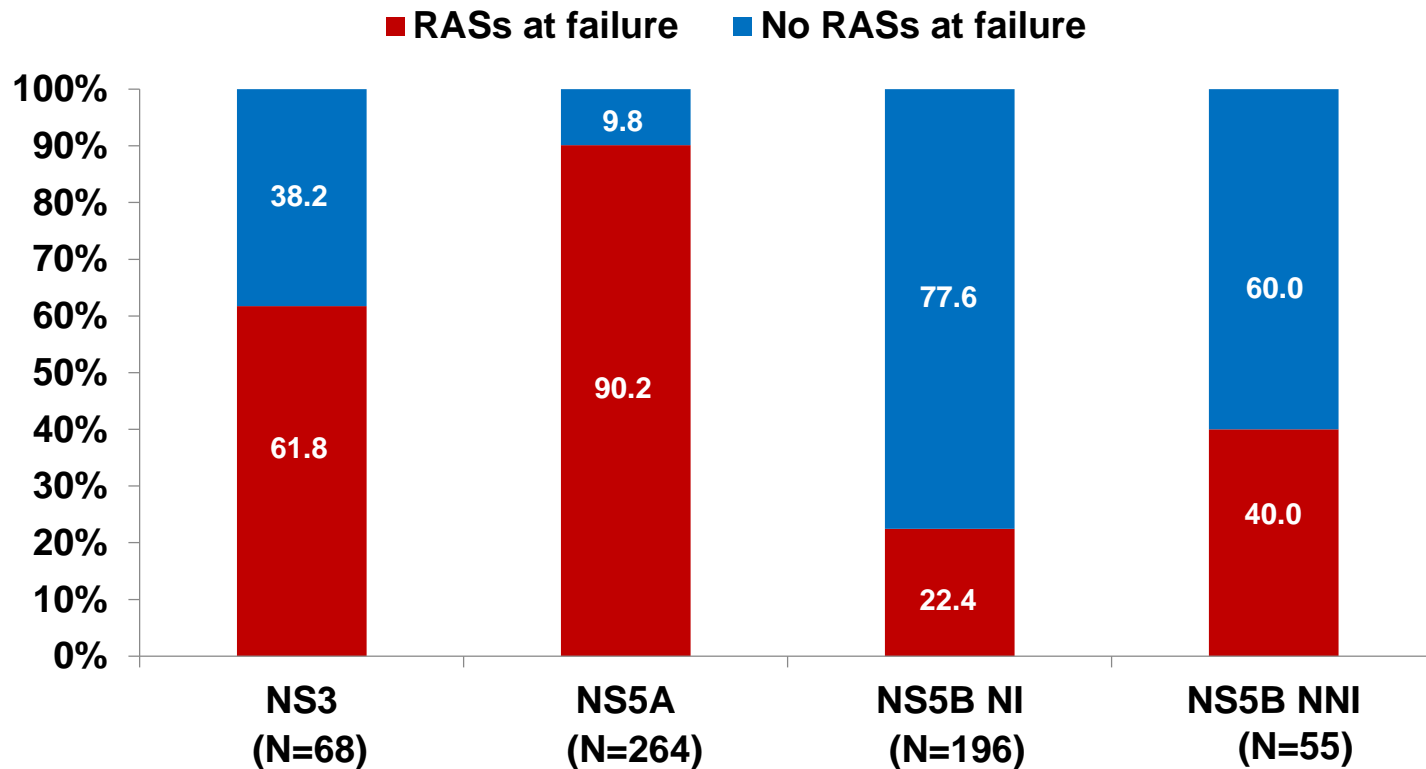
# Broad cross-resistance among NS5A Inhibitors, but not all single RASs and patterns are the same

**Table 1. Examples of NS5A and NS3 RASs and their reported phenotypic effect on DAA activity in transient HCV replicons.**

NS5A RAS <sup>1</sup>	NS5A Inhibitors (Fold-Change in EC <sub>50</sub> Values)					
	Ledipasvir	Ombitasvir	Daclatasvir	Elbasvir	Velpatasvir	Pibrentasvir
GT1a-K24R	4	≤1	2	≤1	≤1	≤1
GT1a-M28T	61	8965	205	15	8	2
GT1a-M28V	≤1	58	1	1	≤1	2
GT1a-Q30H	183	3	435	6	2	≤1
GT1a-Q30R	632	800	365	16	2	2
GT1a-L31M	554	2	105	10	16	≤1
GT1a-H58D	1127	243	367	6	7	≤1
GT1a-H58P	≤1	≤1	≤1	ND	≤1	≤1
GT1a-Y93H	1677	41383	1600	220	609	7
GT1a-M28T+Q30H	ND	ND	76,833	2286	ND	ND
GT1a-Q30H+Y93H	34,960	ND	98,167	ND	2835	17
GT1a-Q30R+Y93H	33,691	354,981	52,667	ND	18,698	260
GT1b-L31M	3	≤1	3	1 <sup>2</sup>	2	2
GT1b-Y93H	1807	77	12	17 <sup>2</sup>	3	≤1
GT1b-L31M+Y93H	20,270	142	16,000	ND	44	≤1
GT3a-A30K	n/a	n/a	117	n/a	50	≤1
GT3a-Y93H	n/a	n/a	3733	n/a	724	2
References	(18, 32, 67)	(18, 37)	(18, 48, 49, 67)	(19, 51, 68)	(55, 67, 69)	(59, 70)

**RASs prevalence was found in all genes tested:  
NS5A very frequent (90.2%), NS3 frequent (61.8%),  
NS5B less common (22.4% NI and 40.0% NNI)**

**RASs prevalence at failure was high in almost all HCV genotypes/subtypes**



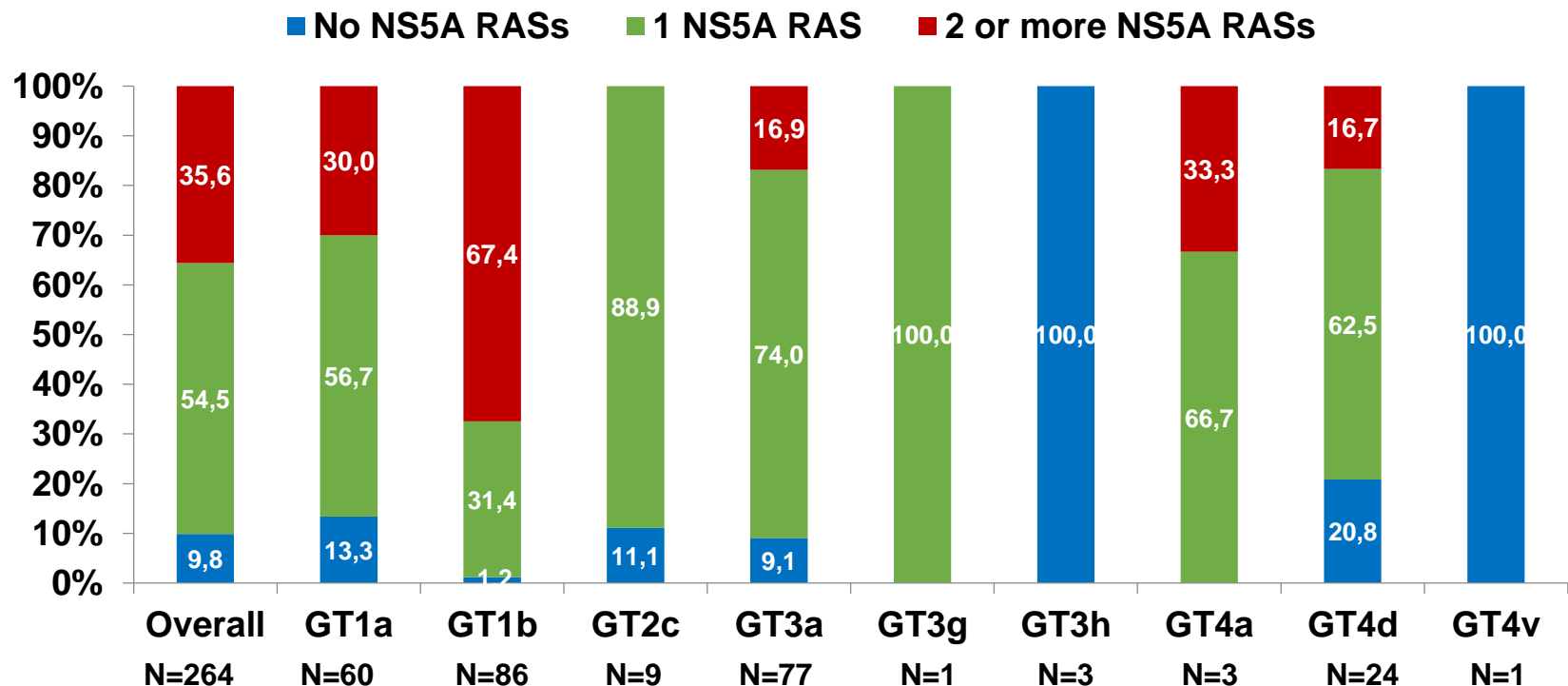
**264 HCV-infected patients failed a currently recommended INF-free NS5A containing regimen**

NI, Nucleotide inhibitor; NNI Non-Nucleoside Inhibitor

*UPDATE of Vironet C from Di Maio VC et al. J Hepatol. 2017  
Di Maio VC et al European Drug Resistance Workshop 2018*

# 94/264 (35.6%) of NS5A-failing patients presented $\geq 2$ NS5A-RASs

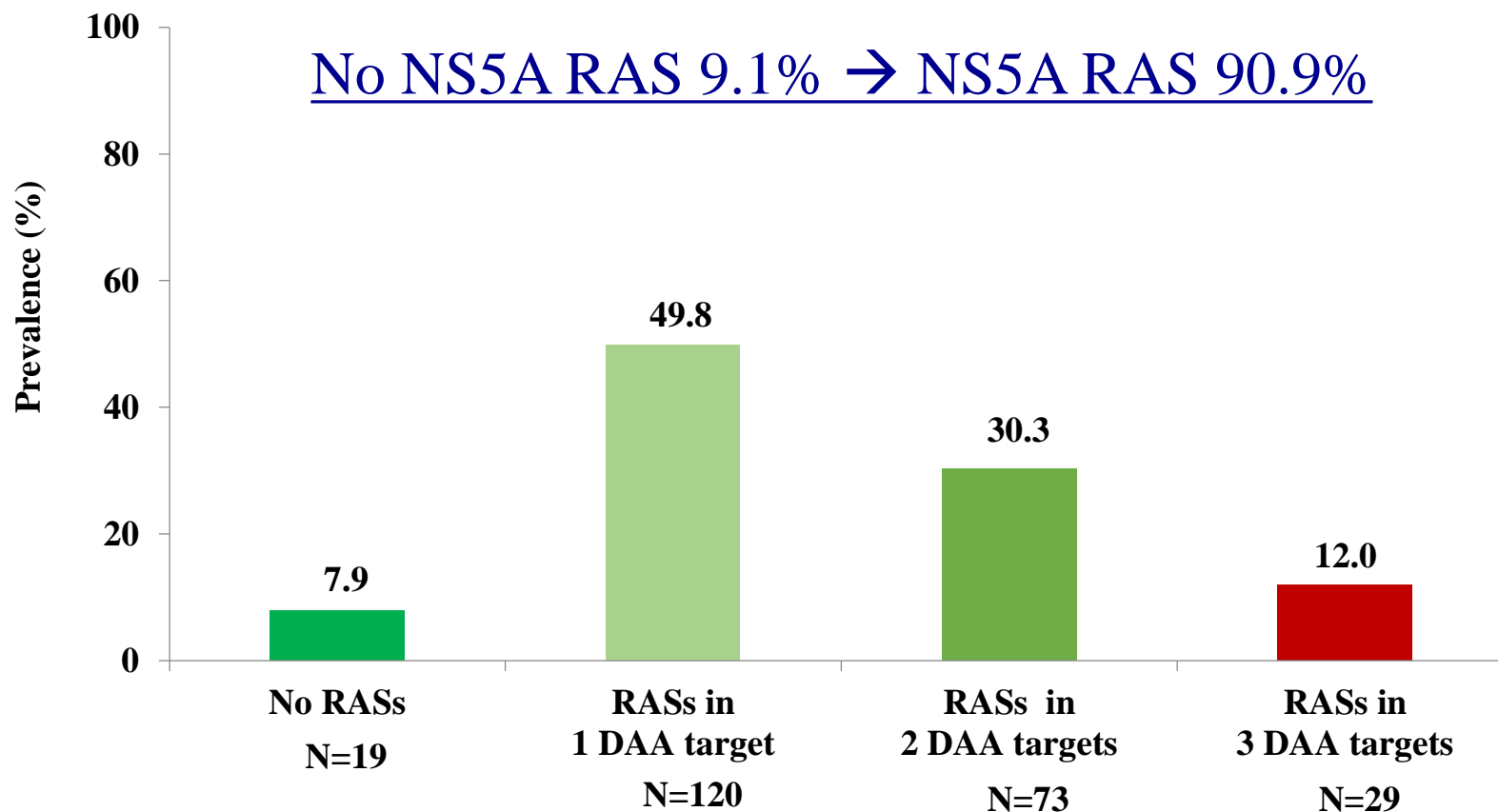
*9.8% (26/264) of DAA failing patients didn't show NS5A RASs at failure*



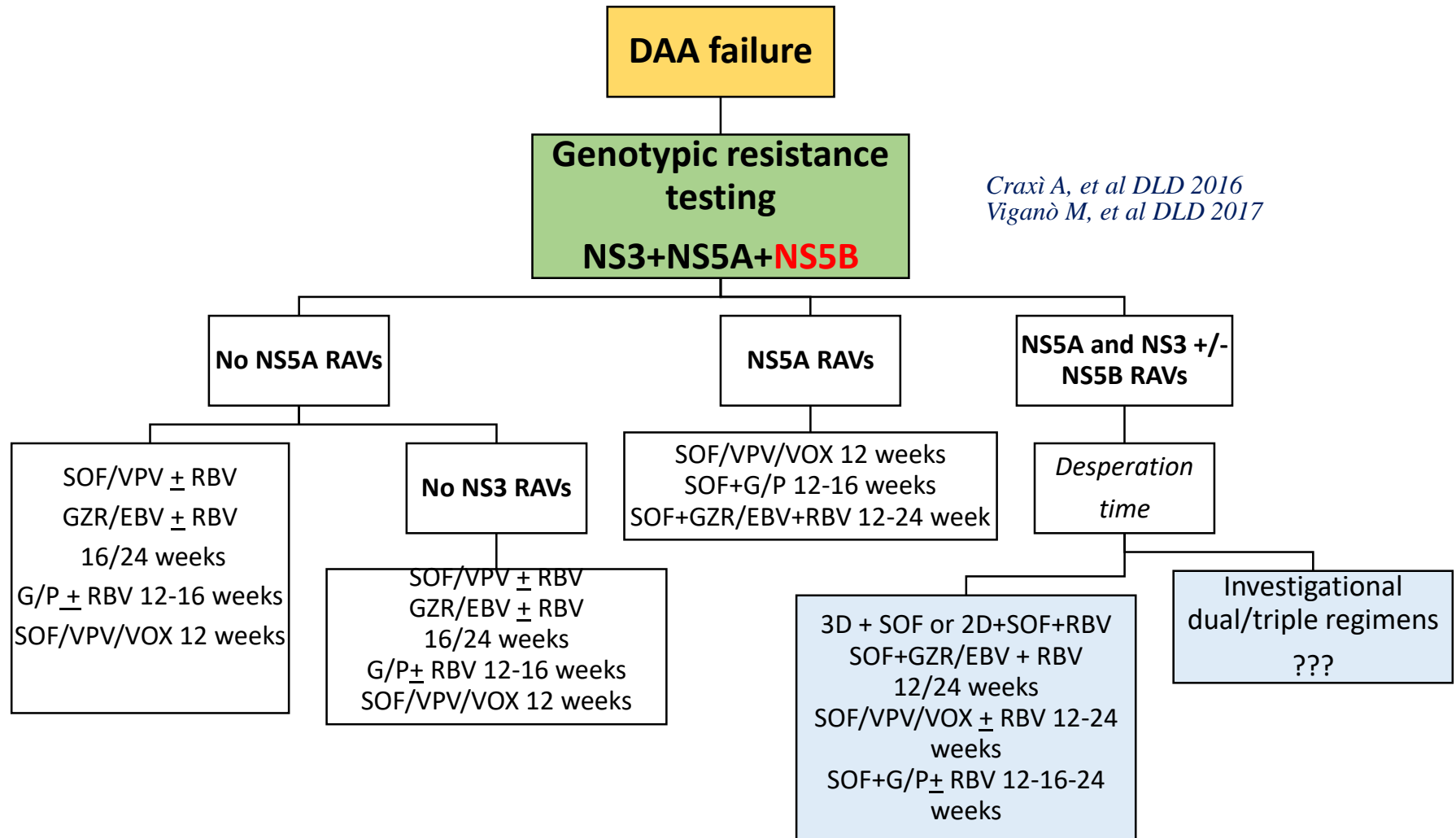
\*One GT3h infected patient who experienced a virological failure to daclatasvir+sofosbuvir regimen showed the major SOF RAS S282T in NS5B gene.

# 42.3% HCV-infected patients that failed a currently recommended INF-free NS5A containing regimen showed RASs on $\geq 2$ DAA-targets at failure

*All patients were treated with  $\geq 2$  DAA classes*



# Retreatment may require «unconventional» approaches with multiple DAAs



# Retreatment of DAA Failures

- HCV resistance testing useful to guide retreatment
- Recommendations for patients who experienced DAA regimen (PI and/or NS5AI) failure: management should be in context of multidisciplinary team including experienced treaters and virologists

Failure of DAA (PI and/or NS5AI)-Containing Regimen	Retreatment Recommendation
± Compensated cirrhosis	SOF/VEL/VOX for 12 wks
± Compensated cirrhosis with predictors of lower response*	GLE/PIB + SOF for 12 wks <sup>†</sup>
Very difficult to cure: NS5A RASs after 2 failures of PI and/or NS5AI-containing regimens	SOF/VEL/VOX or GLE/PIB + SOF: + RBV for 12 wks, no RBV for 16-24 wks, or + RBV for 16-24 wks <sup>†</sup>
Decompensated cirrhosis	SOF/VEL + RBV for 24 wks <sup>†</sup>

\*Advanced liver disease, multiple courses of DAA-based treatment, complex NS5A RAS profile.

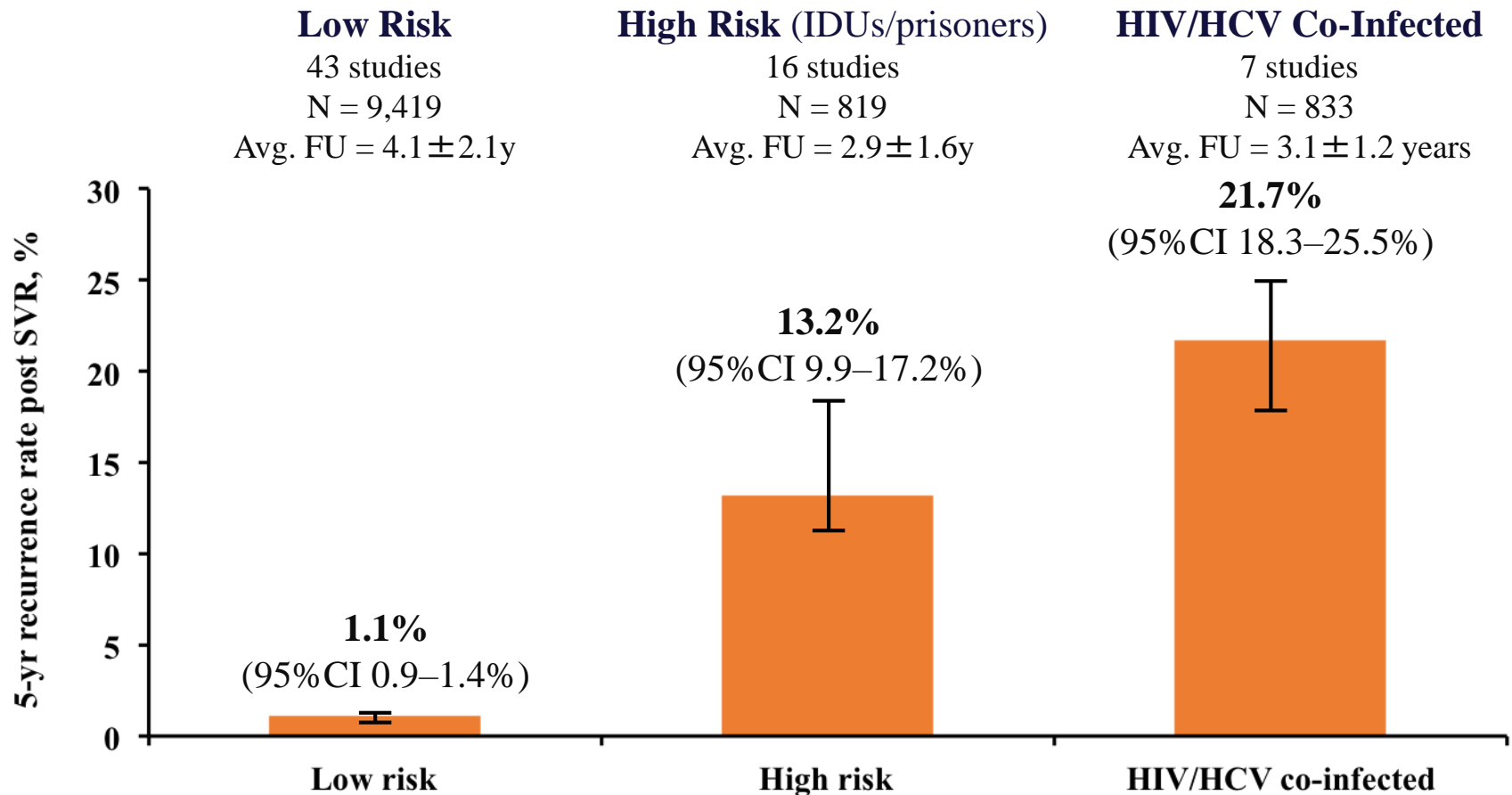
<sup>†</sup>Based on individual decision.

*EASL recommendations on the treatment of hepatitis C 2018. J Hepatol 2018*



# Risk of Late Relapse or Re-Infection with Hepatitis C After Sustained Virological Response: Meta-Analysis of 66 Studies in 11,071 Patients

## Five-Year Rate (95%CI) of Recurrence Post-SVR, by Risk Group



## Hepatitis C virus reinfection after successful treatment with direct-acting antiviral therapy in a large population-based cohort

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**BACKGROUND & AIMS:** Direct-acting antiviral therapies (DAA) are an important tool for hepatitis C virus (HCV) elimination. However, reinfection among people who inject drugs (PWID) may hamper elimination targets. Therefore, we estimated HCV reinfection rates among DAA-treated individuals, including PWID.

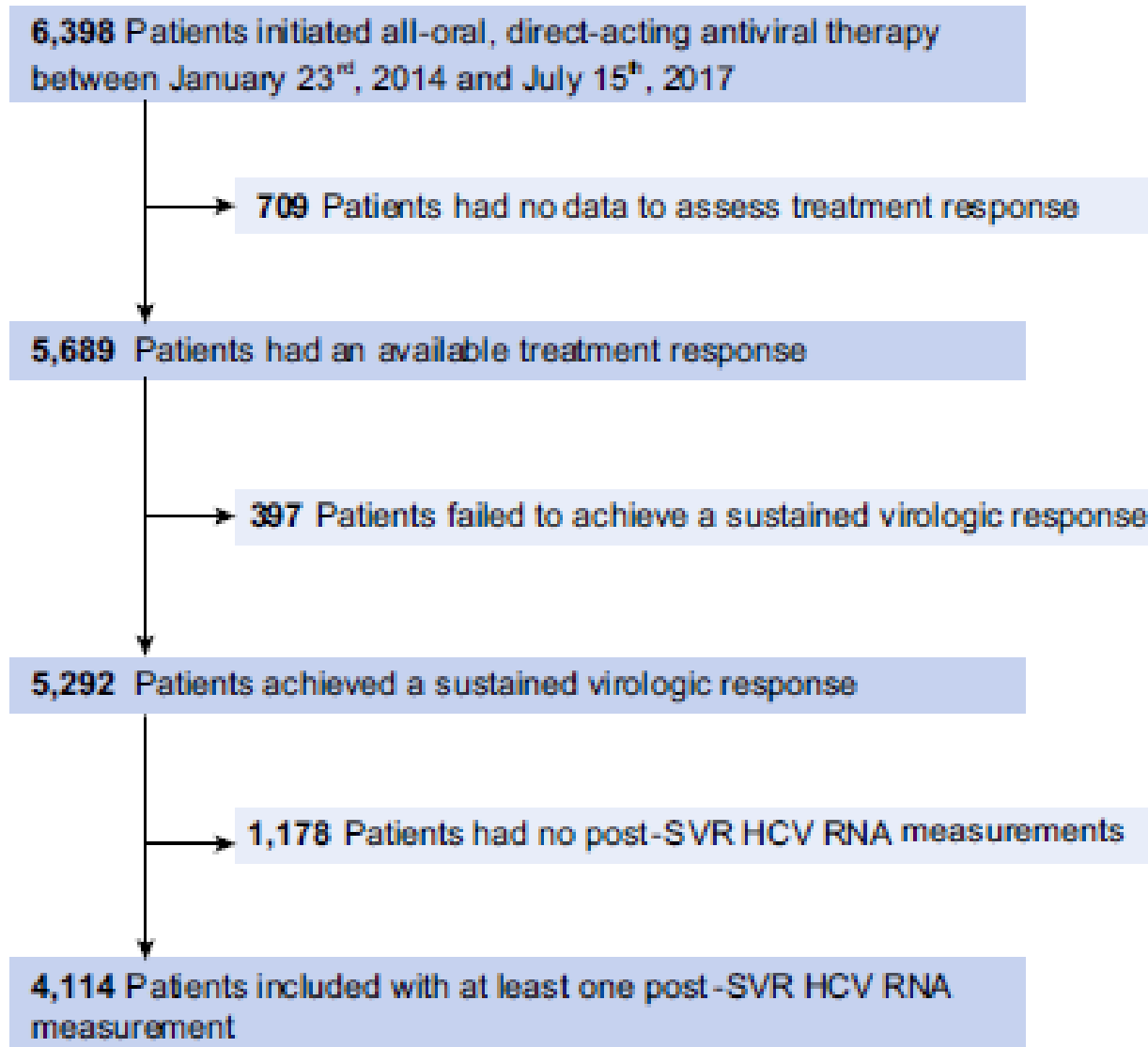
**METHODS:** We analyzed data from the British Columbia Hepatitis Testers Cohort which included ~1.7 million individuals screened for HCV in British Columbia, Canada. We followed HCV-infected individuals treated with DAAs who achieved a sustained virologic response (SVR) and had  $\geq 1$  subsequent HCV RNA measurement to April 22nd, 2018. Reinfection was defined as a positive RNA measurement after SVR. PWID were identified using a validated algorithm and classified based on recent ( $< 3$  years) or former ( $\geq 3$  years before SVR) use. Crude reinfection rates per 100 person-years (PYs) were calculated. Poisson regression was used to model adjusted incidence rate ratios (IRRs) and 95% CIs.

**RESULTS:** Of 4,114 individuals who met the inclusion criteria, most were male ( $n = 2,692$ , 65%), born before 1965 ( $n = 3,411$ , 83%) and were either recent ( $n = 875$ , 21%) or former PWID ( $n = 1,793$ , 44%). Opioid-agonist therapy (OAT) was received by 19% of PWID. We identified 40 reinfections during 2,767 PYs. Reinfection rates were higher among recent (3.1/100 PYs; IRR 6.7; 95% CI 1.9-23.5) and former PWID (1.4/100 PYs; IRR 3.7; 95% CI 1.1-12.9) than non-PWID (0.3/100 PYs). Among recent PWID, reinfection rates were higher among individuals born after 1975 (10.2/100 PYs) and those co-infected with HIV (5.7/100 PYs). Only one PWID receiving daily OAT developed reinfection.

**CONCLUSIONS:** Population-level reinfection rates remain elevated after DAA therapy among PWID because of ongoing exposure risk. Engagement of PWID in harm-reduction and support services is needed to prevent reinfections.

**LAY SUMMARY:** Direct-acting antivirals are an effective tool for the treatment of hepatitis C virus, enabling the elimination of the virus. However, some patients who have been successfully treated with direct-acting antivirals are at risk of reinfection. Our findings showed that the risk of reinfection was highest among people with recent injection drug use. Among people who inject drugs, daily use of opioid-agonist therapy was associated with a lower risk of reinfection.

# Study population



**The overall and persistent reinfection rates were 1.44 (95% CI 1.03–1.97) and 1.19 per 100 PYs (95% CI 0.82–1.68), respectively. The higher overall and persistent reinfection rates was among younger individuals (<45 years)**

	Person-years	All reinfections		Persistent reinfections	
		n	Rate (95% CI)*	n	Rate (95% CI)*
Overall	2,766.80	40	1.44 (1.03–1.97)	33	1.19 (0.82–1.68)
Age group					
<45 years	216.24	9	4.16 (1.90–7.90)	9	4.16 (1.90–7.90)
45–64 years	2,026.04	29	1.43 (0.96–2.06)	23	1.14 (0.72–1.70)
≥65 years	524.52	2	0.38 (0.05–1.38)	1	0.19 (0–1.06)
Birth cohort					
<1965	2,263.34	25	1.10 (0.71–1.63)	19	0.84 (0.51–1.31)
1965–1974	352.64	9	2.55 (1.17–4.84)	8	2.27 (0.98–4.47)
≥1975	150.81	6	3.98 (1.46–8.66)	6	3.98 (1.46–8.66)
Year of HCV diagnosis					
1990–1997	760.89	13	1.71 (0.91–2.92)	9	1.18 (0.54–2.25)
1998–2004	921.25	17	1.85 (1.07–2.95)	14	1.52 (0.83–2.55)
≥2005	1,084.43	10	0.92 (0.44–1.70)	10	0.92 (0.44–1.70)
Gender					
Male	1,805.26	32	1.77 (1.21–2.50)	28	1.55 (1.03–2.24)
Female	961.53	8	0.83 (0.36–1.64)	5	0.52 (0.17–1.21)
PWID					
Recent (<3 years before SVR)	674.28	21	3.11 (1.93–4.76)	18	2.67 (1.58–4.22)
Former (≥3 years before SVR)	1,137.60	16	1.41 (0.80–2.28)	13	1.14 (0.61–1.95)
No	954.91	3	0.31 (0.06–0.92)	2	0.21 (0.03–0.76)
OAT, in previous 12 weeks, among recent or former PWIDs					
Daily use	52.59	1	1.90 (0.05–10.6)	1	1.90 (0.05–10.6)
Non-daily use	292.62	12	4.10 (2.12–7.16)	12	4.10 (2.12–7.16)
Any past major mental illness					
Yes	901.92	19	2.11 (1.27–3.29)	16	1.77 (1.01–2.88)
No	1,864.87	21	1.13 (0.70–1.72)	17	0.91 (0.53–1.46)
Any previous problematic alcohol use					
Yes	667.96	16	2.40 (1.37–3.89)	13	1.95 (1.04–3.33)
No	2,098.84	24	1.14 (0.73–1.70)	20	0.95 (0.58–1.47)
HIV co-infection					
Yes	378.44	13	3.44 (1.83–5.87)	12	3.17 (1.64–5.54)
No	2,388.36	27	1.13 (0.75–1.64)	21	0.88 (0.54–1.34)

HCV, hepatitis C virus; OAT, opioid-agonist therapy; PWID, people who inject drugs; SVR, sustained virologic response.

\* Rate per 100 person-years.

**Reinfection rates were highest among recent PWID born after 1975 (10.2 per 100 PYs; 95% CI 3.74–22.2; Table 3), those with HIV co-infection (5.67 per 100 PYs; 95% CI 2.59–10.8) and those with problematic alcohol use (4.55 per 100 PYs; 95% CI 2.35–7.94)**

	All PWIDs (n = 2,668)		Recent PWIDs (n = 875)		Former PWIDs (n = 1,793)	
	All reinfections	Persistent reinfections	All reinfections	Persistent reinfections	All reinfections	Persistent reinfections
Age group						
<45 years	5.64 (2.58–10.7)	5.64 (2.58–10.7)	10.4 (4.74–19.7)	10.4 (4.74–19.7)	0 (0–5.07)	0 (0–5.07)
45–64 years	2.00 (1.32–2.91)	1.55 (0.96–2.38)	2.26 (1.17–3.94)	1.69 (0.77–3.21)	1.83 (1.02–3.02)	1.46 (0.76–2.56)
≥65 years	0.33 (0–1.85)	0.33 (0–1.85)	0 (0–6.58)	0 (0–6.58)	0.41 (0.01–2.27)	0.41 (0.01–2.27)
Birth cohort						
<1965	1.54 (0.97–2.34)	1.19 (0.69–1.91)	1.88 (0.86–3.58)	1.47 (0.59–3.02)	1.37 (0.73–2.35)	1.06 (0.51–1.94)
1965–1974	3.26 (1.49–6.19)	2.90 (1.25–5.71)	4.35 (1.60–9.47)	3.63 (1.18–8.46)	2.17 (0.45–6.34)	2.17 (0.45–6.34)
≥1975	5.42 (1.99–11.8)	5.42 (1.99–11.8)	10.2 (3.74–22.2)	10.2 (3.74–22.2)	0 (0–7.14)	0 (0–7.14)
Year of HCV diagnosis						
1990–1997	2.04 (1.05–3.56)	1.36 (0.59–2.68)	2.22 (0.72–5.18)	1.78 (0.48–4.55)	1.93 (0.77–3.97)	1.10 (0.30–2.82)
1998–2004	2.44 (1.39–3.96)	2.13 (1.17–3.58)	3.83 (1.75–7.27)	2.98 (1.20–6.14)	1.74 (0.70–3.58)	1.74 (0.70–3.58)
≥2005	1.59 (0.73–3.01)	1.59 (0.73–3.01)	3.57 (1.44–7.35)	3.57 (1.44–7.35)	0.54 (0.07–1.95)	0.54 (0.07–1.95)
Gender						
Male	2.49 (1.68–3.56)	2.16 (1.41–3.17)	3.82 (2.23–6.12)	3.37 (1.89–5.57)	1.71 (0.91–2.93)	1.45 (0.72–2.59)
Female	1.15 (0.46–2.37)	0.82 (0.27–1.92)	1.74 (0.47–4.46)	1.31 (0.27–3.82)	0.79 (0.16–2.31)	0.53 (0.06–1.90)
Any past major mental illness						
Yes	2.53 (1.52–3.95)	2.13 (1.22–3.46)	3.02 (1.45–5.56)	3.02 (1.45–5.56)	2.15 (0.98–4.07)	1.43 (0.52–3.11)
No	1.70 (1.00–2.68)	1.41 (0.79–2.33)	3.20 (1.60–5.73)	2.33 (1.01–4.59)	0.97 (0.39–2.01)	0.97 (0.39–2.01)
Any previous problematic alcohol use						
Yes	2.69 (1.54–4.37)	2.19 (1.17–3.74)	4.55 (2.35–7.94)	3.41 (1.56–6.48)	1.21 (0.33–3.10)	1.21 (0.33–3.10)
No	1.72 (1.07–2.63)	1.48 (0.88–2.34)	2.19 (1.00–4.16)	2.19 (1.00–4.16)	1.49 (0.77–2.60)	1.11 (0.51–2.12)
HIV co-infection						
Yes	3.97 (2.12–6.80)	3.67 (1.90–6.41)	5.67 (2.59–10.8)	5.04 (2.18–9.93)	2.38 (0.65–6.08)	2.38 (0.65–6.08)
No	1.62 (1.04–2.41)	1.28 (0.77–2.00)	2.33 (1.20–4.07)	1.94 (0.93–3.57)	1.24 (0.64–2.16)	0.93 (0.42–1.76)

HCV, hepatitis C virus; OAT, opioid-agonist therapy; PWID, people who inject drugs.

\*Rate per 100 person-years.

**In the multivariable Poisson model, PWID with recent (IRR 6.7; 95% CI 1.9–23.5) and former use (IRR 3.7; 95% CI 1.1–12.9) had a significantly elevated risk of overall reinfection (Table 4). Major mental health illness, problematic alcohol use, or HIV coinfection were not associated with HCV reinfection after SVR.**

	All reinfections		Persistent reinfections	
	Age and sex-adjusted IRR (95% CI)	Fully adjusted IRR* (95% CI)	Age and sex-adjusted IRR (95% CI)	Fully adjusted IRR* (95% CI)
<b>PWID</b>				
Recent (<3 years before SVR)	8.0 (2.4–26.9)	6.7 (1.9–23.5)	9.7 (2.2–42.3)	8.1 (1.8–36.9)
Former (≥3 years before SVR)	4.1 (1.2–14.2)	3.7 (1.1–12.9)	5.0 (1.1–22.0)	4.4 (1.0–19.8)
No	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
<b>Any past major mental illness</b>				
Yes	1.8 (0.9–3.3)	1.1 (0.5–2.1)	1.8 (0.9–3.6)	1.1 (0.5–2.3)
No	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
<b>Any previous problematic alcohol use</b>				
Yes	1.8 (1.0–3.4)	1.2 (0.6–2.4)	1.7 (0.9–3.5)	1.1 (0.5–2.4)
No	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
<b>HIV co-infection</b>				
Yes	2.1 (1.1–4.2)	1.6 (0.8–3.3)	2.3 (1.1–4.9)	1.8 (0.8–3.7)
No	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)

IRR, incidence rate ratio; PWID, people who inject drugs; SVR, sustained virologic response.

\*Models adjusted for age, sex and all other predictors shown in the table.



# First documentation of a transmission of an HCV DAA resistant variant from a DAA treated patient to his sexual HIV-infected partner

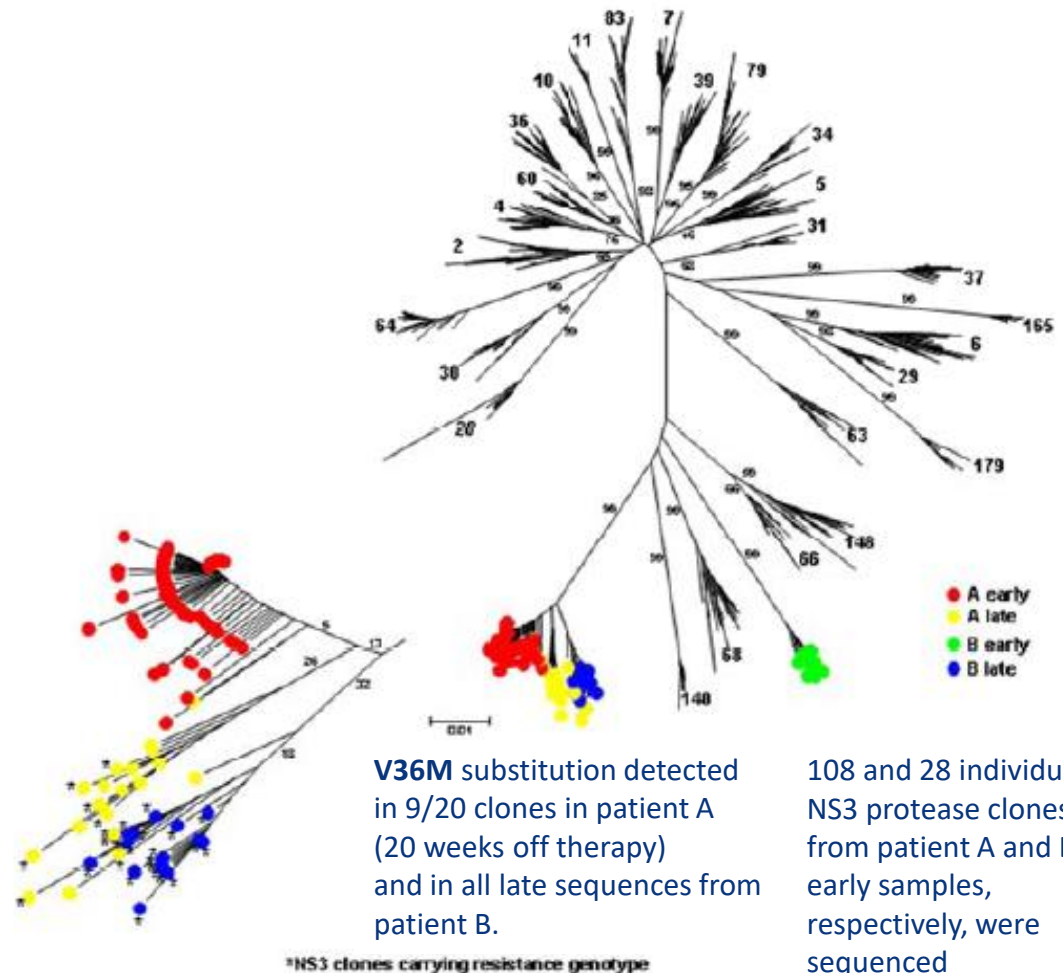
**Patient A**, a man chronically infected with HCV genotype 1a and co-infected with HIV- 1, treated with pegIFN/RBV plus telaprevir in July 2012 with HCV breakthrough. HCV NS3 protease sequences before treatment with telaprevir did not have any major substitution associated with NS3 PIs.

**Patient B**, a man also HIV-1 infected and sexual partner of patient A, diagnosed of acute HCV co-infection in January 2011, with HCV genotype 1a. This patient refused therapy with pegIFN/RBV during the acute phase of HCV infection.

In April 2012 he entered a clinical HCV trial and was treated for 24 weeks with pegIFN/RBV plus Daclatasvir, with undetectable HCV RNA at week 24 and 36 after the end of treatment.

**However, at week 48 after stopping therapy, presented elevated transaminase and detectable HCV RNA, suggesting a HCV re-infection.** The patient denied any known risk for HCV infection except unprotected sexual intercourse with his partner (patient A).

After 12 weeks, patient B tested negative for HCV infection.




RESEARCH

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# A policy analysis exploring hepatitis C risk, prevention, testing, treatment and reinfection within Australia's prisons

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## Abstract

**Background:** Hepatitis C (HCV) is a global public health concern. There is a global prevalence of 15% among the world's prisoner population, suggesting the need for priority HCV treatment among this population group. New highly efficacious therapies with low side effects, known as direct-acting antivirals, became available under Australia's universal healthcare scheme on 1 March 2016. This creates an opportune time to trial treatment as prevention as an elimination strategy for HCV in prison settings. This paper examines whether policies in Australian jurisdictions support treatment scale-up to achieve elimination among this priority population.

**Methods:** A comprehensive search was conducted using Google and other web-based search functions to locate all publicly available policies in each Australian state and territory related to HCV health and HCV-related prison health. Ministers (corrections and health) were contacted from each jurisdiction to identify any additional policies. Inductive and deductive analyses were conducted for each jurisdiction, with documents being assessed against a set of four a priori criteria. Documents included in the analysis were current at 1 September 2017, or 18 months following treatment availability.

**Results:** A total of 18 documents were located, including both health ( $n = 12$ ) and corrections/prison health ( $n = 6$ ) documents relevant to HCV. Jurisdictions ranged in their commitments for delivering HCV harm reduction strategies and treatment availability within the prison setting.

**Conclusion:** Few jurisdictions have updated or published HCV-related health or prisoner health policies following availability of direct-acting antivirals. Current policies do not provide effective support for implementing treatment scale-up that could be possible under universal access to HCV treatment among this priority population.

**Keywords:** Hepatitis C, Prisoner health, Treatment as prevention, Policy analysis

**Findings of each jurisdictional report card. The extent to which each of the four criteria were present in jurisdictional documents ranges from 0% (TAS; NT) to 75% (VIC) with an overall score of 47%. The overall presence of criteria was higher for HCV risks, HCV prevention and HCV testing and treatment in prison (61% for each) compared with reinfection (6%).**

Case (number of documents)	Does the set of policy documents mention HCV risks e.g. high prevalence in prison?	Does the set of policy documents mention HCV prevention/harm reduction in prison?	Does the set of policy documents mention HCV testing and treatment in prison?	Does the set of policy documents mention HCV reinfection in prison?	Total score (out of 4 indicators)
ACT (3)	2/3 (67%)	2/3 (67%)	3/3 (100%)	0/3 (0%)	7/12 (58%)
NSW (2)	2/2 (100%)	1/2 (50%)	1/2 (50%)	0/2 (0%)	4/8 (50%)
NT (0)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
QLD (2)	1/2 (50%)	1/2 (50%)	0/2 (0%)	0/2 (0%)	2/8 (25%)
SA (4)	3/4 (75%)	3/4 (75%)	3/4 (75%)	0/4 (0%)	9/16 (56%)
TAS (2)	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/8 (0%)
VIC (2)	1/2 (50%)	2/2 (100%)	2/2 (100%)	1/2 (50%)	6/8 (75%)
WA (3)	2/3 (67%)	2/3 (67%)	2/3 (67%)	0/3 (0%)	6/12 (50%)
Australia (18)	11/18 (61%)	11/18 (61%)	11/18 (61%)	1/18 (6%)	34/72 (47%)

RESEARCH ARTICLE

# Relapse or reinfection after failing hepatitis C direct acting antiviral treatment: Unravelling by phylogenetic analysis

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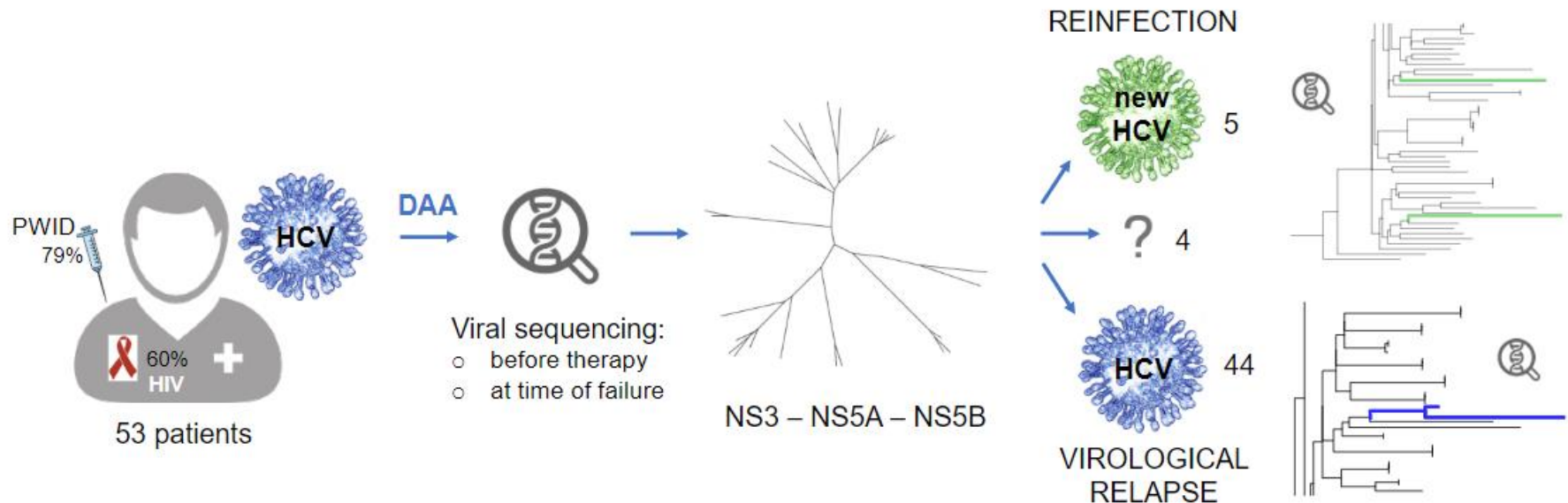
**Data Availability Statement:** All sequences generated within this study, have been submitted to Genbank (accession numbers MG983221–MG983474).

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## Abstract

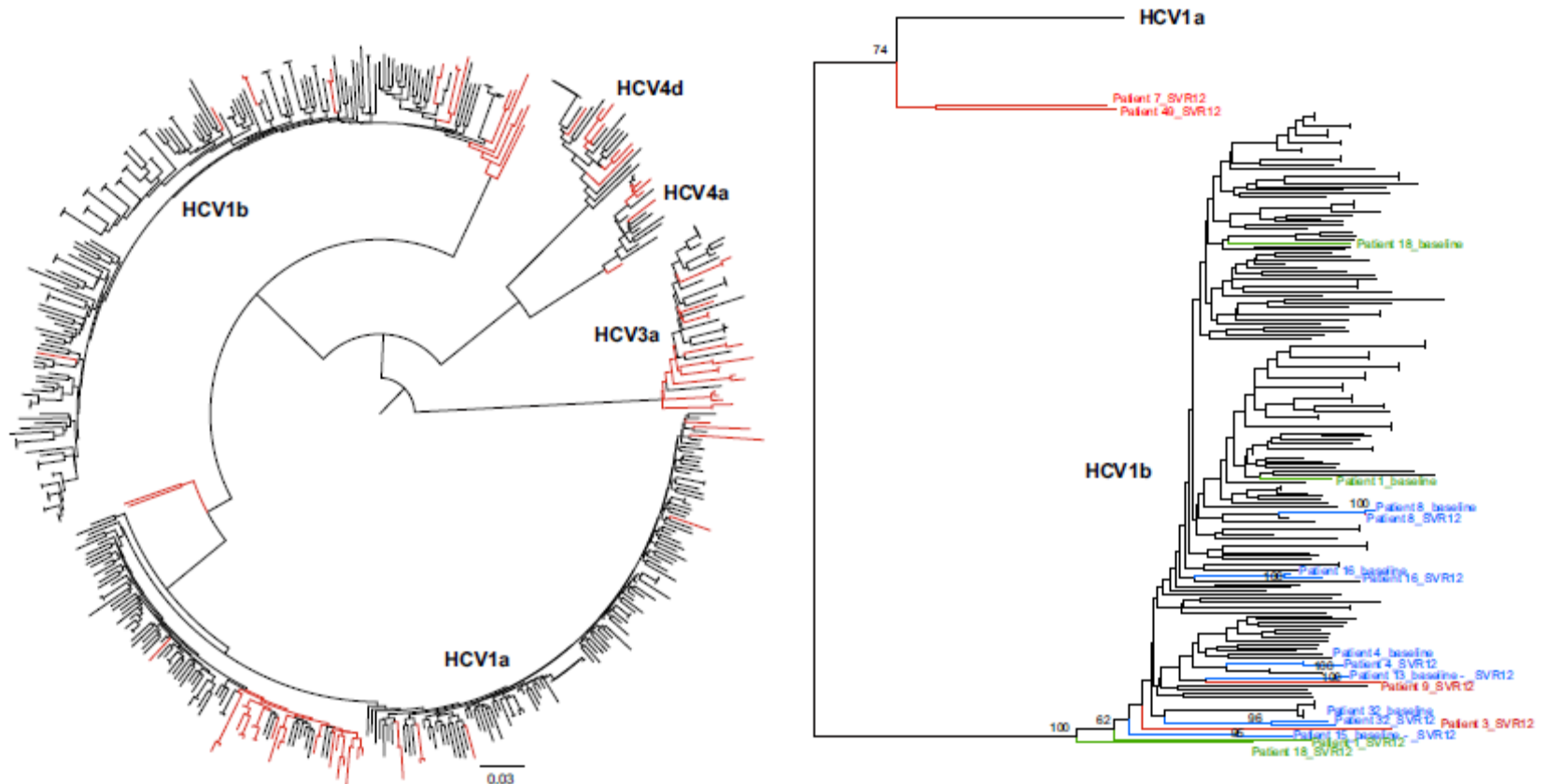
Despite high response rates associated to hepatitis C virus (HCV) treatment, no protective immunity is acquired, allowing for reinfection and continued infectiousness. Distinguishing between relapse and reinfection is crucial for patient counselling and to choose the most appropriate retreatment. Here, refined phylogenetic analysis using multiple genes served to assess genotype and reinfection for 53 patients for whom the virus was sampled before start of therapy and at time of sustained virological response evaluation at week 12. At baseline, genotypes were determined as HCV1a (41.5%), HCV1b (24.5%), HCV4 (18.9%) and HCV3a (15.1%), while six cases revealed to be discordantly assigned by phylogeny and commercial assays. Overall, 60.4% was co-infected with HIV. The large majority was classified as people who inject drugs (78.6%), often co-infected with HIV. Transmission was sexual in seven cases, of which five in HIV-positive men-who-have-sex-with-men. Overall, relapse was defined for 44 patients, while no conclusion was drawn for four patients. Five patients were reinfected with a different HCV strain, of which three with a different genotype, showing that phylogeny is needed not only to determine the genotype, but also to distinguish between relapse and intra-subtype reinfection. Of note, phylogenies are more reliable when longer fragments of the viral genome are being sequenced.

# Graphical overview of the study cohort, methodology and results





**Two patients (patients 1 and 18) were reinfected with the same HCV subtype, phylogenetically clustering in a different clade for the two sampled time points. Of the five patients that were defined to be reinfected, three were classified as PWID, one identified himself as MSM and for one the potential route of transmission was unknown**





# **Summary & Conclusions**

## **HCV - a curable disease**

We can cure HCV. SVR a validated surrogate of clinical efficacy because it predicts long-term clinical benefit.

To cure everyone with HCV we need to find it!!!

When we have found it we need to link to care and treat it properly!! Accurate diagnostics and treatment will be key to reduce HCV infections and to reduce the morbidity and mortality HCV-related.

SVR rates are very high with new IFN-free regimens (in both mono and co-infected HIV populations)...2-5-10% virologic failures = already around 10000 patients in Italy, with antiviral resistance...Surveillance resistance studies are warranted



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# Thanks for your attention

