



Casistica ASST Lariana: problemi e prospettive future

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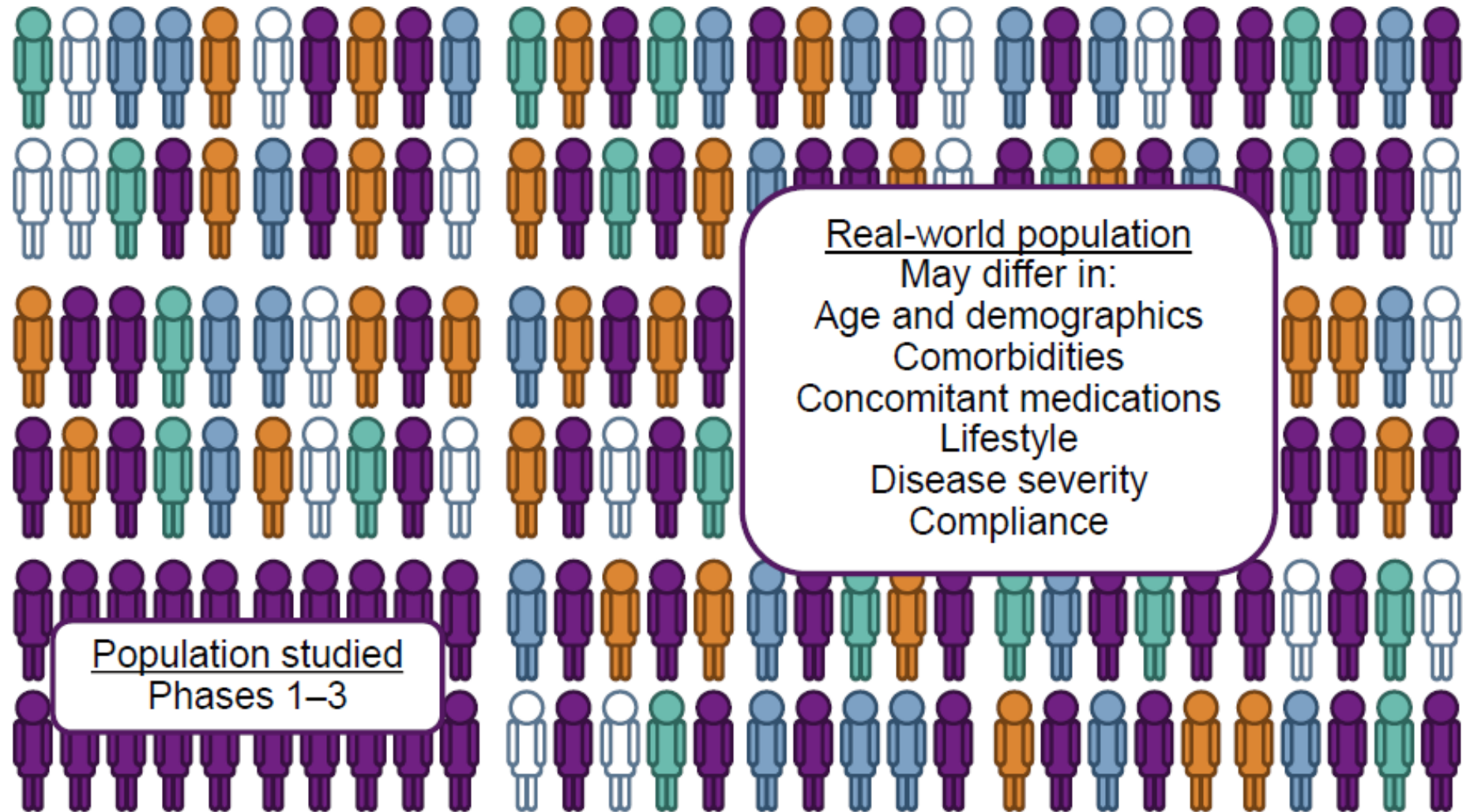
Clinical Evidence



Real-world Evidence



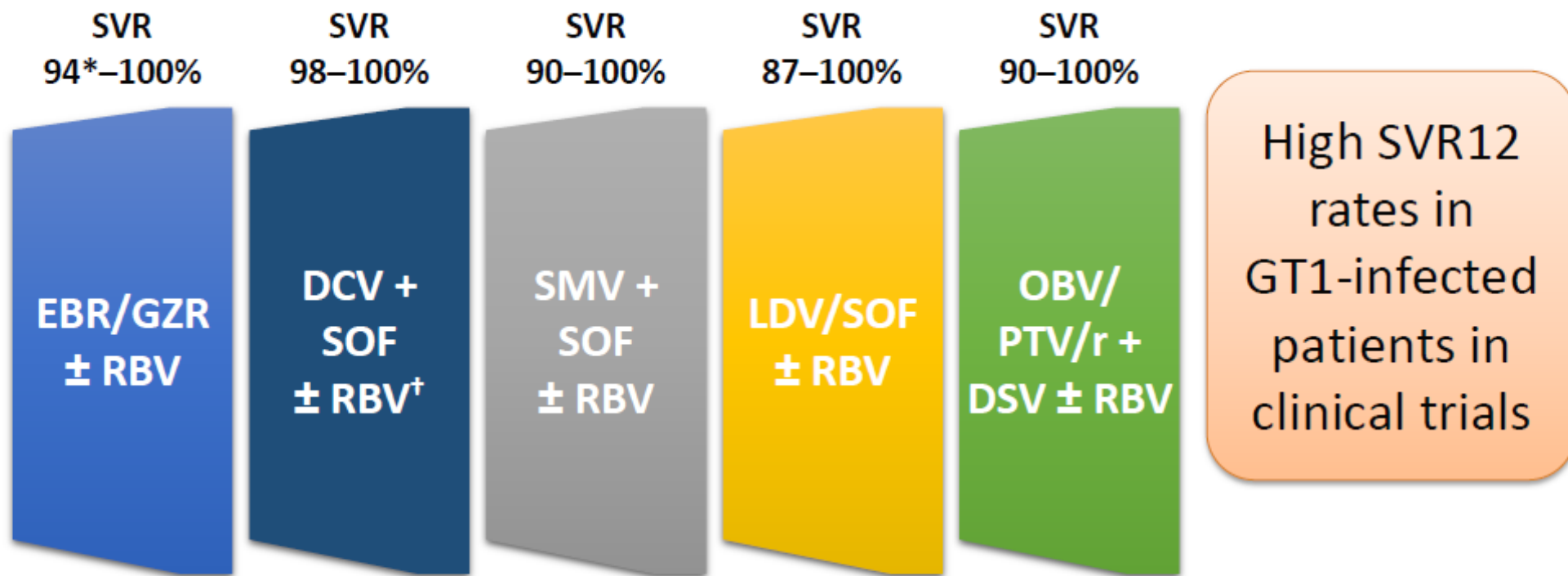
Differences between clinical trial populations and utilization population



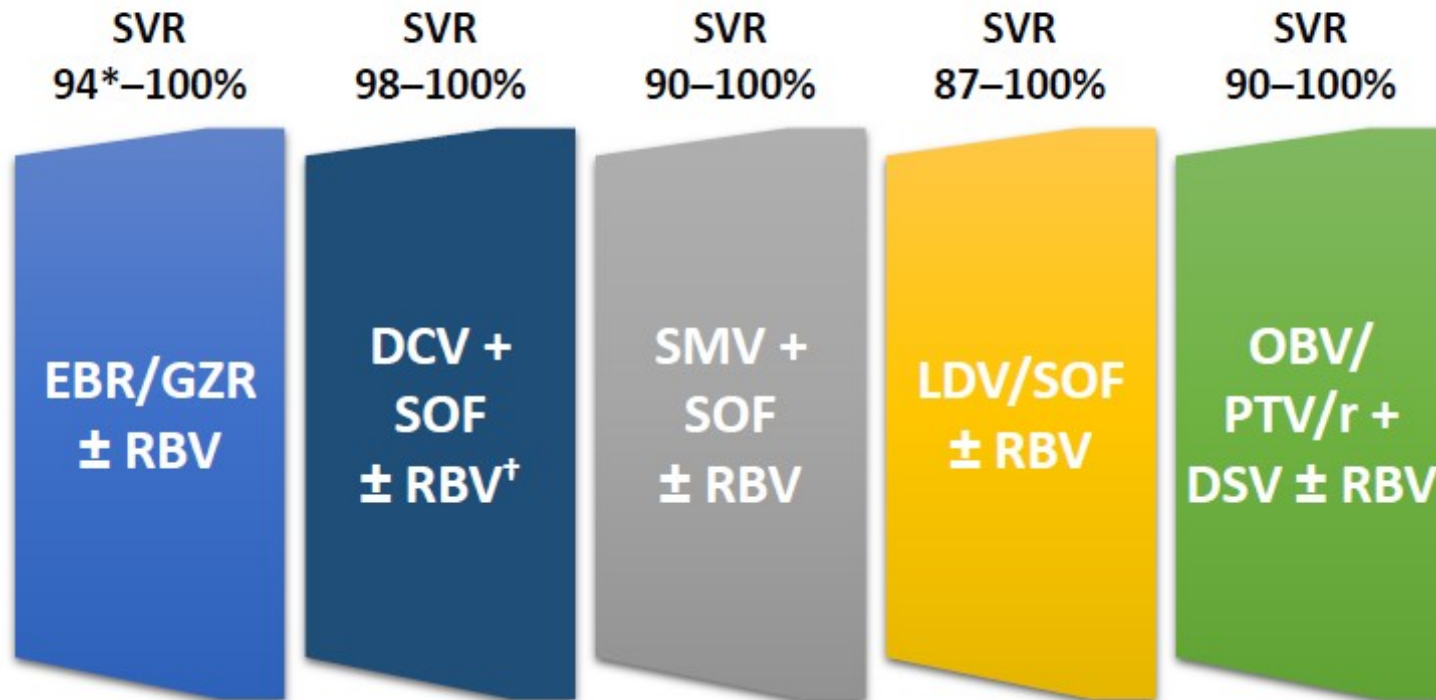
RCTs versus RWE

Variables	RCTs	RWE
Purpose	Efficacy	Effectiveness
Setting	Experimental setting	Real-world setting
Follow up	Designed	In actual practice
Treatment	Fixed pattern	Variable pattern
Study group	Homogenous	Heterogeneous
Attending physician	Investigator	Many practitioners
Comparator	Placebo/selective alternative interventions	Many alternative interventions
Patient monitoring	Continuous, per protocol	Changeable

High rates of SVR in HCV GT1 mono-infected patients in clinical trial



Are we replicating this in the real world?

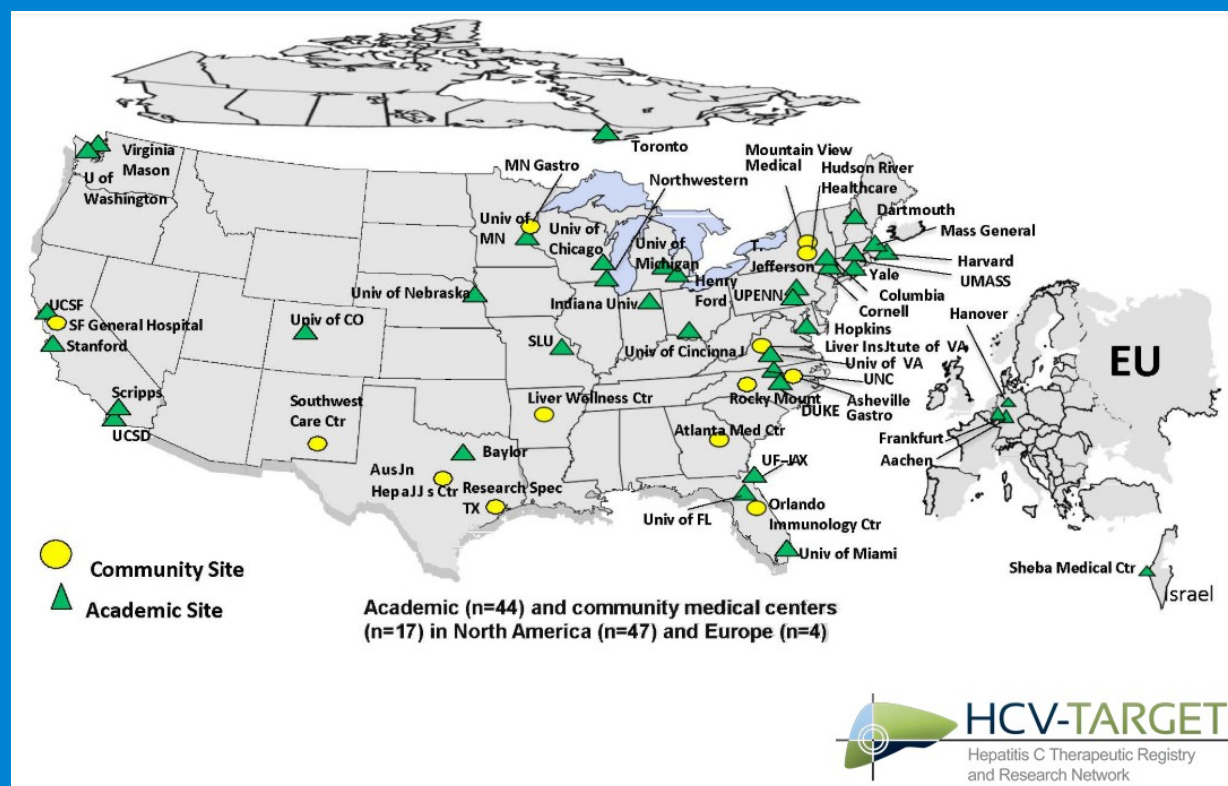


Zepatier US Prescribing Information

Viekirax & Exviera, Harvoni, Olysio and Daklinza, Summary of product characteristics



In the World



HCV-TARGET is a consortium of academic (n=39) and community (n=13) medical centers in the U.S., Germany, Israel and Canada conducting a longitudinal, observational study

HCV treatment is administered according to local standard of care, and regimen selection is made by the patient's health care provider

Data from sequentially enrolled patients undergoing HCV therapy is captured from medical records within a common database utilizing novel, centralized data abstraction

Demographic, clinical, adverse event, and virologic data is collected through treatment and follow-up

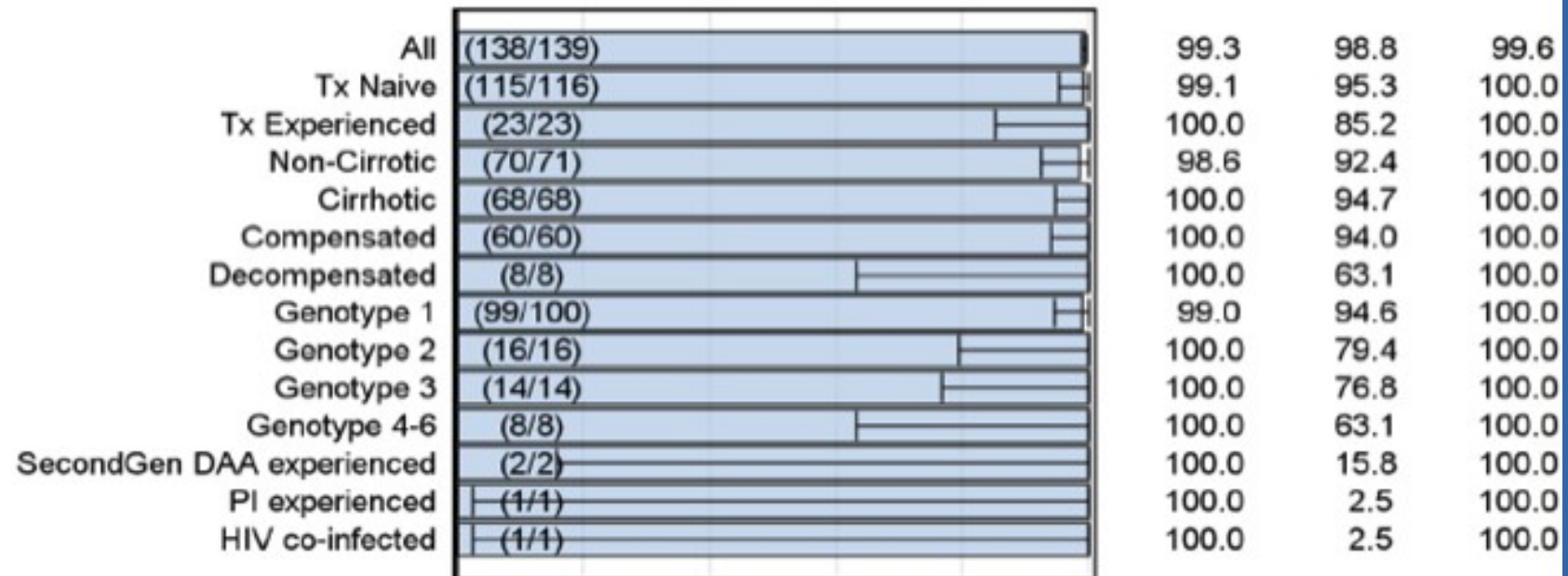
BASELINE CHARACTERISTICS – ALL PTS WHO STARTED TX

	8 wks	12 wks	16 wks	Other	TOTAL
N	430 (100)	184 (100)	25 (100)	30 (100)	726 (100)
Demographics N(%)					
Male	237 (55)	131 (71)	18 (72)	16 (53)	433 (60)
Age 60+	123 (29)	85 (46)	11 (44)	6 (20)	243 (34)
Genotype: 1	294 (68)	132 (72)	18 (72)	22 (73)	512 (71)
2	59 (14)	20 (11)	1 (4)	3 (10)	88 (12)
3	63 (15)	21 (11)	5 (20)	1 (3)	96 (13)
4-6	13 (3)	10 (5)	.	2 (7)	25 (3)
Nos	1 (0)	1 (1)	1 (4)	2 (7)	5 (1)
Tx Experienced	36 (8)	28 (15)	17 (68)	3 (10)	88 (12)
Cirrhotic	17 (4)	83 (45)	12 (48)	4 (13)	120 (17)
Liver Transplant	.	8 (4)	2 (8)	.	10 (1)
History of Decomp.	3 (1)	9 (5)	1 (4)	1 (3)	14 (2)
Dialysis	6 (1)	9 (5)	1 (4)	.	16 (2)
Prior SecondGen DAA	2 (1)	3 (2)	12 (48)	2 (7)	19 (3)
PI Experience	.	2 (1)	2 (8)	.	4 (1)
HIV co-infection	7 (2)	3 (2)	1 (4)	.	12 (2)
NS5A RAS Tested	44 (10)	20 (11)	6 (24)	5 (17)	78 (11)
RAS Present	11 (3)	7 (4)	2 (8)	3 (10)	23 (3)
Baseline Chemistry Median (Min-Max)					
Albumin (g/dL)	4.2 (1.5-5.3)	4 (1.8-4.9)	4.1 (2.8-4.7)	4.3 (2.9-5.2)	4.2 (1.5-5.3)
ALT (IU/L)	42 (8-493)	55.5 (3-509)	52 (8-156)	39 (18-141)	47 (3-509)
T. Billirubin (mg/dL)	0.5 (0.2-3)	0.6 (0.2-2.2)	0.4 (0.2-2.1)	0.6 (0.2-1.3)	0.5 (0.2-3)
Platelets (10 ³ /uL)	225.5 (29-581)	179 (40-443)	180 (57-371)	229 (35-575)	215.5 (29-581)
MELD (among cirrhotics)	7 (6-11)	8 (6-23)	7 (6-14)	7 (7-8)	7 (6-32)
HCV RNA (log10 IU/mL)	6.2 (2.3-8.1)	6.3 (3.6-7.6)	6.4 (4.9-7.2)	5.9 (1.5-7.4)	6.2 (0.6-8.1)

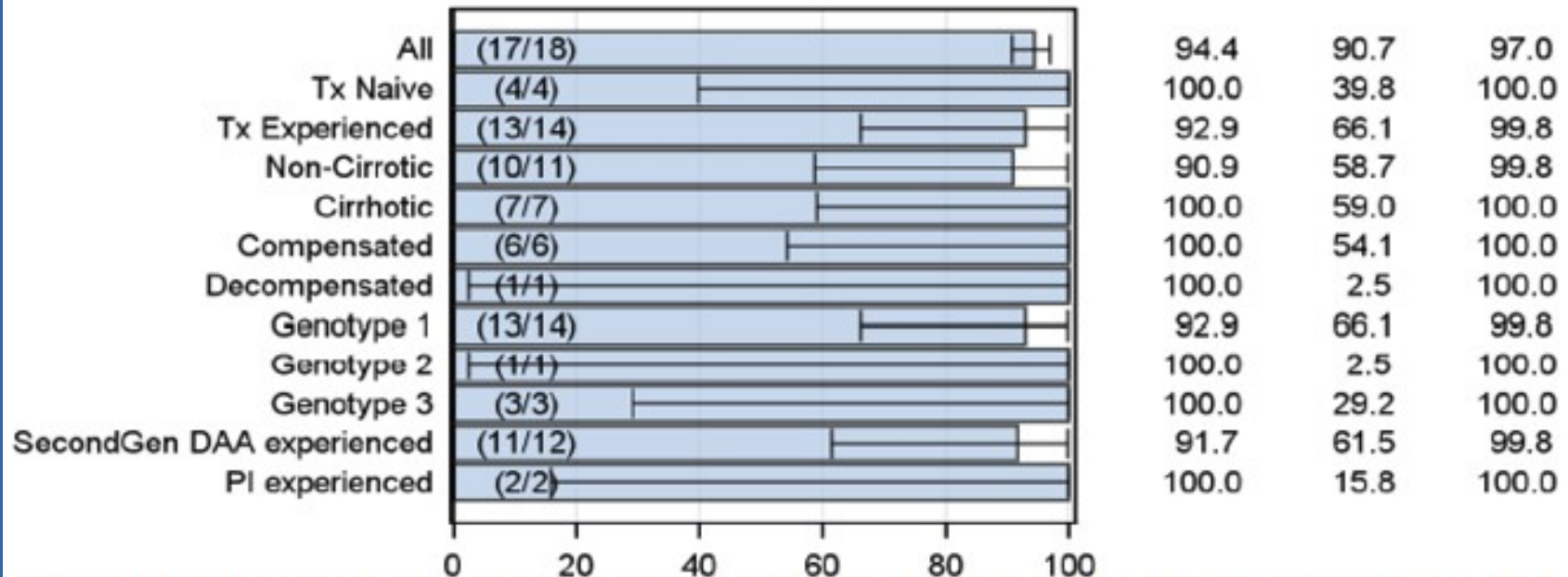
* 57 patients with records pending.

* Second Gen DAA regimens: SOF/SMV, SOF/LDV, SOF/VEL, SOD/DCV, or EBR/GZR containing regimens

12 weeks



16 weeks



Clinical practice experience with pangenotypic therapies glecaprevir-pibrentasvir and sofosbuvir-velpatasvir; data from the TRIO Network

¹Michael Curry, ²Bruce Bacon, ³Steven L. Flamm, ⁴Nicole Wick, ⁴Scott Milligan, ⁵Naoky Tsai, ⁶Zobair Younossi and ¹Nezam Afdhal

¹Beth Israel Deaconess Medical Center, ²Saint Louis University School of Medicine, ³Northwestern University Feinberg School of Medicine, ⁴Trio Health Analytics, ⁵University of Hawaii, and ⁶Center for Liver Diseases, Department of Medicine, Inova Fairfax Hospital



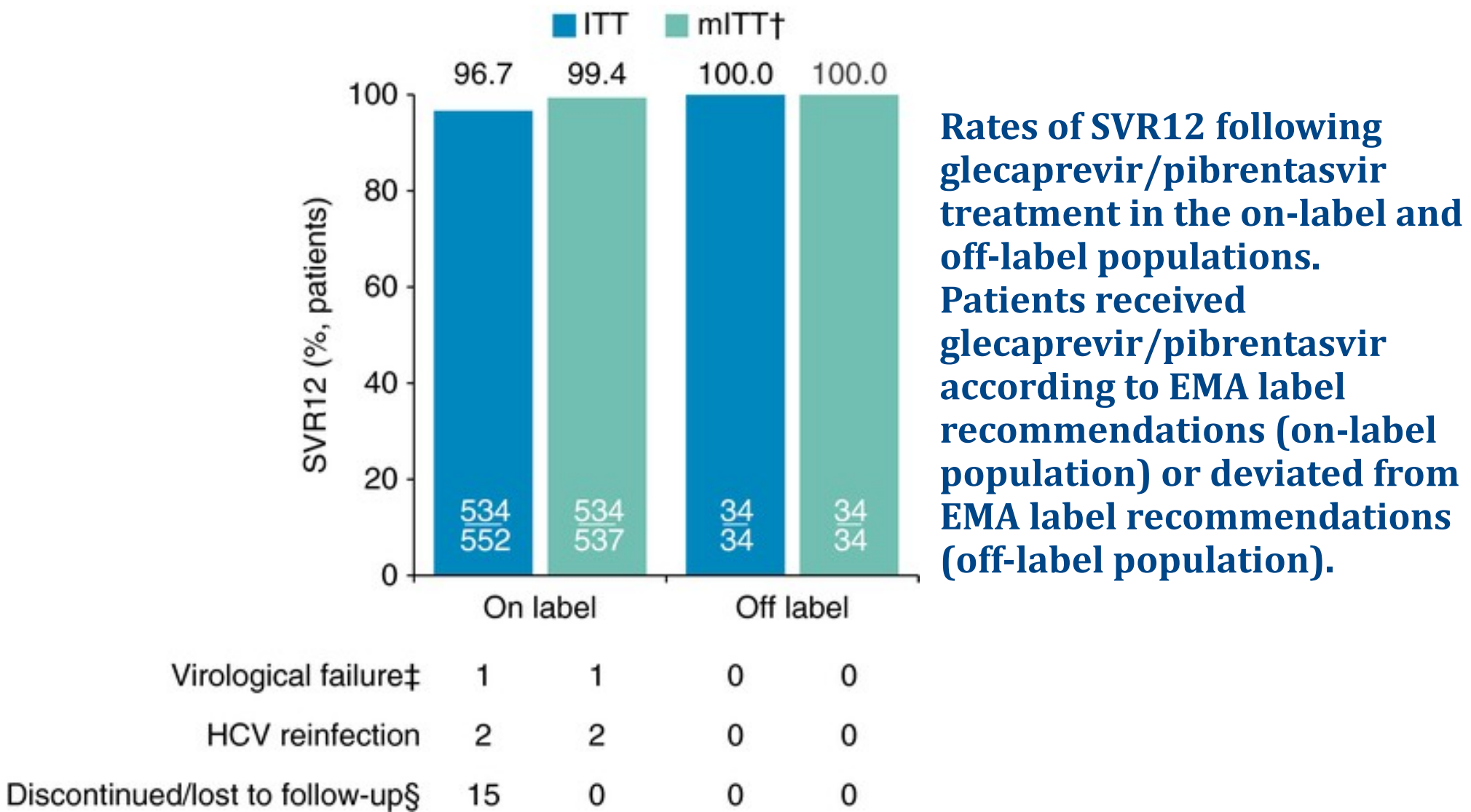
SVR Rates	Per Protocol		
	GLE-PIB	SOF-VEL	p
GT1-6	98% (1049/1066)	98% (701/716)	0.435
GT1-6, TN	99% (936/945)	98% (614/625)	0.162
GT1-6, TN, F0-3	99% (805/812)	98% (464/473)	0.105
GT1-6, TN, F4	98% (131/133)	99% (150/152)	0.897
GT1-6, TE	93% (113/121)	96% (87/91)	0.490
GT1-6, TE, F0-3	98% (85/87)	96% (50/52)	0.596
GT1-6, TE, F4	82% (28/34)	95% (37/39)	0.087
GT1-6, F0-3	99% (890/899)	98% (514/525)	0.091
GT1-6, F4	95% (159/167)	98% (187/191)	0.159
GT1-6, VL >6MM	97% (209/215)	97% (160/165)	0.889
GT1-6, Concurrent PPI	98% (135/138)	100% (79/79)	0.187
GT3	98% (126/129)	97% (228/234)	0.889
GT3, TN	98% (117/119)	98% (206/211)	0.674
GT3, TN, F0-3	100% (99/99)	98% (156/160)	0.112
GT3, TN, F4	90% (18/20)	98% (50/51)	0.131
GT3, TE	90% (9/10)	96% (22/23)	0.521
GT3, TE, F0-3	100% (5/5)	94% (15/16)	1.000
GT3, TE, F4	80% (4/5)	100% (7/7)	0.417
GT3, F0-3	100% (104/104)	97% (171/176)	0.084
GT3, F4	88% (22/25)	98% (57/58)	0.044
GT3, VL >6MM	86% (19/22)	97% (38/39)	0.093
GT3, Concurrent PPI	100% (14/14)	100% (27/27)	1.000

Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of chronic hepatitis C infection: data from the **German Hepatitis C-Registry**

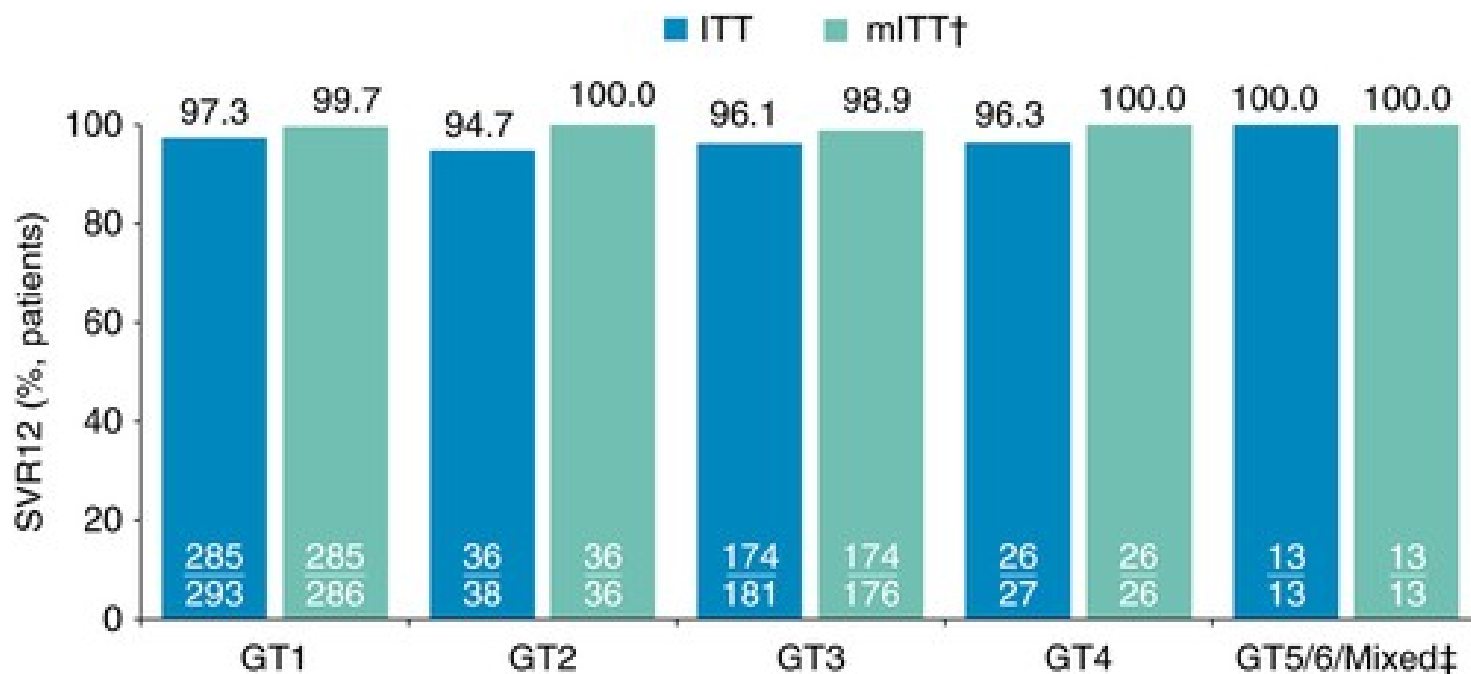
Demographics and Clinical Characteristics at Baseline

Characteristic	Total Population N = 1698	No Key Comorbidities* N = 985	OST N = 439	Active Drug Use N = 47	Psychiatric Disorders N = 247	Alcohol Abuse/ Dependence N = 106	HIV Coinfection N = 107
Male	1170 (69)	615 (62)	348 (79)	39 (83)	175 (71)	84 (79)	94 (88)
Age, median (range), years	46 (18–87)	48 (18–87)	43 (21–69)	43 (23–65)	46 (18–83)	47 (18–66)	43 (24–66)
HCV genotype							
1	892 (53)	541 (55)	204 (46)	20 (43)	126 (51)	51 (48)	59 (55)
2	104 (6)	60 (6)	27 (6)	6 (13)	18 (7)	7 (7)	5 (5)
3	590 (35)	323 (33)	189 (43)	20 (43)	86 (35)	40 (38)	20 (19)
4	79 (5)	37 (4)	15 (3)	1 (2)	15 (6)	5 (5)	22 (21)
Other*	33 (2)	24 (2)	4 (<1)	0	2 (<1)	3 (3)	1 (<1)
HCV RNA, median (IQR), Log ₁₀ IU/mL	6.1 (5.4–6.6)	6.0 (5.5–6.6)	6.1 (5.4–6.6)	6.5 (5.7–6.9)	6.2 (5.4–6.7)	6.1 (5.5–6.7)	6.1 (5.4–6.7)
HCV treatment-naïve	1514 (89)	885 (90)	387 (88)	41 (87)	215 (87)	98 (92)	95 (89)
Non-cirrhotic	1585 (93)	924 (94)	402 (92)	42 (89)	229 (93)	92 (87)	103 (96)
HCV treatment-naïve non-cirrhotic†	1421 (84)	837 (85)	354 (81)	37 (79)	201 (81)	85 (80)	93 (87)
Platelets per µL, median (range)‡	217,000 (31,000–616,000)	220,000 (31,000–616,000)	206,000 (36,000–564,000)	198,000 (47,000–336,000)	220,000 (69,000–564,000)	211,000 (57,000–468,000)	215,000 (47,000–372,000)

Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of chronic hepatitis C infection: data from the German Hepatitis C-Registry



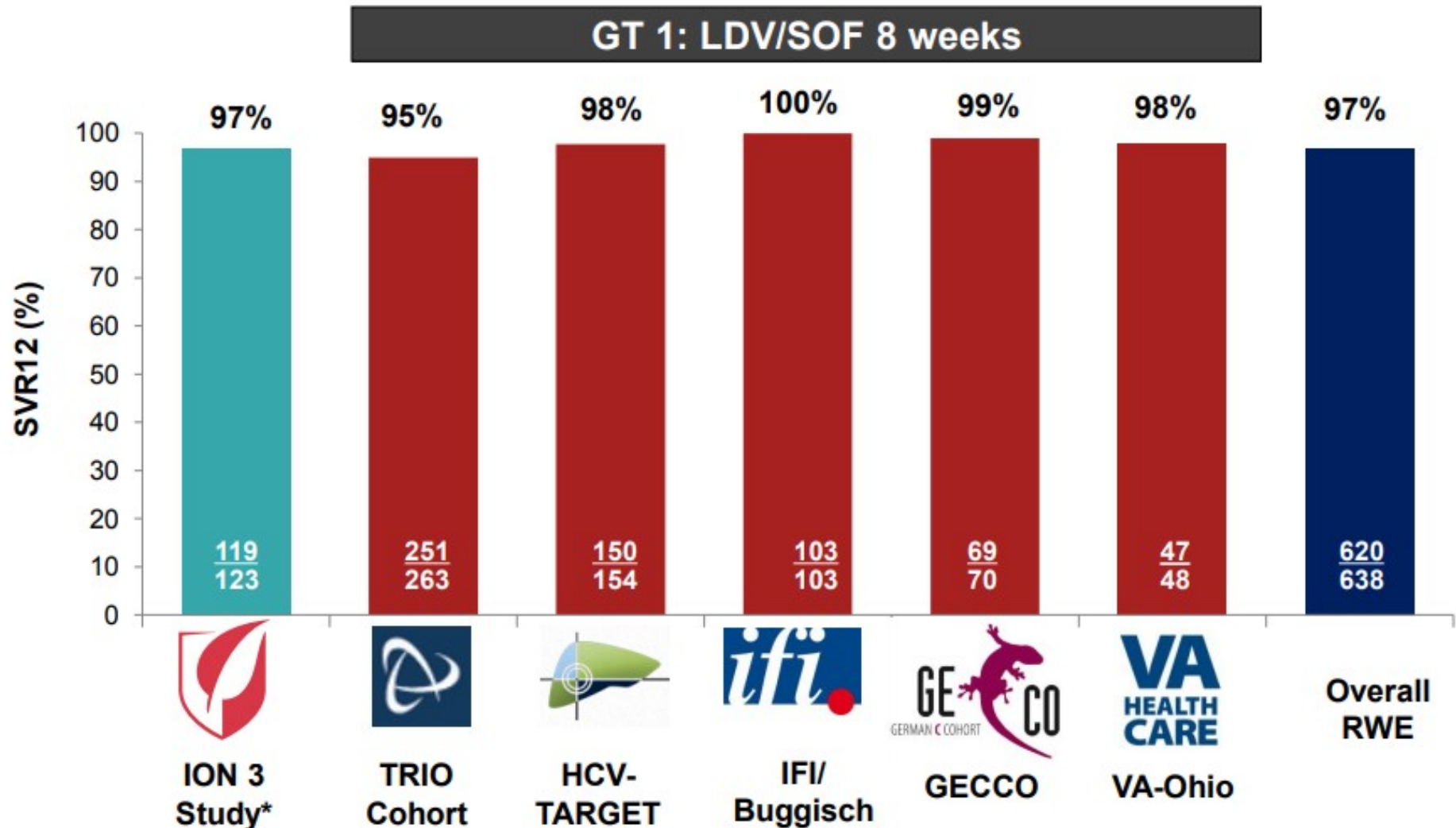
Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of chronic hepatitis C infection: data from the **German Hepatitis C-Registry**



Rates of SVR12 by HCV genotype following glecaprevir/pibrentasvir treatment in the on-label population. SVR12 was defined as HCV RNA ≤ 25 IU/mL and the visit window was 70-153 d after end of treatment.

Patients received glecaprevir/pibrentasvir according to EMA label recommendations.

SVR 12 in ION-3 Compared to Real-World Cohorts



Kowdley KV et al. N Engl J Med 2014;370:1879-88

Curry M et al AASLD 2015

Terrault N et al AASLD 2015

Buggisch P et al AASLD 2015

Christensen et al AASLD 2015

Marshall et al AASLD 2015



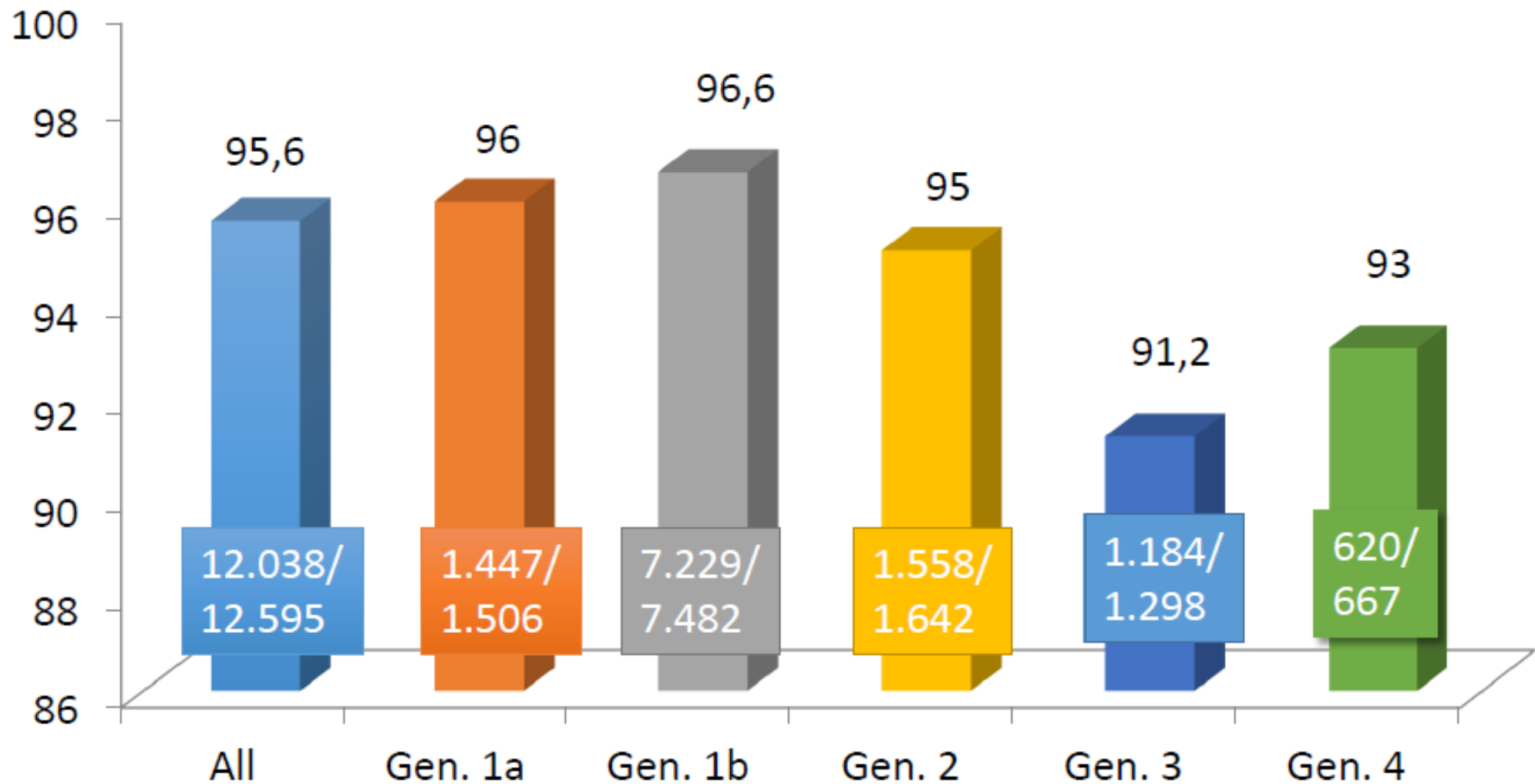
In Italy

Demographic and virological characteristics of 23.384 HCV patients included in 4 regional registries according to HCV genotypes (Campania, Lombardia, Sicilia, Veneto)

Gen	Age	F4	F3	TE	PLT	Bil	Alb	HIV+	On OLT WL
1a	54.5 (21-84)	63%	26%	18.7 (2.8-75)	141 (12-980)	0.94 (0.2-49)	3.89 (2.2-5.5)	26%	0.7%
1b	65 (18-90)	63%	27%	17.3 (2-75)	144 (14-994)	0.93 (0.1-33)	3.88 (1.7-5.6)	3.2%	0.7%
2	68.7 (29-84)	60%	25%	16.3 (2-70)	148 (11-660)	1.0 (0.2-37)	3.9 (2.3-5.5)	2.3%	0.5%
3	52.3 (25-81)	69%	21%	20.7 (5-75)	131 (15-597)	1.11 (0.1-39)	3.94 (1.9-5.2)	21%	1.3%
4	55.8 (24-80)	68%	21%	18.5 (2-72)	143 (20-449)	0.91 (0.2-7.6)	3.92 (1.9-4.9)	24%	1%

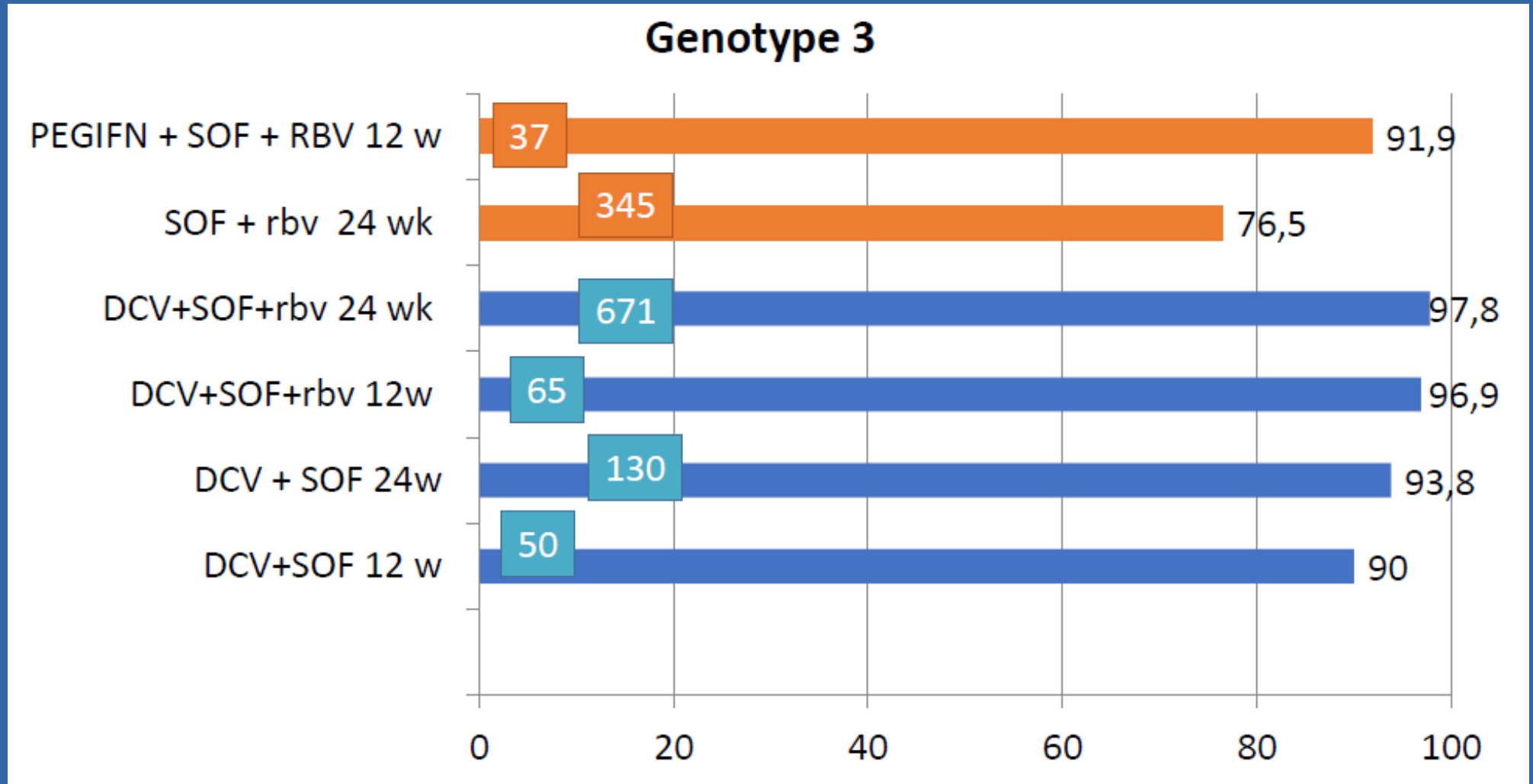
Viganò M, Perno CF, Craxì A. Treatment of Hepatitis C virus infection in Italy: A consensus report from an expert panel. Dig Liver Dis. 2017 Jul;49(7):731-741

SVR12 in 12.595 HCV infected patients in 4 Italian Regional Registries (66% F4 and 28% F3 stratified according to HCV Genotypes)



Viganò M, Perno CF, Craxì A. Treatment of Hepatitis C virus infection in Italy: A consensus report from an expert panel. Dig Liver Dis. 2017 Jul;49(7):731-741

SVR12 in 1298 HCV G3 infected patients in 4 Italian Regional Registries



Viganò M, Perno CF, Craxì A. Treatment of Hepatitis C virus infection in Italy: A consensus report from an expert panel. Dig Liver Dis. 2017 Jul;49(7):731-741



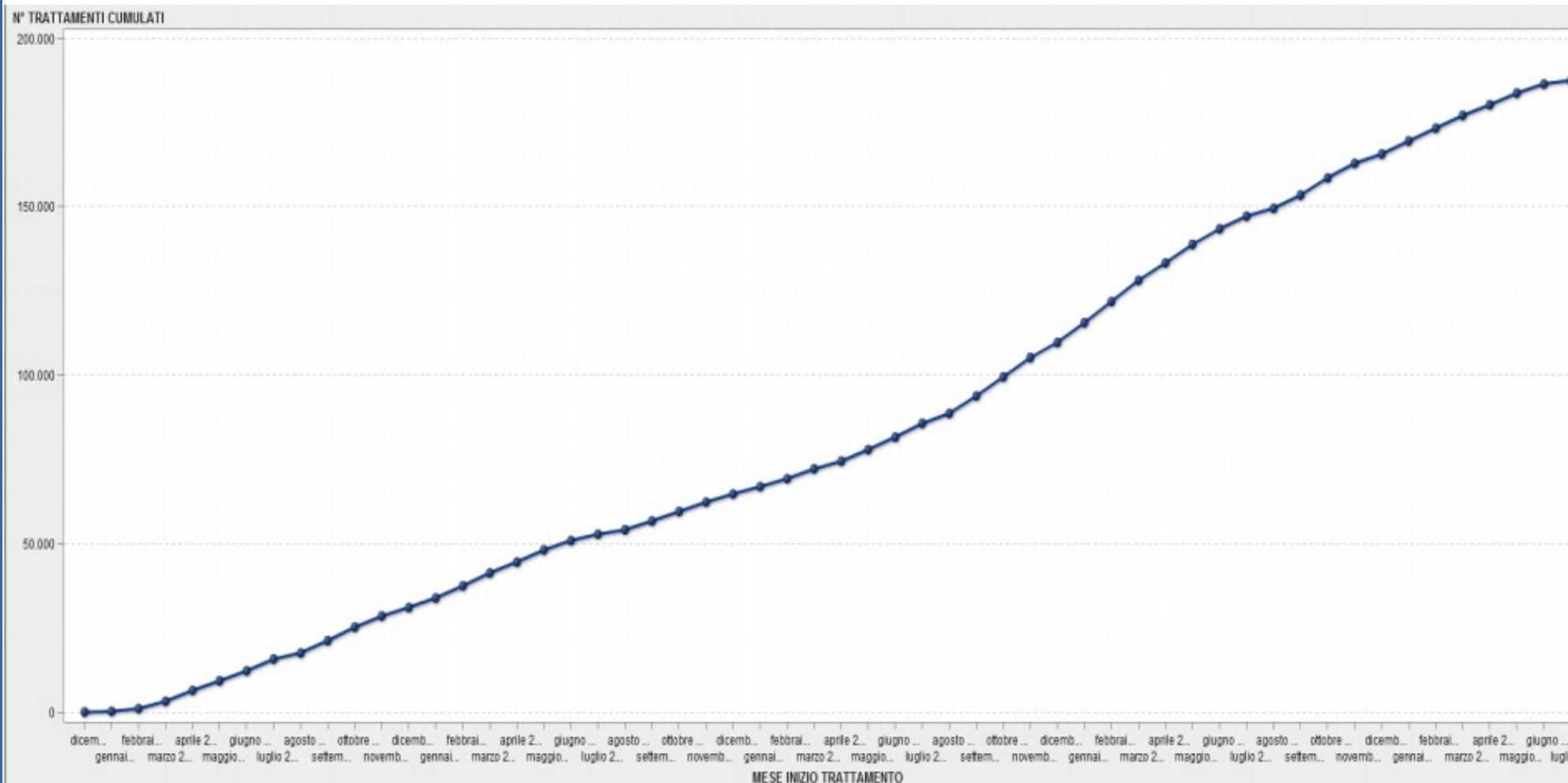
Aggiornamento dati

Registri AIFA DAAs - Epatite C cronica

15 Luglio 2019

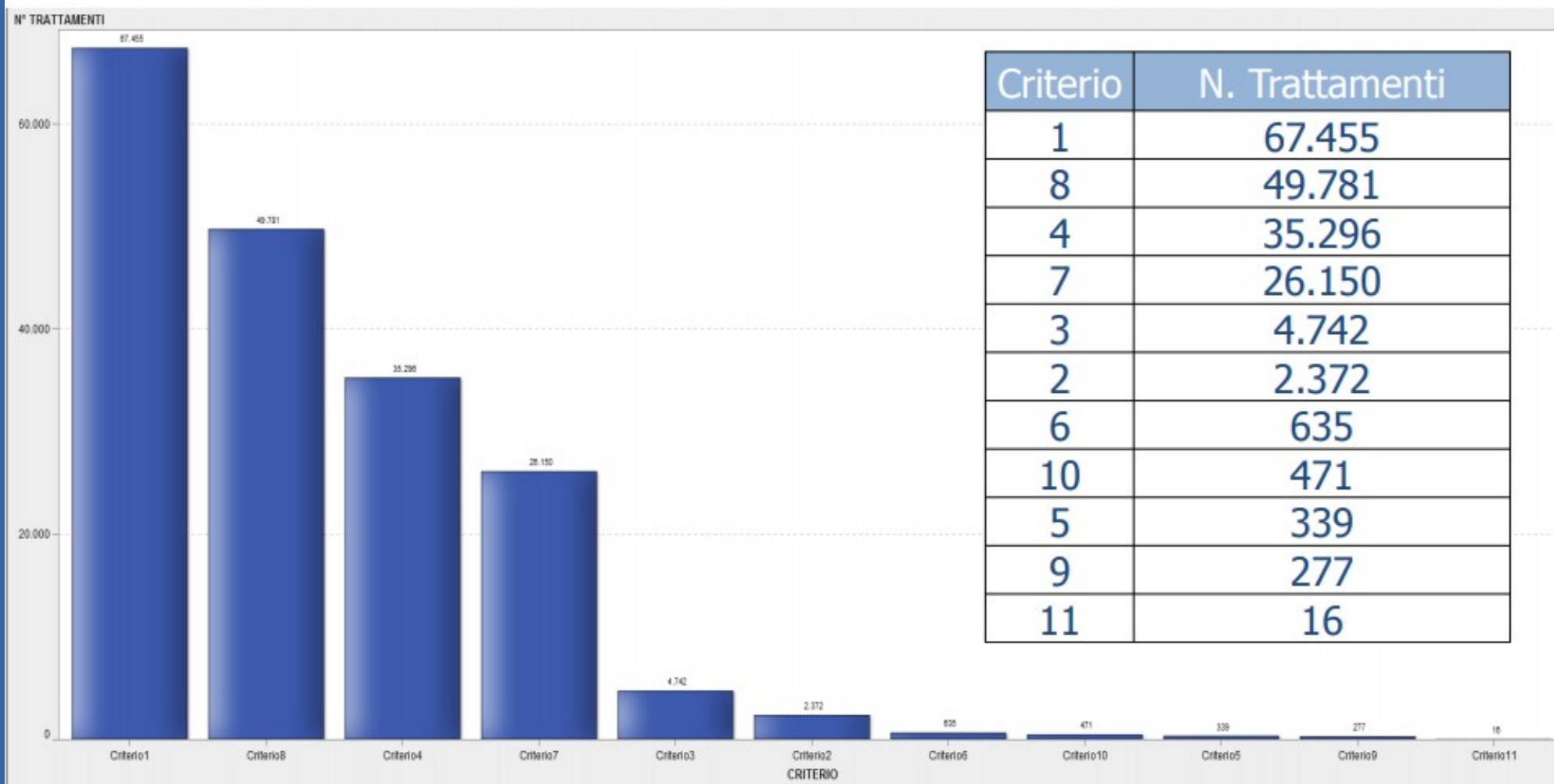
Ufficio Registri di Monitoraggio

Trend cumulativo dei trattamenti avviati

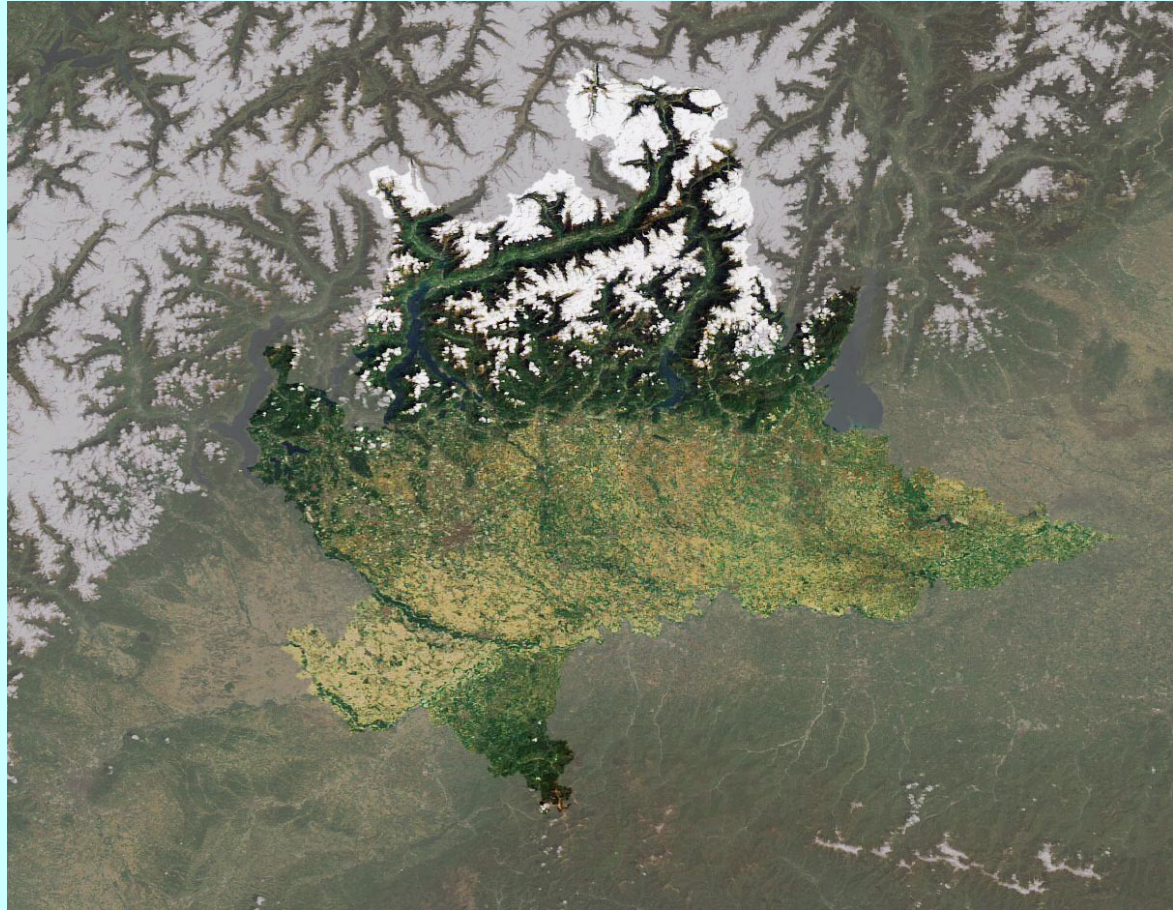


187.534 «avviati» sono i trattamenti (solo pazienti eleggibili)
con almeno una scheda di Dispensazione farmaco

Trattamenti avviati per criterio



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



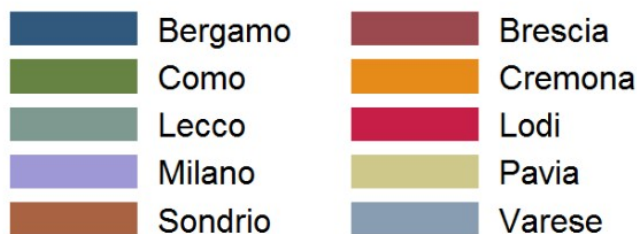
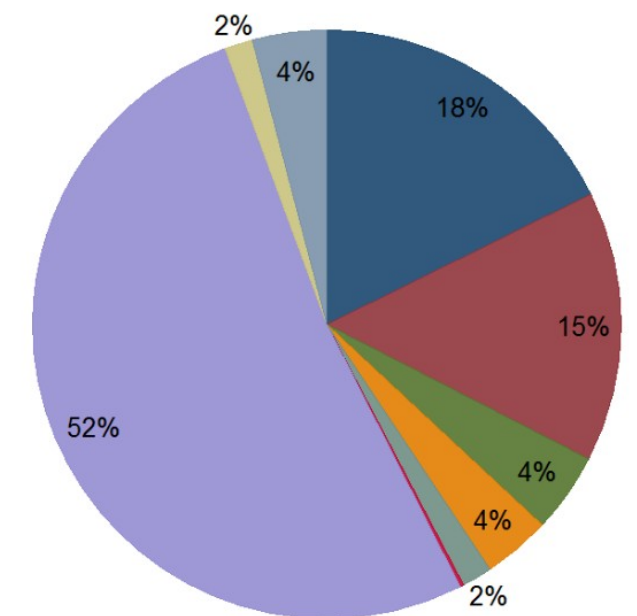
**In
Lombardy**

HCV trattamenti totali

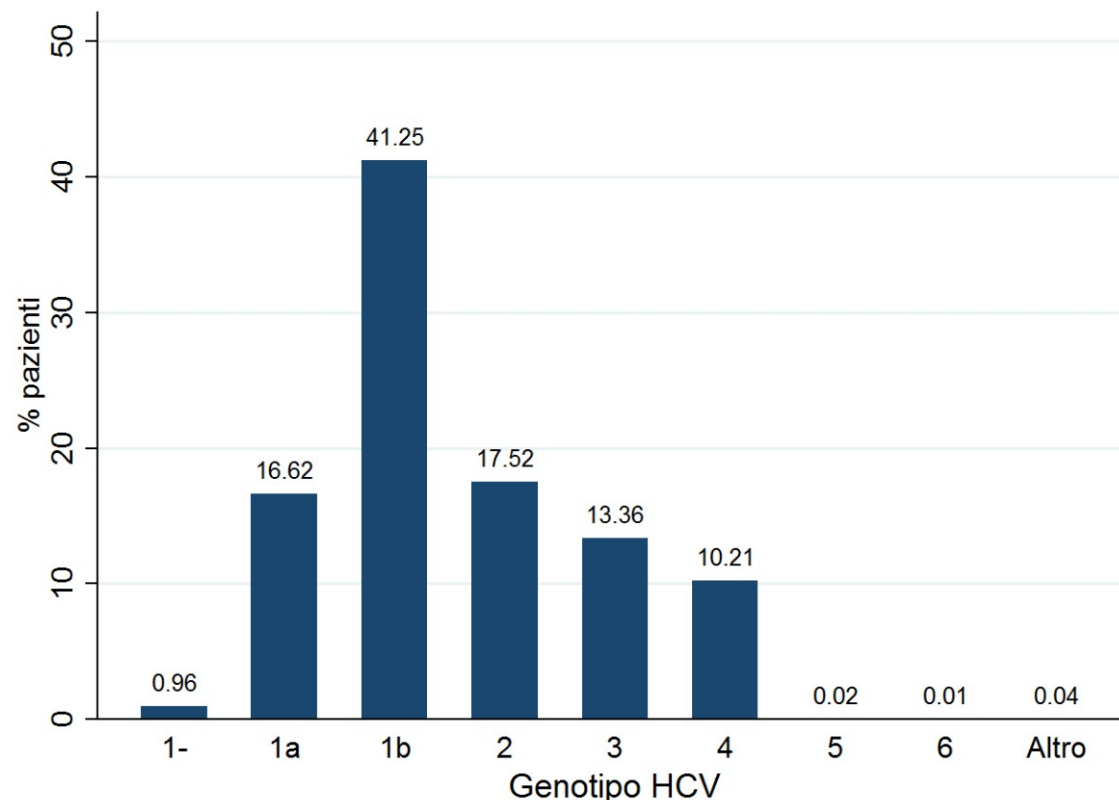
Regione Lombardia

(Dicembre 2018)

14880



(Frequenze sotto l'1% non segnalate)



Caratteristiche al baseline dei pazienti partecipanti al Registro HCV

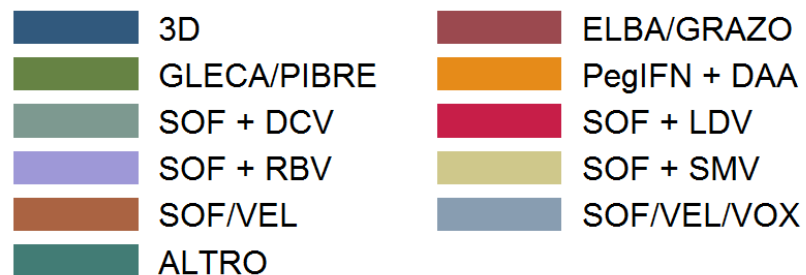
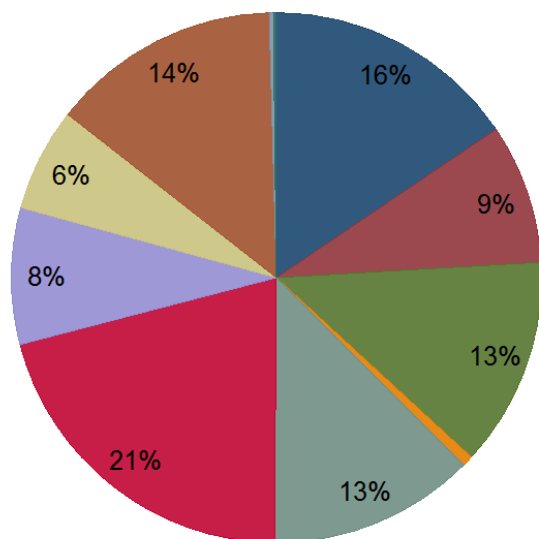
Età media: 60 anni

M: 58%

Metavir F4: 47%; Metavir F3: 23%

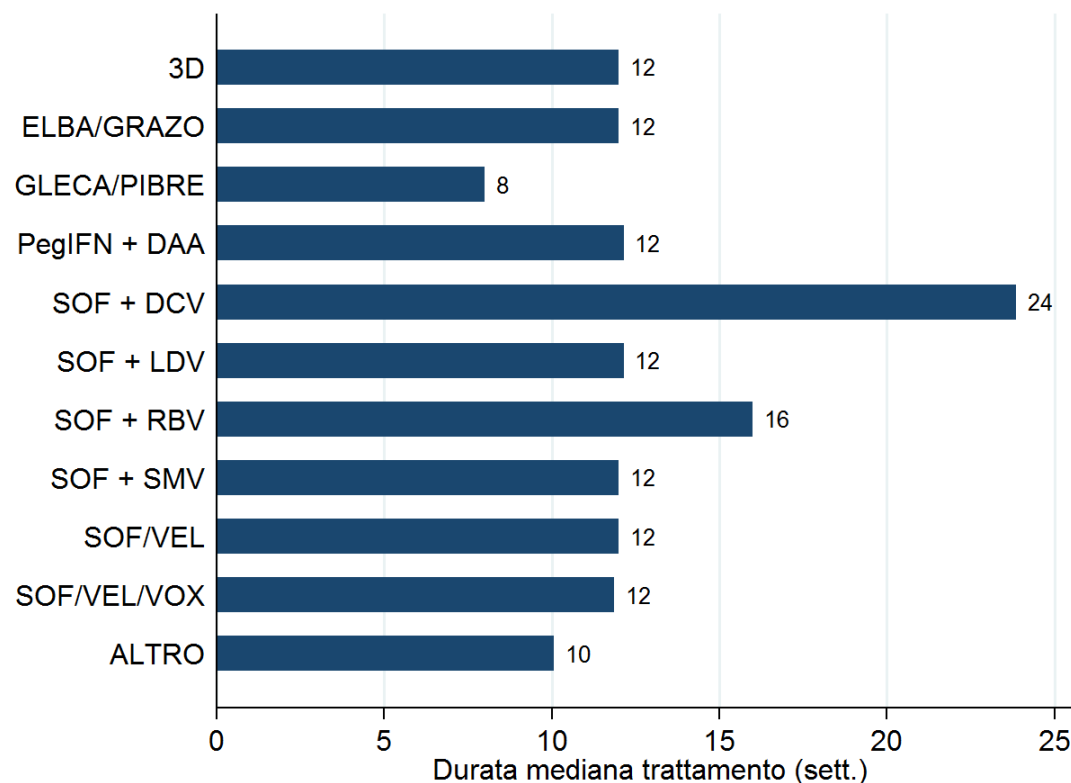
Co- infezione HIV: 15%

Co- infezione HBV: 23%



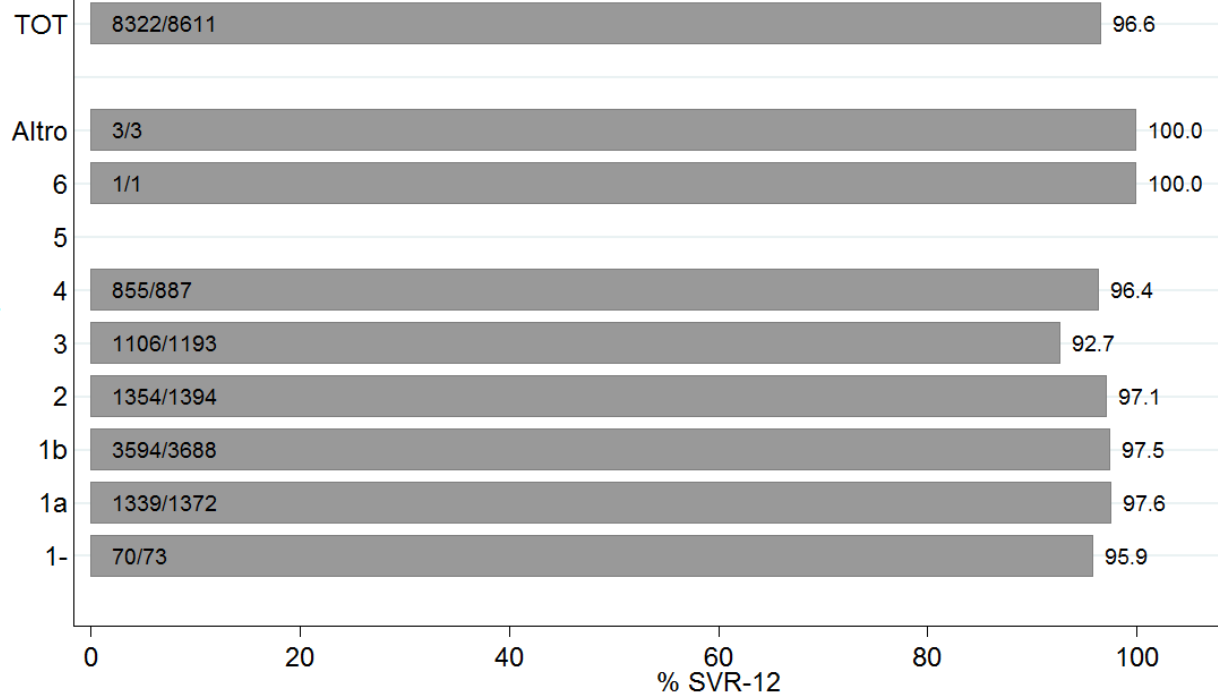
(Frequenze sotto l'1% non segnalate)

Categorie di trattamento per i pazienti della Rete HCV (in percentuale)



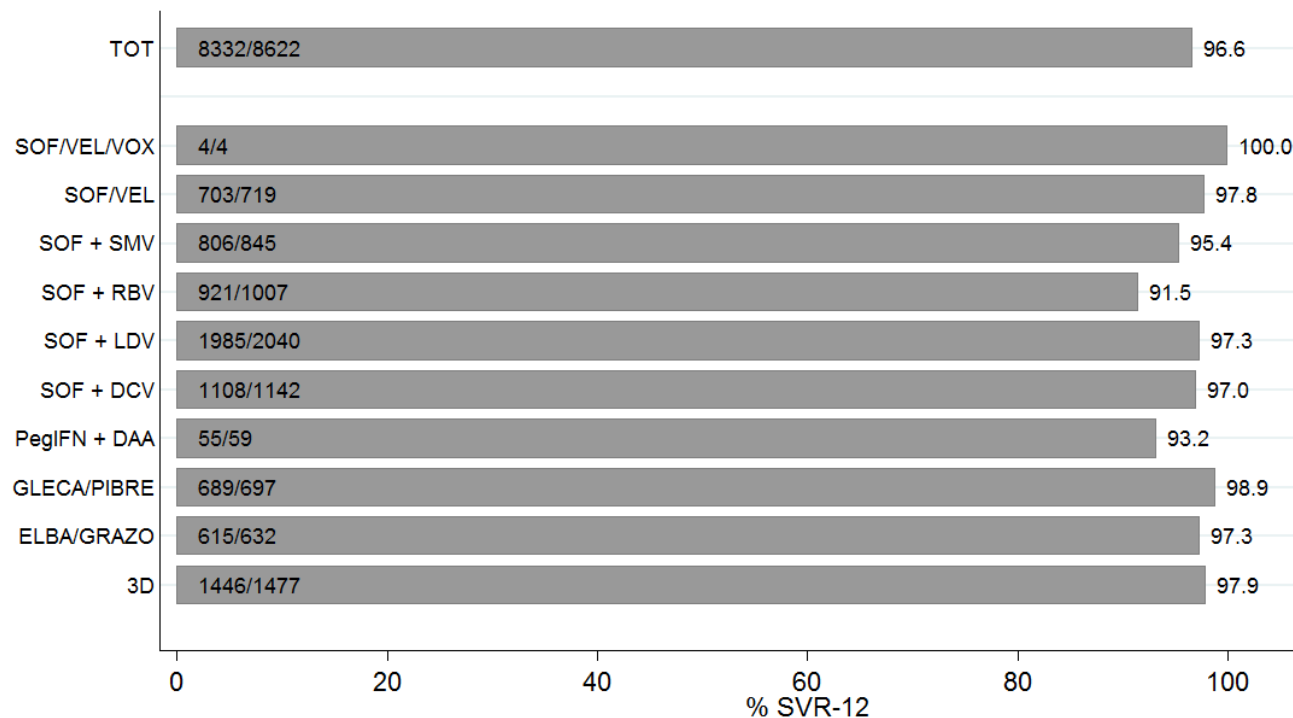
Durata mediana della terapia con i nuovi antivirali (in settimane)

Genotipo HCV



Distribuzione delle risposte (SVR 12) per genotipo

Trattamento



Distribuzione delle risposte (SVR 12) per tipologia di trattamento



CASISTICA ASST LARIANA

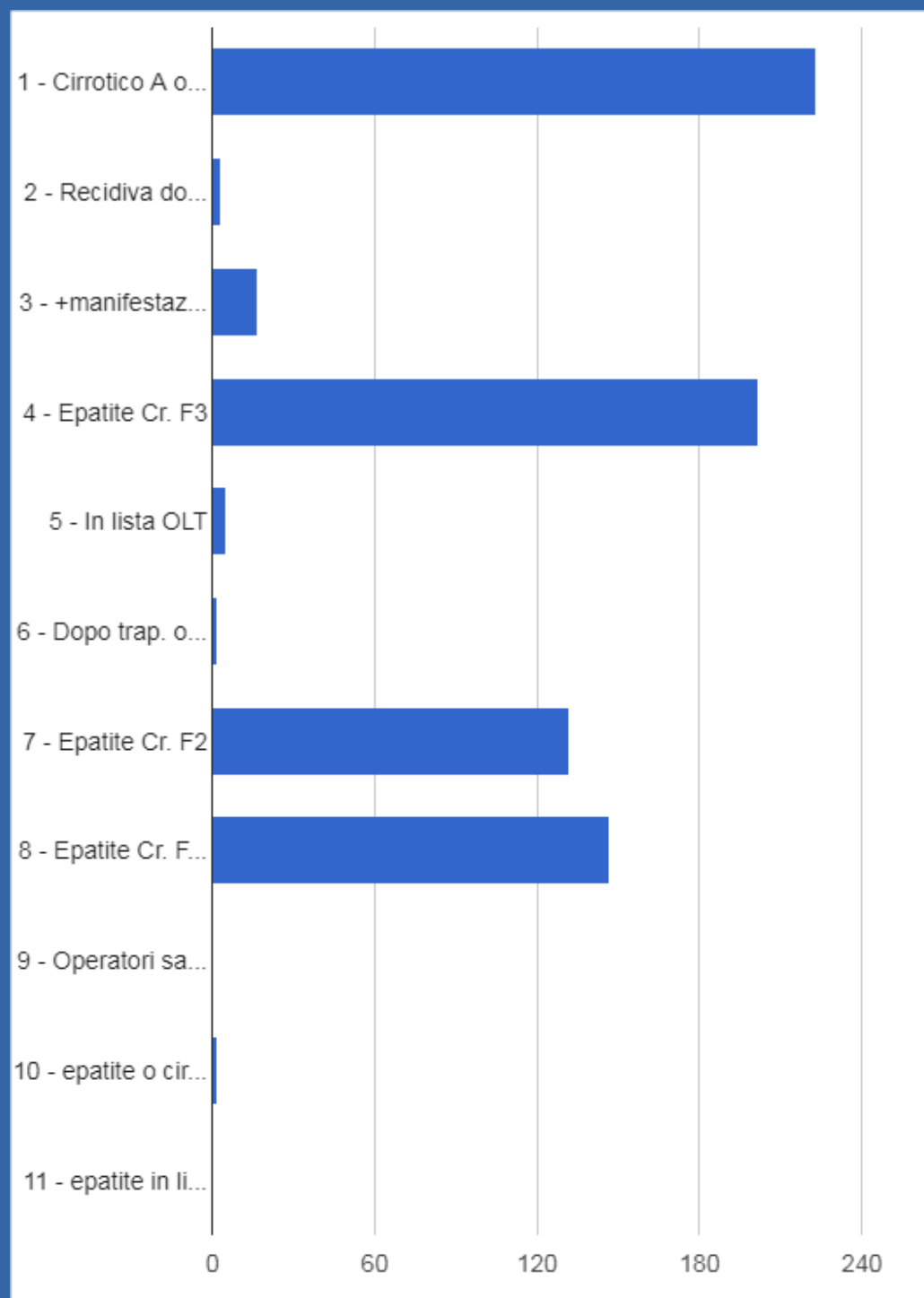


Baseline characteristics of the 737 patients

	TOTALE PAZIENTI
NUMERO PAZIENTI	737 (100%)
ETA' MEDIA	63.18
SESSO M (%)	448 (61.9%)
BMI	26.00
CO-INFEZIONE HIV/HBV (%)	18.6/2.9
FUMO	251 (34.1%)
ALCOOL	75 (10.2%)
HCV-RNA BASALE (UI/L)	1 521 000
IFN-EXPERIENCED	257 (34.9%)
LSM, kPa	9.90 (3.1-43)
FIBROSI F4	231 (31.4)
FIBROSI F3	213 (29.0)
FIBROSI F0-F2	193 (39.6)
MELD	8
PLT (10 ³ /mm ³)	178
ALT (U/L)	63
INR	1.02
ALBUMINA (g/dl)	4.1
CO-MEDICATIONS (%)	44.5%

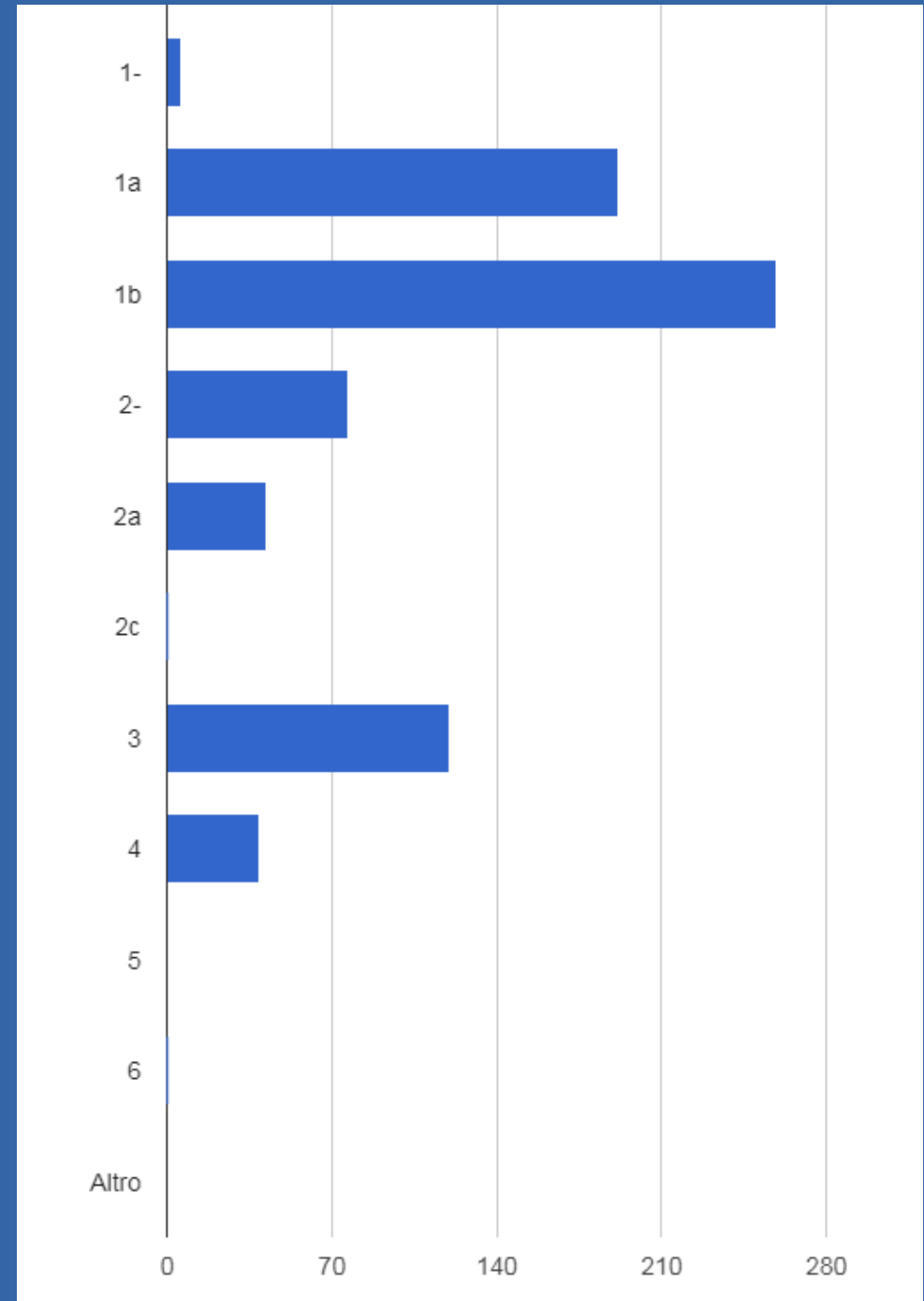
Criterio ALFA

CRITERIO	PAZIENTI (%)
1	223 (30.4%)
2	3 (0.4%)
3	17 (2.3%)
4	202 (27.6%)
5	5 (0.7%)
6	2 (0.3%)
7	132 (18%)
8	147 (20.1%)
9	0
10	2 (0.3%)
11	0

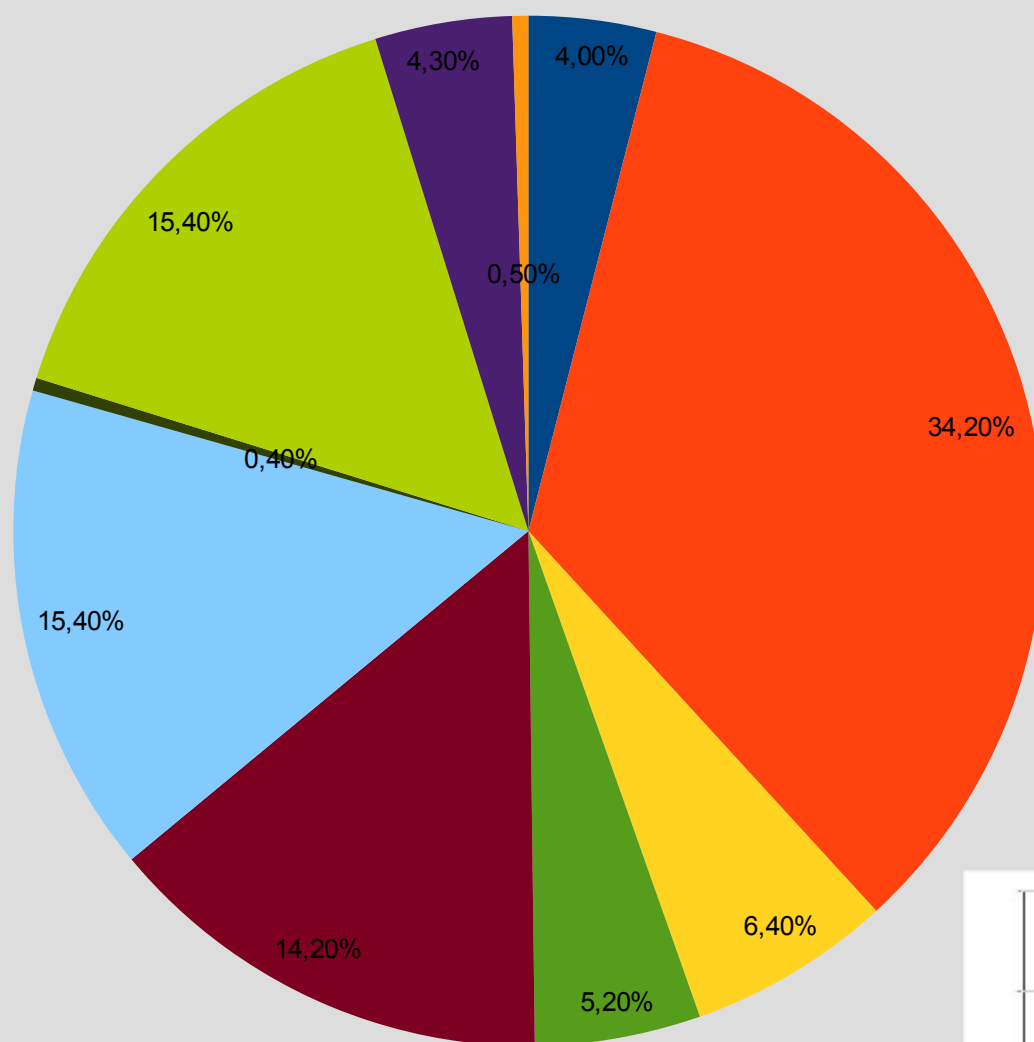


Genotipo HCV

GENOTIPO	PAZIENTI (%)
1	6 (0.8%)
1a	192 (26.1%)
1b	259 (35.1%)
2	77 (10.4%)
2a/c	43 (5.8%)
3	120 (16.3%)
4	39 (5.3%)
5	0
6	1 (0.1%)

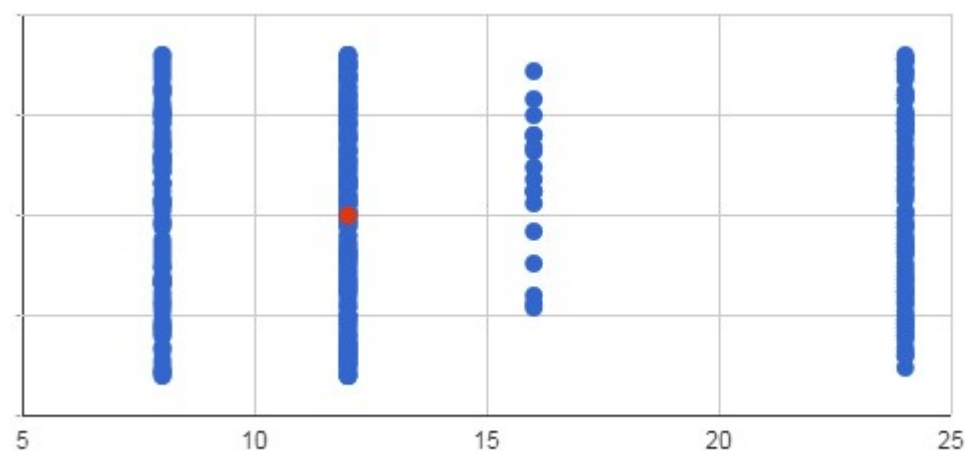


Trattamenti HCV

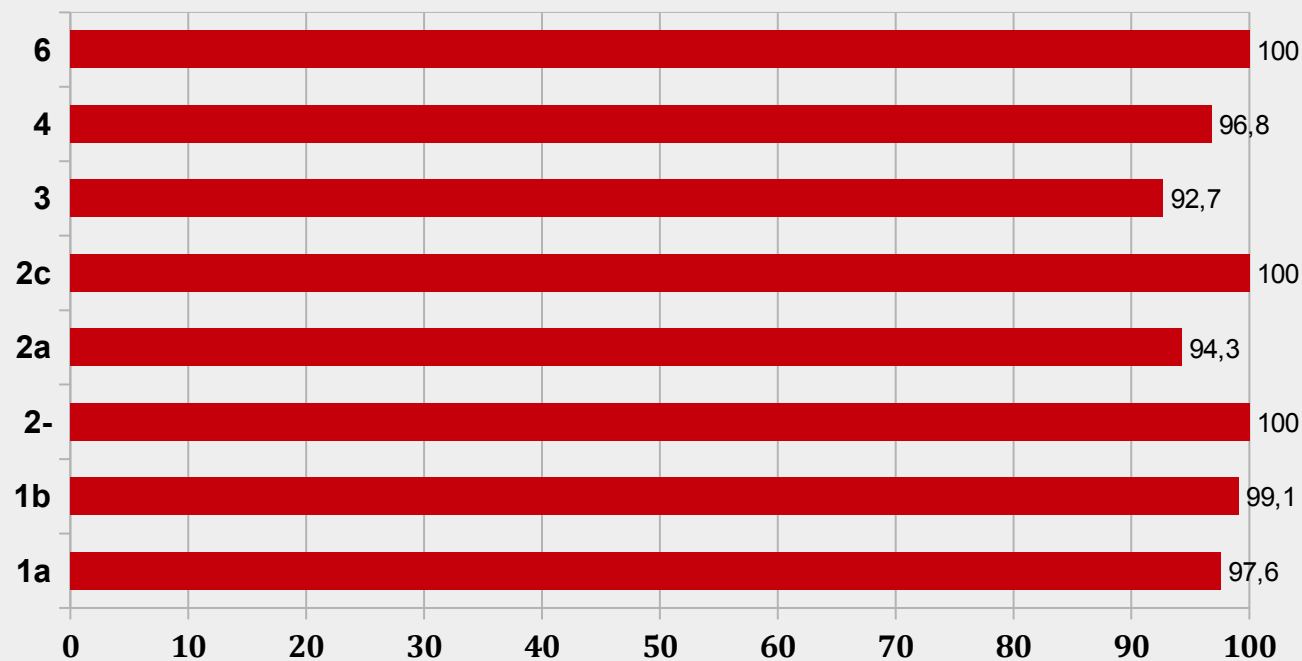
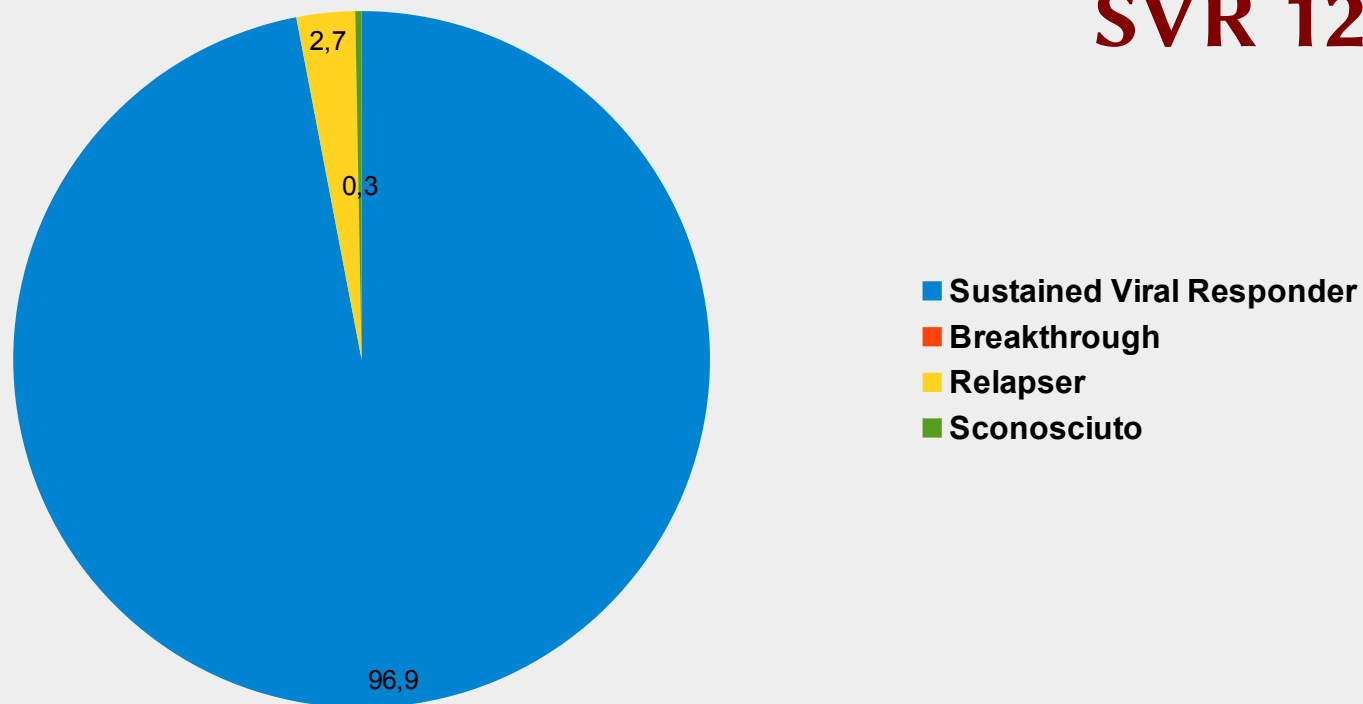


- 3D/2D
- GLECA/PIBRE
- SOF + DCV
- SOF + RBV
- SOF/VEL
- ELBA/GRAZO
- PegIFN + DAA
- SOF + LDV
- SOF + SIM
- SOF/VEL/VOX

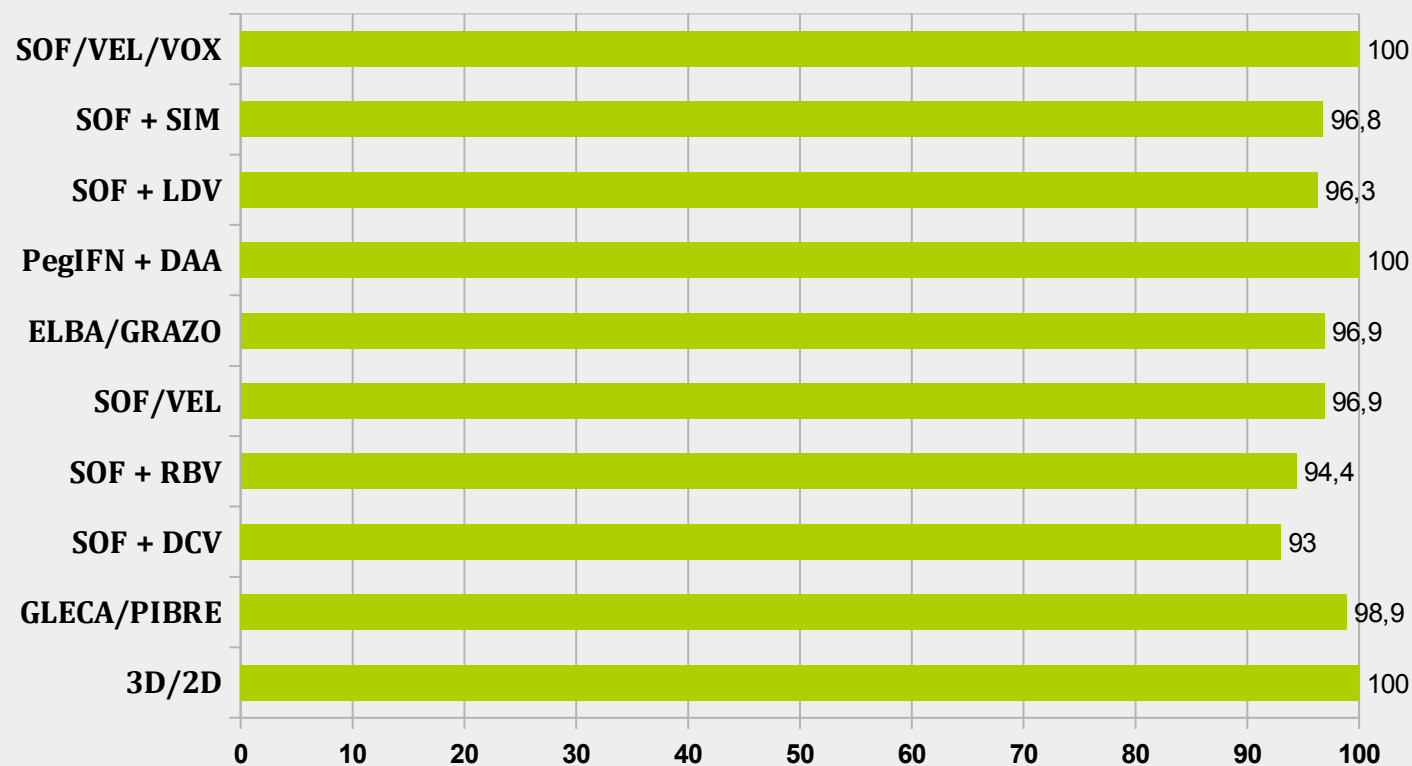
Durata prevista del trattamento (settimane)



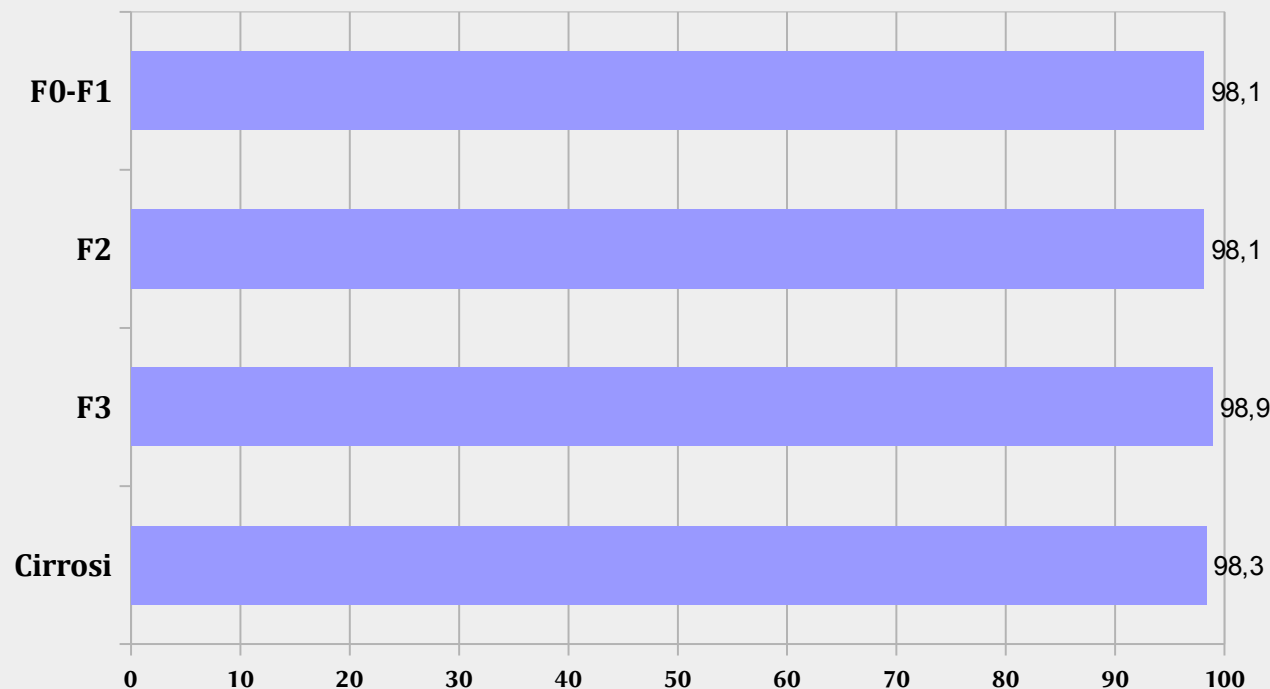
SVR 12 settimane



**Distribuzione delle risposte
(SVR 12) per genotipo**

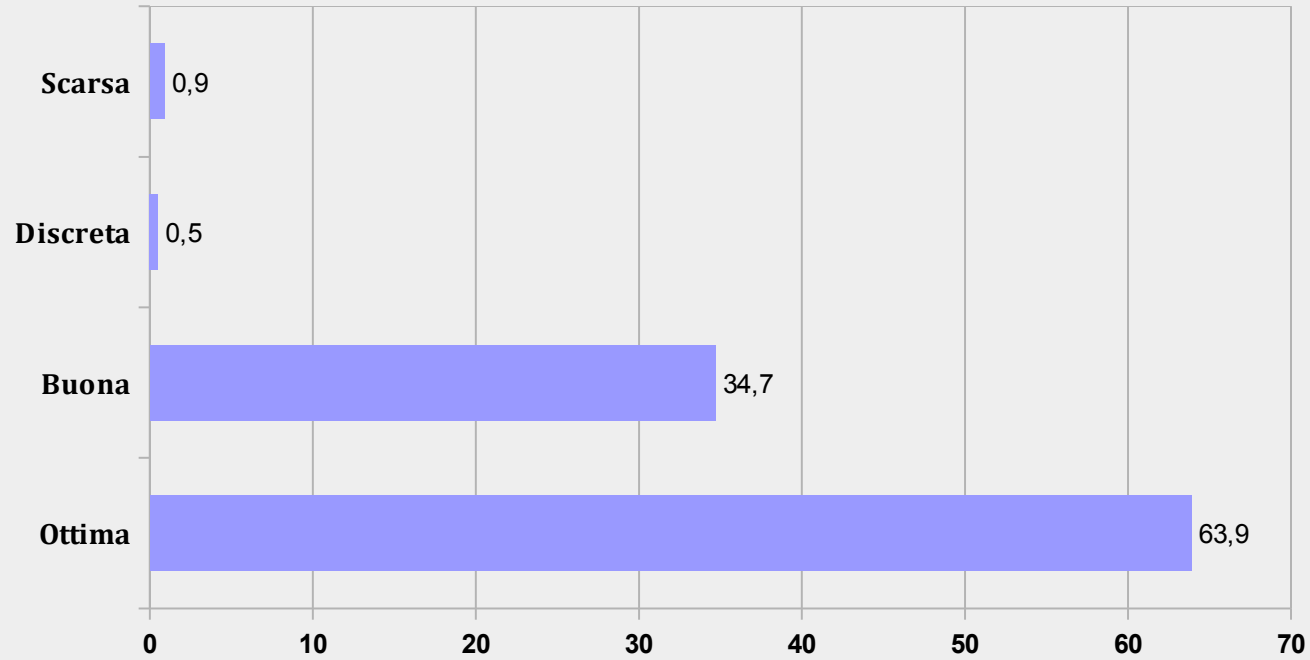


**Distribuzione delle
risposte (SVR 12) per
tipologia di trattamento**

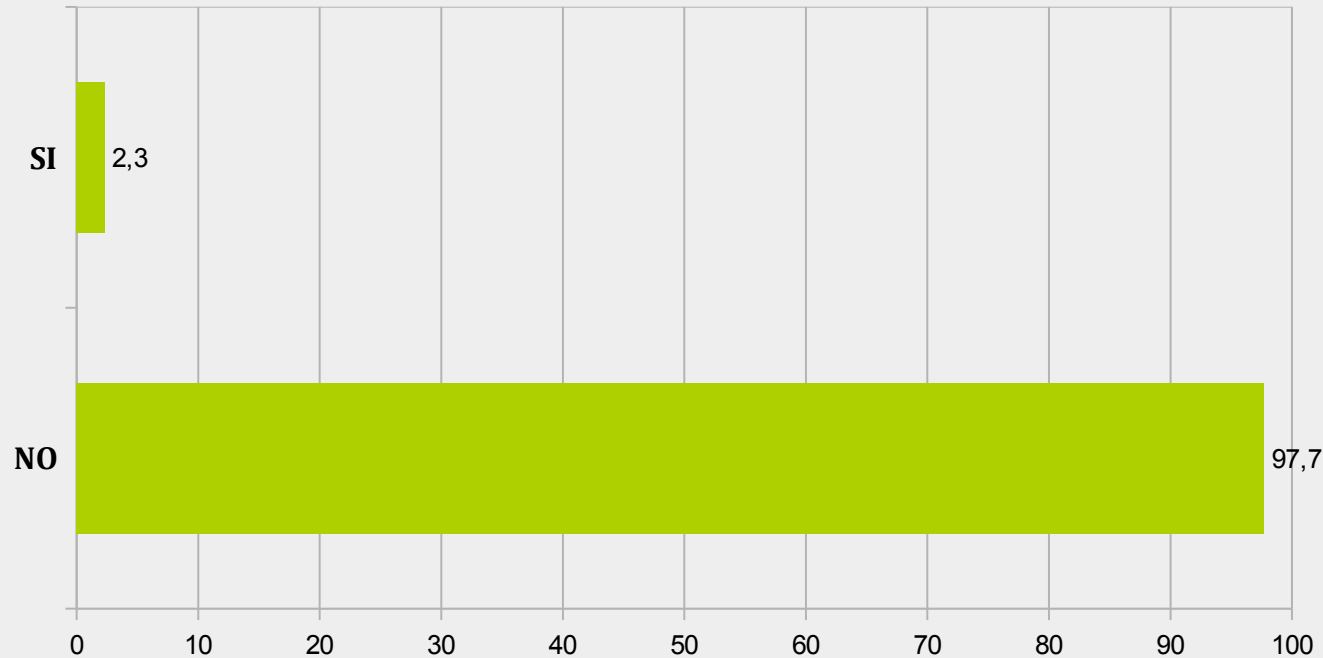


**Distribuzione delle risposte
(SVR 12) per grado di fibrosi**

Eventi avversi



**Giudizio di tollerabilità
generale**



Comparsa di eventi avversi

	TRATTAMENTO	DURATA EFFETTIVA	SINTOMI	ESITO
1	SOF/r 16W	16	Nausea	Completato
2	SOF/LDV/r 24W	12	Eteroplasia del colon	Non completato, SVR 12W
3	SOF/SIM 12W	12	Acne rosacea	Completato
4	SOF/LDV/r 12W	12	Reazione orticaroide al viso da RBV	Completato
5	SOF/SIM 12W	12	Acne rosacea	Completato
6	3D/r 12W	12	Nausea	Completato
7	GLE/PIB 12W	9	Decesso (non correlato alla terapia)	Non completato
8	GLE/PIB 12W	8	Prurito	Non completato, SVR 12W
9	GLE/PIB 12W	8	Tendinopatie diffuse agli arti	Completato
10	GLE/PIB 8W	3	Intolleranza gastrica (nausea, vomito)	Non completato, no SVR
11	SOF/LDV/r 12W	4	Vomito, cefalea	Non completato, no SVR
12	SOF/DAC/r 24W	1	Vomito	Non completato, no SVR
13	SOF/DAC/r 24W	3	Vomito	Non completato, no SVR

PZ	ETA	SESSO	TERAPIA	GENOTIPO	EXPERIENCED	DURA TA	HIV	HCV-RNA	FIBROSCAN
PA	48	M	SOF/DAC	3	N	24	N	3560000	27,7
PR	68	F	SOF/SIM	1	N	12	N	1012979	28,3
PC	53	M	SOF/DAC/r	3	N	24	N	574812	25
BG	40	M	SOF/r	3	N	24	N	628875	14,6
PG	53	M	SOF/r	3	N	24	S	184843	46
BG	49	M	SOF/LDV/r	4	S (PEG/r)	12	S	858502	46,4
ML	80	F	SOF/LDV	1	S (PEG/r)	24	N	2102346	14,8
GG	80	M	SOF/VEL	2a	N	12	N	343311	24
PA	55	M	SOF/LDV/r	1a	S (PEG/r)	12	N	6609676	27
FF	80	F	SOF/r	2a	S (PEG/r)	24	N	10040069	19,6
LL	84	F	ELB/GRA	1b	N	12	N	1980108	16,1
CA	69	M	GLE/PIB	1	N	8	N	961550	6,1
ER	64	M	ELB/GRA	1b	S (PEG/r/DAA)	12	N	5550000	6,0
BC	48	M	SOF/VEL/r	3	N	12	S	985666	48
ZM	52	F	ELB/GRA/r	1a	S (PEG/r)	16	S	1250669	7,7
BV	58	M	SOF/VEL	1a	N	12	S	9687774	7,4
SF	53	M	GLE/PIB	3	N	8	S	1254888	10,1

Carcerati

**SER-
D**

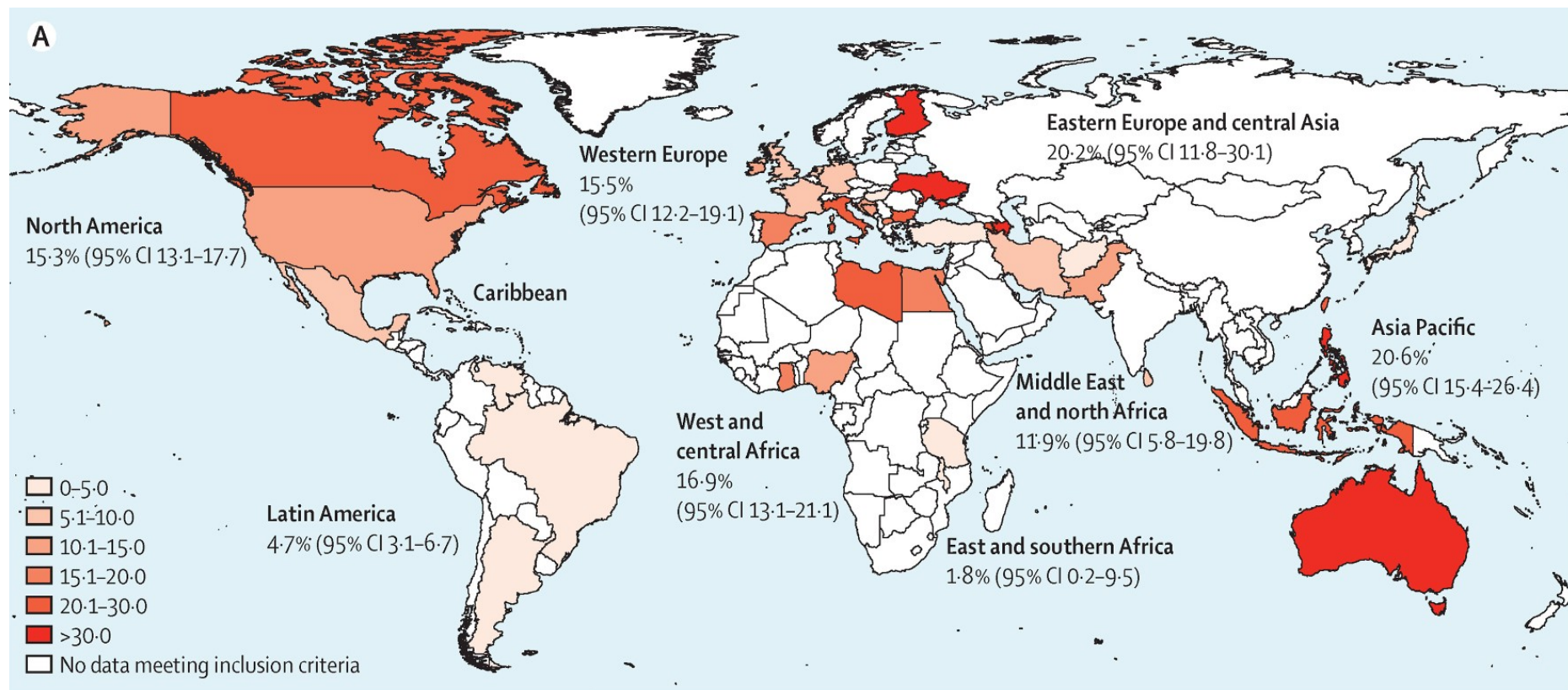
GRUPPI “DIFFICILI”

**MSM
Sex Worker**

Migranti

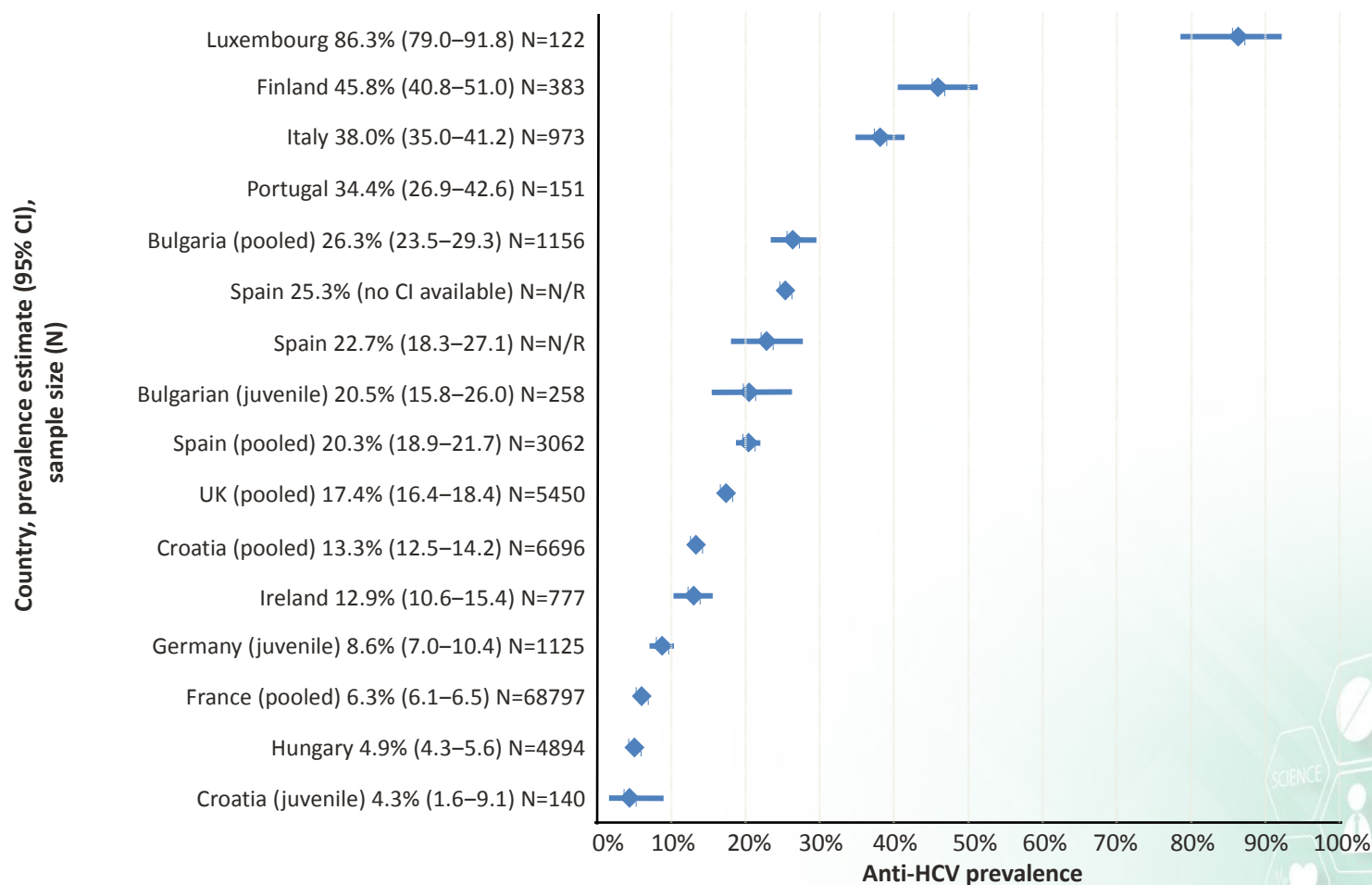
Global and Regional Prevalence of Hepatitis C in Prison Inmates Published Between 2005 and 2015

Percentage **unaware of HCV infection**: 25% to 35%



Dolan K, *et al.* Lancet 2016; 388:1089-1102

Anti-HCV Prevalence among People in Prison across the EU/EEA



All but 4 estimates (Germany, France, Hungary, Croatia) were above 10% prevalence

• EU/EEA, European Union/European Economic Area.

Ostacoli reali al trattamento diffuso di HCV in carcere

- Elevato numero di pazienti da trattare rapidamente a causa dell'elevato turnover
- Lunghi tempi di attesa per gli esami necessari per la stadiazione clinica e l'idoneità per la terapia DAA
- Difficoltà a prendere sangue per i test biochimici e virologici al tempo richiesto dai programmi terapeutici
- Ritardi nel ricevere risultati, essenziali per valutare l'efficacia della terapia
- Numero di operatori sanitari e infermieri insufficienti per trattare contemporaneamente centinaia di pazienti
- Aumento del rischio di trasmissione di HCV all'interno (per sesso, tatuaggi o aghi) fino a quando la prevalenza di pazienti viremici da HCV rimane elevata
- Trasferimenti improvvisi ad altre prigioni



Il progetto in sintesi

IL TAVOLO DI LAVORO INTERDISCIPLINARE



CONDIVISIONE DELLE MODALITA' D'INTERVENTO PER FACILITARE LO SCREENING



ATTIVITA' FORMATIVA E DI SENSIBILIZZAZIONE



AVVIO SCREENING CON ORAL TEST



DIAGNOSI E STADIAZIONE



AVVIO TERAPIA

Gli istituti coinvolti

MILANO

- OPERA

VITERBO

CIVITAVECCHIA

NAPOLI

- SECONDIGLIANO
- POGGIOREALE
- POZZUOLI

SALERNO

SASSARI

COMO

BERGAMO

CREMONA

BRESCIA

BUSTO ARSIZIO

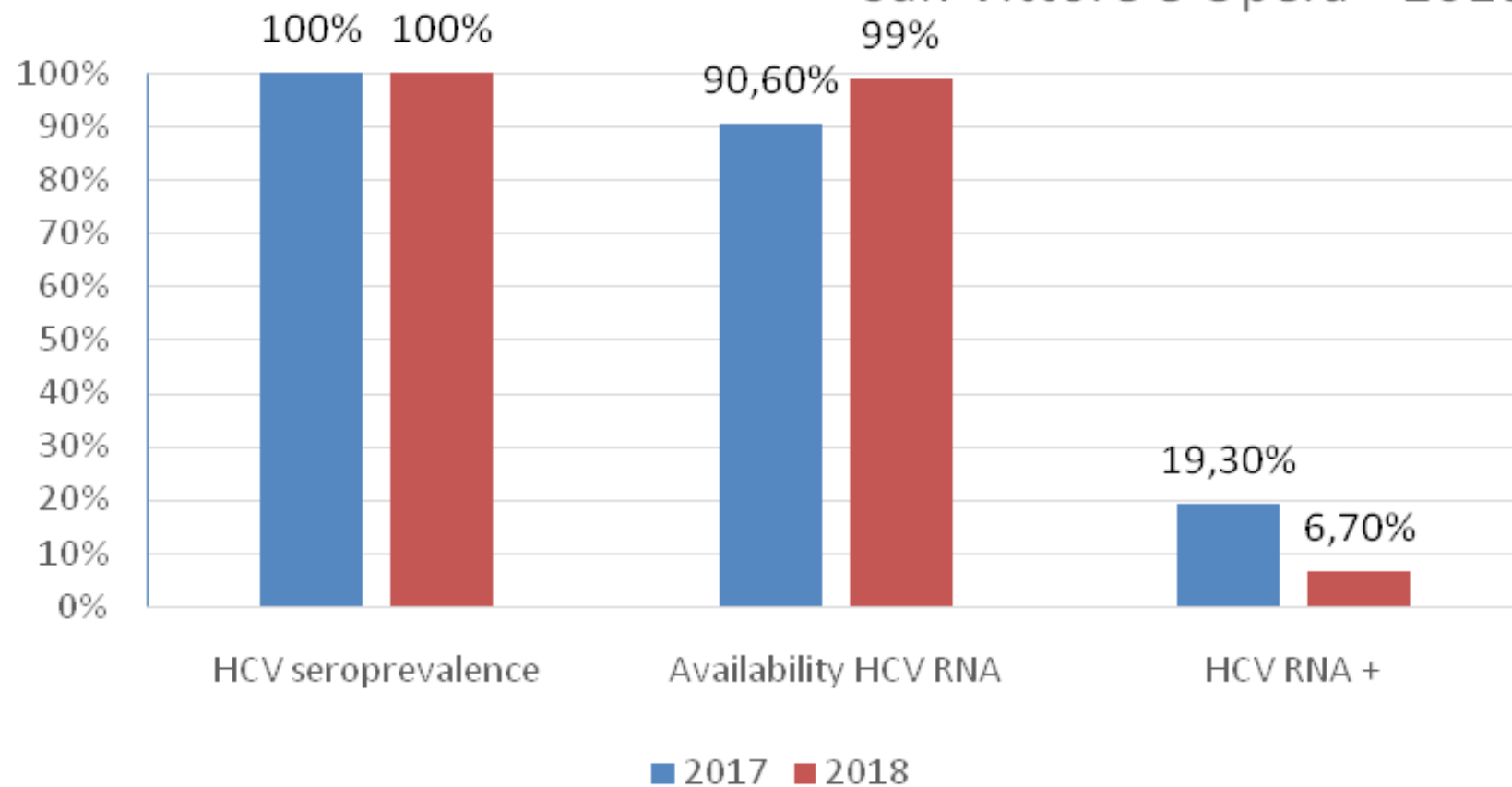
LA SPEZIA



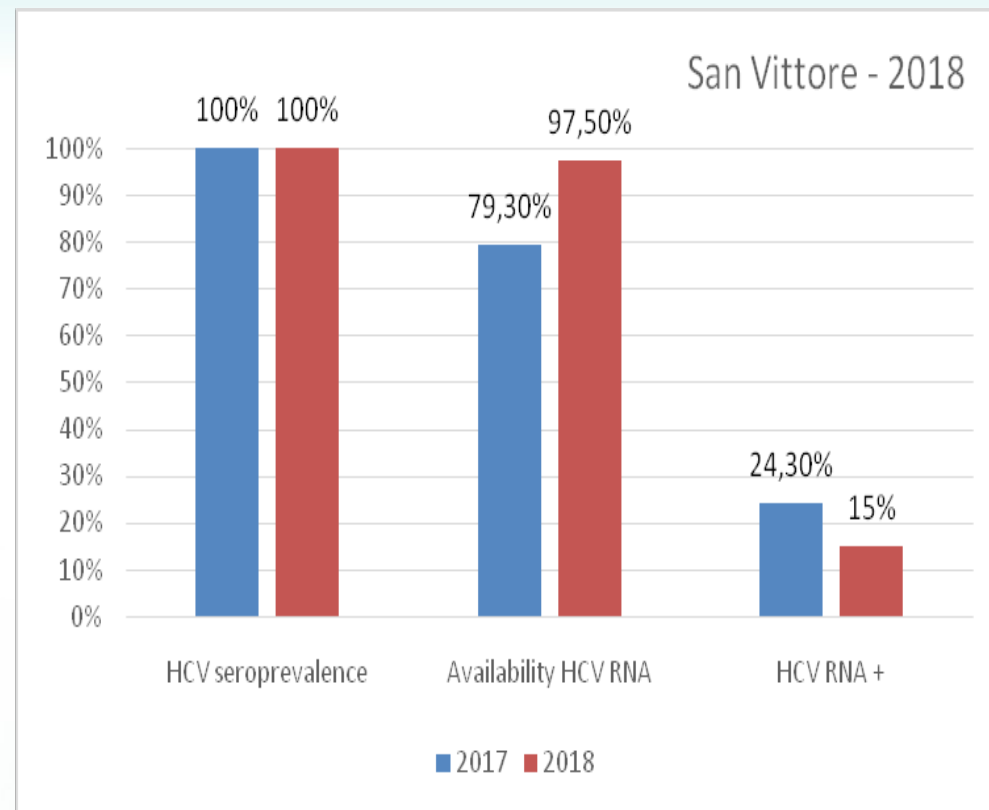
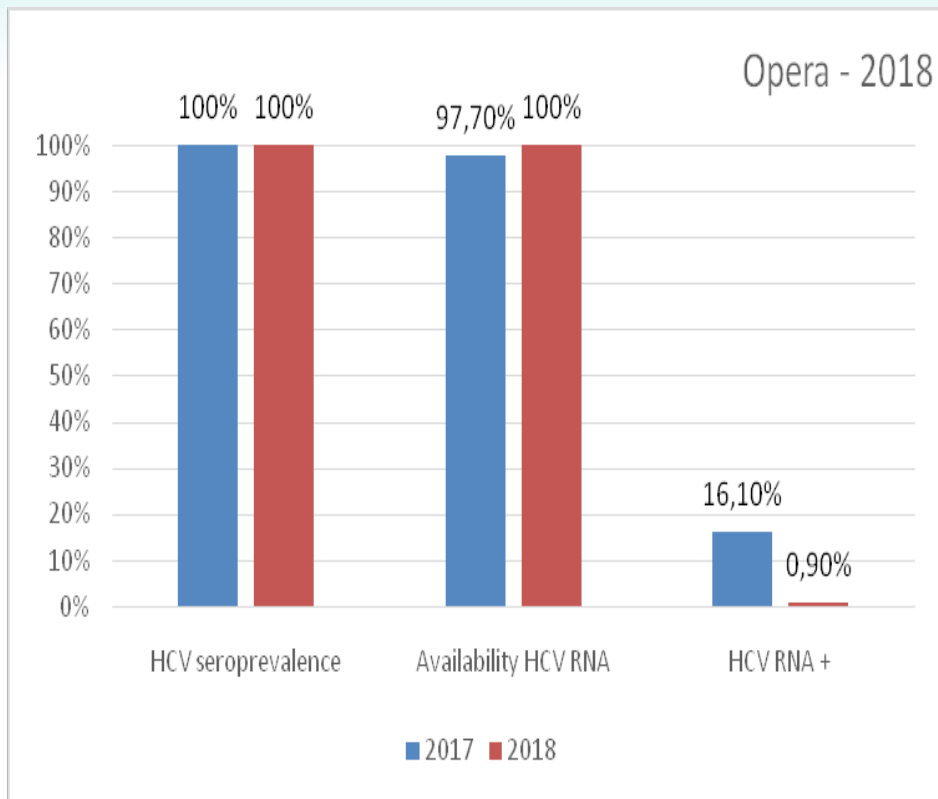
Popolazione carceraria a Milano al 31/10/2018

	San Vittore	Opera	TOTALE
N detenuti TOT	1042 (44,0%)	1327 (56,0%)	2369
Sesso			
M	957 (91,8%)	1327 (100%)	2284 (96,4%)
F	85 (8,2%)	0	85 (3,6%)
N detenuti HCV Ab+	80 (8,8%)	114 (9,5%)	194 (9,6%)
Nazionalità:			
Italiana	57 (71,2%)	106 (93,0%)	163 (84,0%)
Nord Africana	8 (10%)	5 (4,4%)	13 (6,7%)
Americana	1 (1,2%)	0	1 (0,5%)
Est Europa	9 (11,2%)	2 (1,7%)	11 (5,7%)
Africana (altri stati)	0	0	0
Asiatica	4 (5%)	1 (0,9%)	5 (2,6%)
Europea	1 (1,2%)	0	1 (0,5%)
Età mediana e IQR	36, (28-46)	46 (36-55)	41 (31-51)

San Vittore e Opera - 2018



(SCIENCE)





Grazie per l'attenzione