SITA
Società Italiana di Terapia Antinfettiva
Antibatterica Antivirale Antifungina

12° CONGRESSO NAZIONALE
CATANIA | 17-18 novembre 2022

HCV e DAAs: trattamento dei fallimenti e delle reinfezioni

P. Colletti e G. D'Aguanno

UOC Malattie Infettive

Ospedale P. Borsellino. Marsala (ASP TP)

HCV e DAAs: trattamento dei fallimenti e delle reinfezioni

P . Colletti e G. D'Aguanno

- Dimensioni del problema: recidiva e reinfezione
- Perché trattare nuovamente
- Resistenze e failure
- Come ritrattare
- Conclusioni

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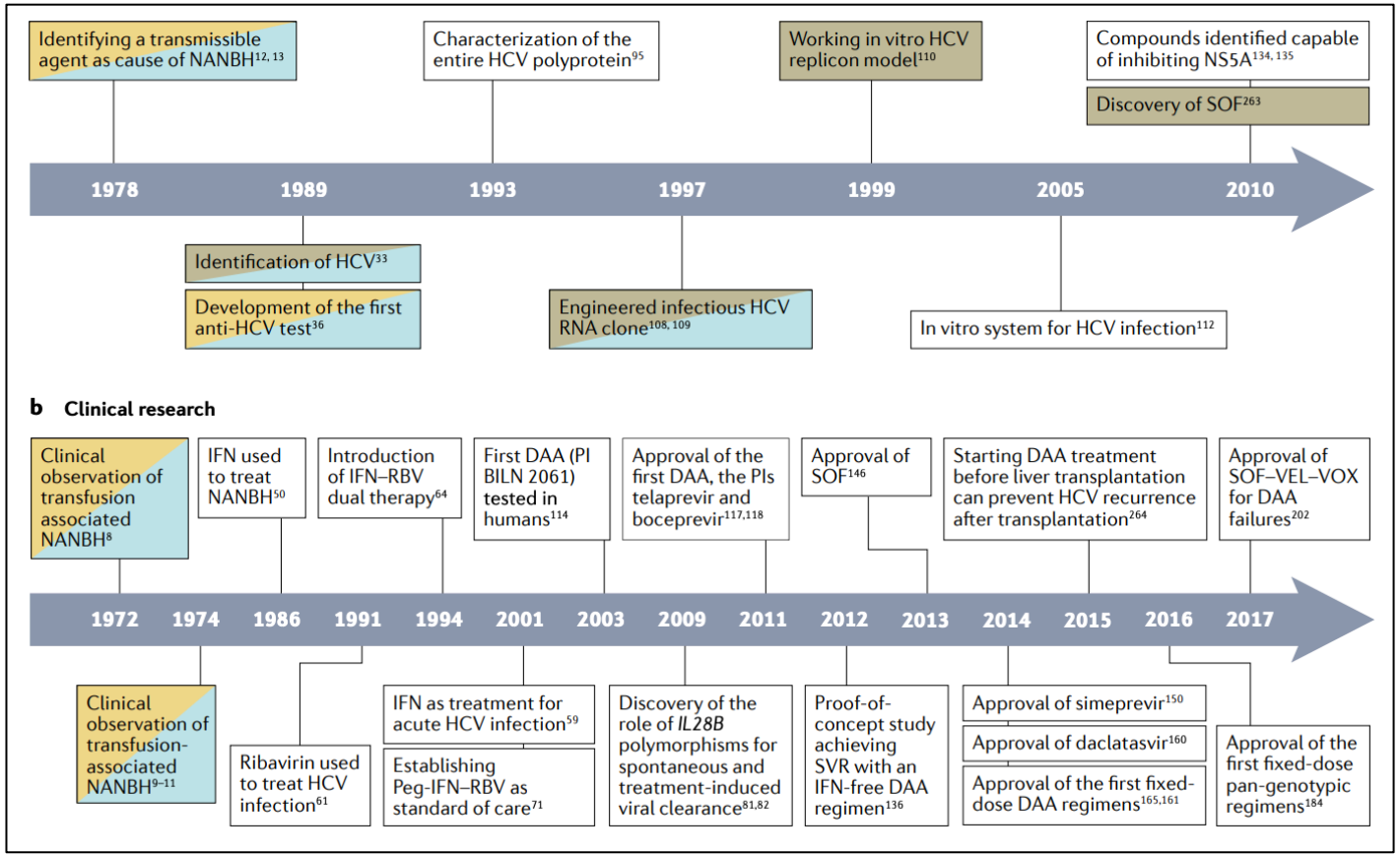
Breakthroughs in hepatitis C research: from discovery to cure

Nature Reviews | Gastroenterology & Hepatology, August 2022

Michael P. Manns and Benjamin Maasoumy

I RIVOLUZIONARI PROGRESSI DELLA RICERCA: DALLA SCOPERTA DEL VIRUS ALLA CURA



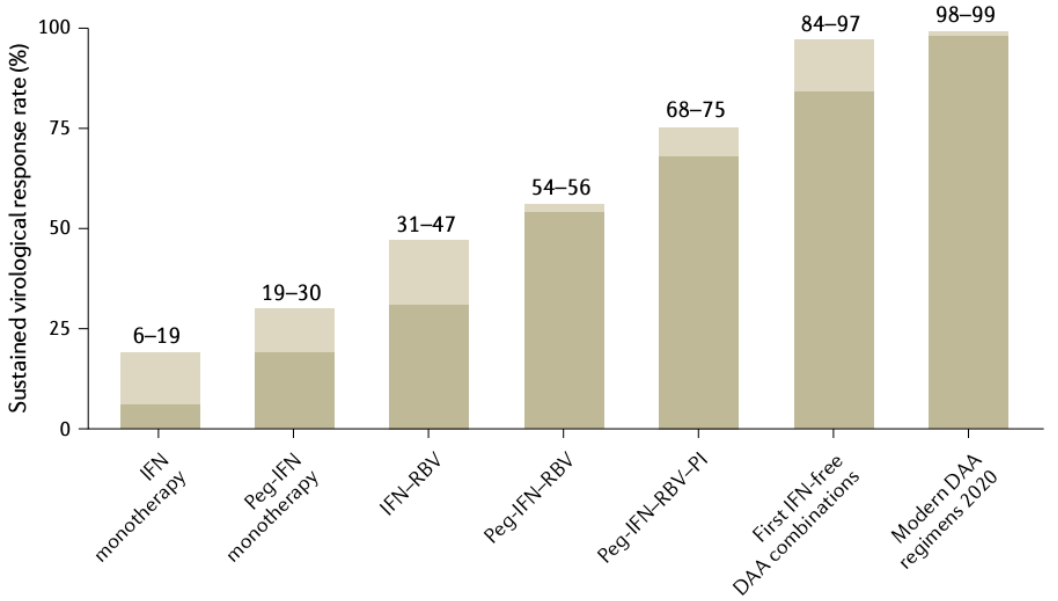


Fig. 5 | **Evolution of HCV therapy.** There has been a continuous increase in sustained virological response rates over time, starting with only 6–19% when using the first interferon-α (IFN) monotherapies to cure rates of >98% in the era of direct-acting antiviral agents (DAAs)[5,65,66,71,73,117,119,146,152,266]. HCV, hepatitis C virus; Peg-IFN, pegylated interferon-α; PI, protease inhibitor; RBV, ribavirin.

Obiettivo del trattamento è ottenimento di **risposta virologica sostenu**ta (12 o 24 settimane) e questo **corrisponde alla CURA definitiva** dell'infezione da HCV

Negli ultimi dieci anni il progressivo modificarsi degli approcci farmacologici permette di raggiungere **SVR nel al 98 %**

Direct-acting antiviral retreatment patterns for hepatitis C

C Shaquib Al Hasan et al , J Manag Care Spec Pharm. 2022

31.553 pts : 1.017 (**3.2%**) required DAAs **RETREATMENT**

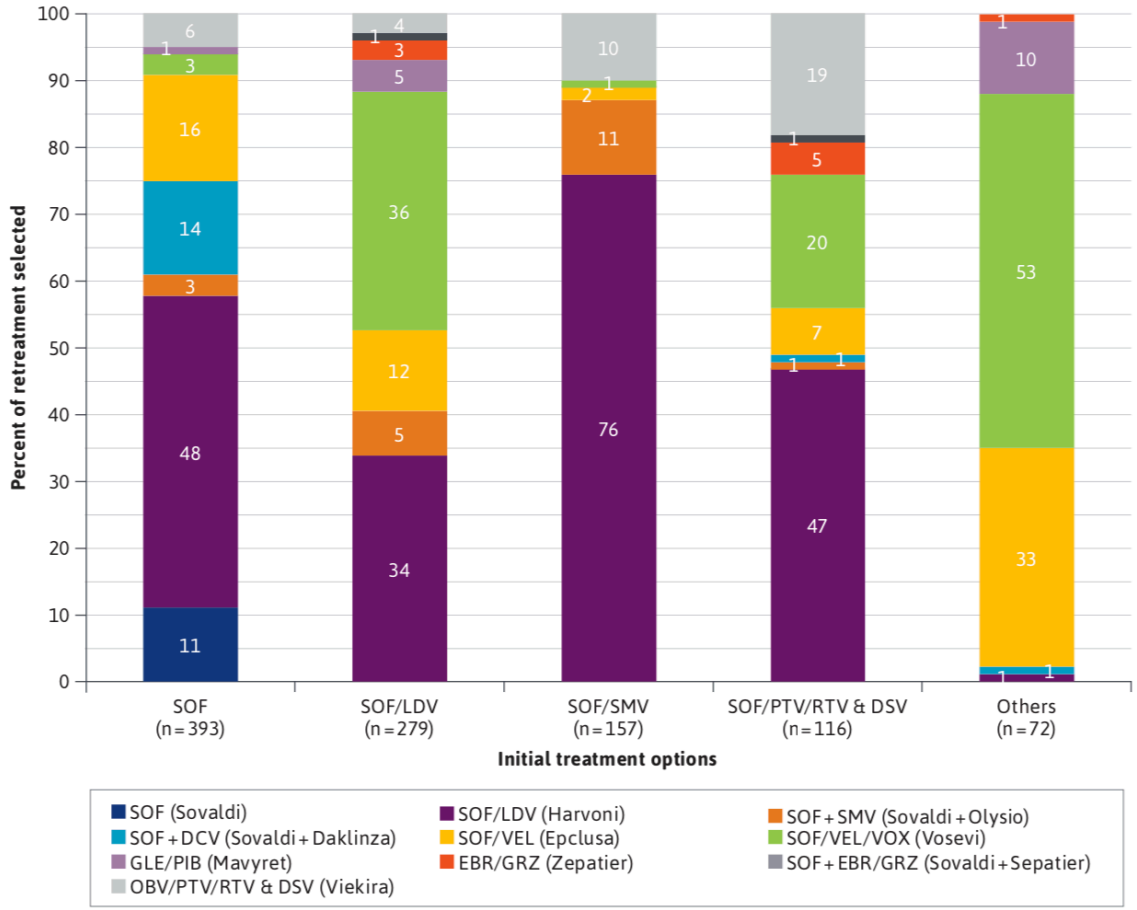
- 44 (**4.3%**) received a **third treatment regimen**
- **2** patients received a **fourth treatment regimen**

more common in **comorbid health conditions** **(high blood pressure, diabetes, alcohol…)**

Patients at risk of retreatment may benefit from careful monitoring to ensure they are **adherent to treatment once started** and have **sustained viral suppression once treatment is complete.**

Improving adherence to decrease reinfection with hepatitis C virus,

FIGURE 2 Retreatment Options Used Among Patients Requiring Secondary Treatment

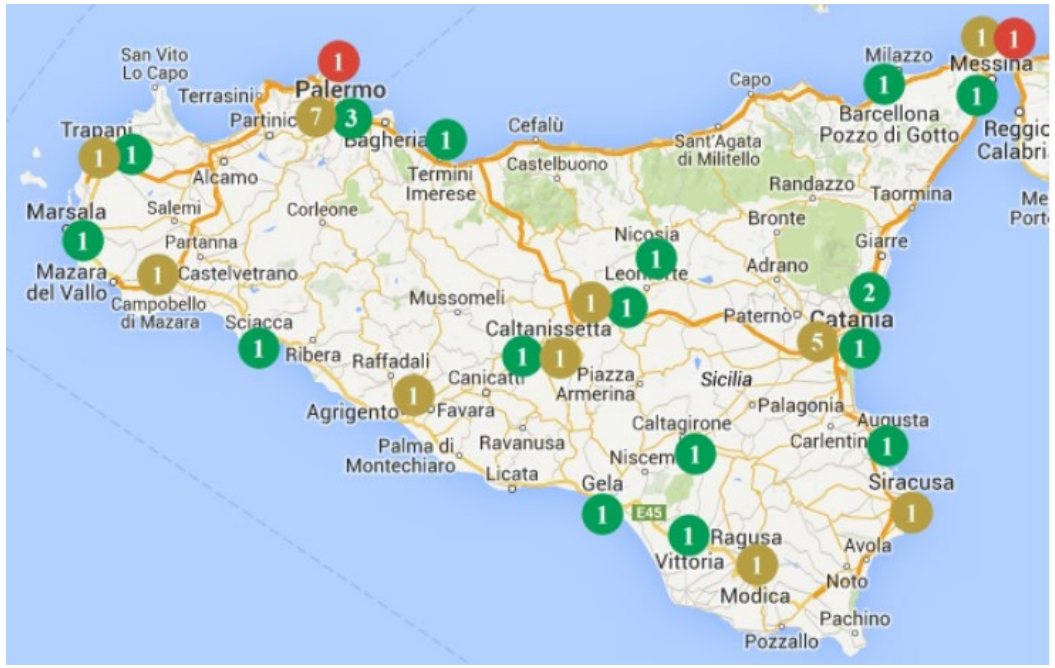


Retreatment 3.2%

In Italia 250.000 pazienti trattati

In Sicilia:

- **22.000 reclutati**
- **18.000 trattati**



Second-generation DAAs for HCV: real-life efficacy in the RESIST-HCV cohort

I. Cacciola et al on behalf RESIST-HCV, meeting AISF 2019, Digestive Liver Disease, October 2019

	SOF/VEL	GLE/PIB	GZR/EBR
Start of treatment	1939	834	1305
Time of treatment • 8 weeks • 12 weeks • 16 weeks	1939	738 94 2	1280 25
• Loss to follow-up or missing SVR12 • Death on therapy or before SVR12 • Adverse Events	50 (2.5) 9 (0.4) 8 (0.4)	20 (2.4) 1 (0.1) 5 (0.6)	24 (1.8) 1(0.07) 7 (0.5)
End of Treatment (**EOT**)	1872 (96.5)	808 (96.9)	1273 (97.5)
• No responder • Relapse	7 (0.3) 11 (0.5)	1 (0.1) 3 (0.3)	6 (0.4) 47 (3.6)
Susteind Virological Response (**SVR**)	1854 (95.6)	804 (96.4)	1220 (93.4)

Efficacia di DAAs di seconda generazione in 4.078 pazienti

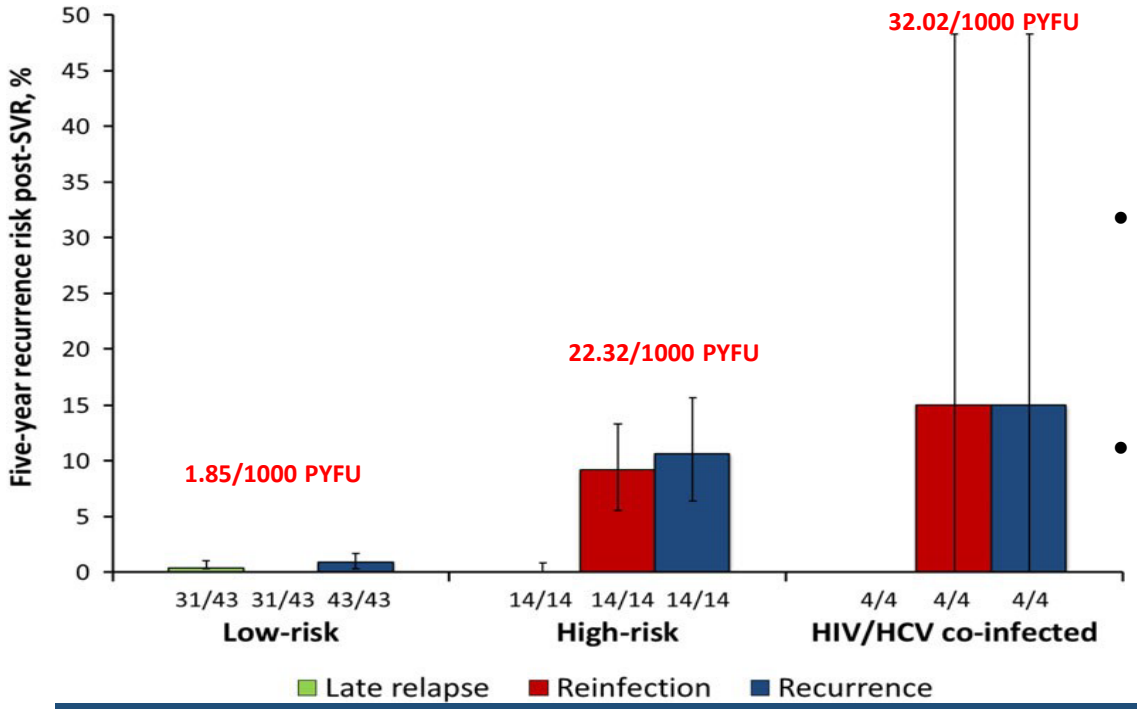
- SVR: da 93 a 96 %
- NON RESPONDER: < 0.5 %
- RELAPSE: da 0.5 a 3.6 %

Risk of Late Relapse or Reinfection With Hepatitis C Virus After Achieving a Sustained Virological Response: A Systematic Review and Meta-analysis

Bryony Simmons et al, Clinical Infectious Diseases March 2016

Clinical Infectious Diseases
MAJOR ARTICLE

- HCV «**recurrence**» was defined as confirmed HCV RNA detectability post-SVR
  - **LATE RELAPSE** detection of HCV RNA of the same virus lineage
  - **REINFECTION** identification of a different virus



Studies were categorized in to 3 groups:

- **Low-risk population**, inclusive of studies of mono-HCV infected patients with no recognized risk factors for reinfection (43 studies, 7969 pts)
- **High-risk population**, inclusive of studies of mono-HCV infected patients with at least 1 identified risk factor for reinfection (14 studies, 771 pts)
- **HIV/HCV coinfection populations**, inclusive of all studies of HIV/HCV coinfected persons, regardless of the presence or absence of other risk factors (4 studies, 309 pts)

THE RISK OF RECURRENCE IS DRIVEN BY REINFECTION IN THOSE WITH HIGH-RISK BEHAVIORS

German GECCO Cohort: HCV Re-infections

- GECCO-Cohort (9 German centres)
  - n=1483
  - 24 re-infections (**1.6 %)**
- Re-infection rate:
  - 11% (19/166) in MSM after median 45 weeks
  - 1% (5/454) in IVDU after median 40 weeks

Characteristics re-infected

	Re-infection n = 24
Median age [years (IQR)]	49 (42–54.5)
Male [n (%)]	24 (100)
Mode of HCV transmission	
• IVDU [n (%)]	5 (21)
• MSM [n (%)]	14 (58)
• MSM + IVDU [n (%)]	5 (21)
HIV co-infection [n (%)]	20 (83)
Median time to re-infection [weeks (IQR)]	41 (25–67)
Previous HCV treatment	
• SOF-PEG-RBV [n (%)]	7 (29)
• SOF/LDV [n (%)]	11 (46)
• PTV/r/OBV+/-DSV+/-RBV	2 (9)
• SOF/RBV	1 (5)
• SOF-DCV	2 (9)
• SIM-SOF	1 (5)

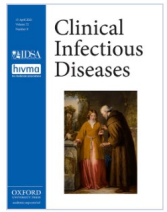
Ingiliz P, *et al.* CROI 2017

Reinfection Following Successful Direct-acting Antiviral Therapy for Hepatitis C Virus Infection Among People Who Inject Drugs

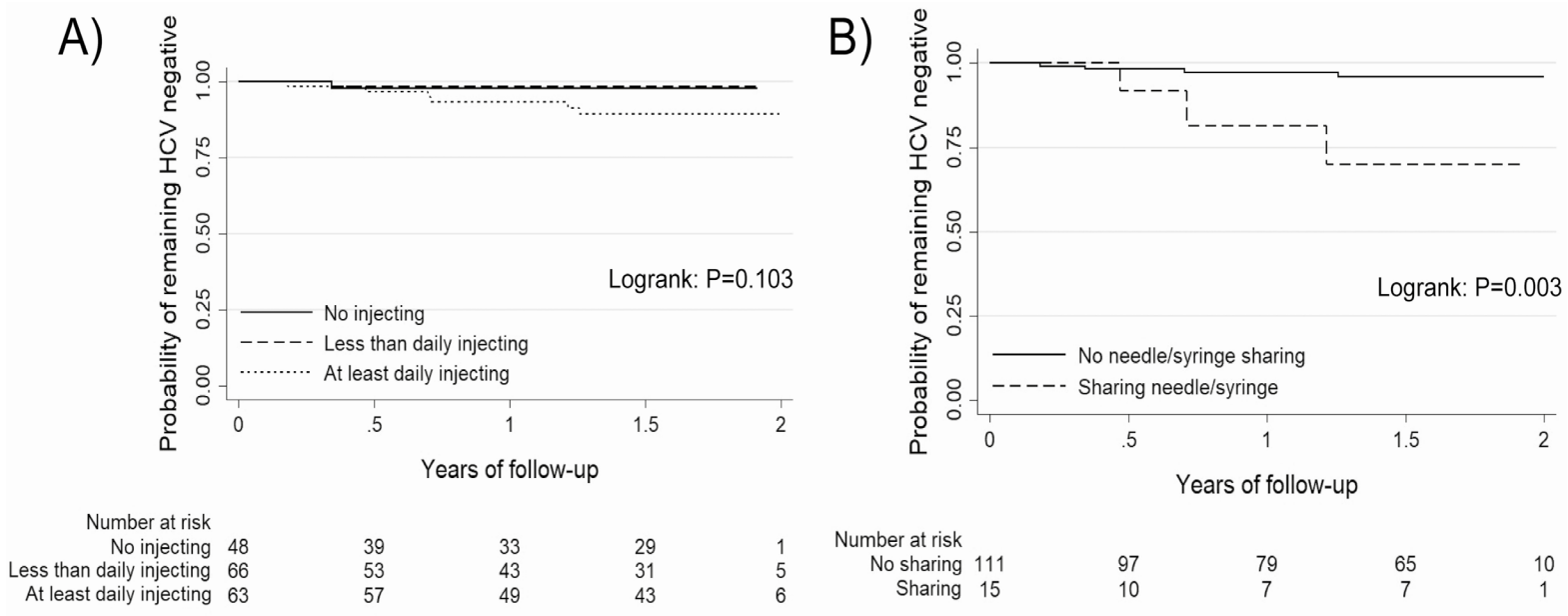
Evan B Cunningham et al Clin Inf Dis April 2021

Clinical Infectious Diseases
MAJOR ARTICLE

Kaplan-Meier graphs of time to HCV reinfection among the study population stratified by A, maximum injecting frequency posttreatment and B, sharing needles/ syringes posttreatment. Abbreviation: HCV, hepatitis C virus.



Volume 72, Issue 8
15 April 2021



correlazione inversa tra la uso condiviso di siringhe e possibilità rimanere HCV RNA negativi dopo trattamento efficace
tasso relativamente modesto di reinfezione in una popolazione ad alto rischio (scambio di siringhe)

Clin Infect Dis, Volume 72, Issue 8, 15 April 2021, Pages 1392–1400, https://doi.org/10.1093/cid/ciaa253

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- Come ritrattare
- Conclusioni

Liver and cardiovascular mortality after hepatitis C virus eradication by DAA: Data from RESIST-HCV cohort

V. Calvaruso et al. Rete Sicilia Selezione Terapia - HCV (RESIST-HCV)
J Viral Hepat. 2021;28:1190–1199.

4207 pts : SVR (4084) versus No SVR (376)

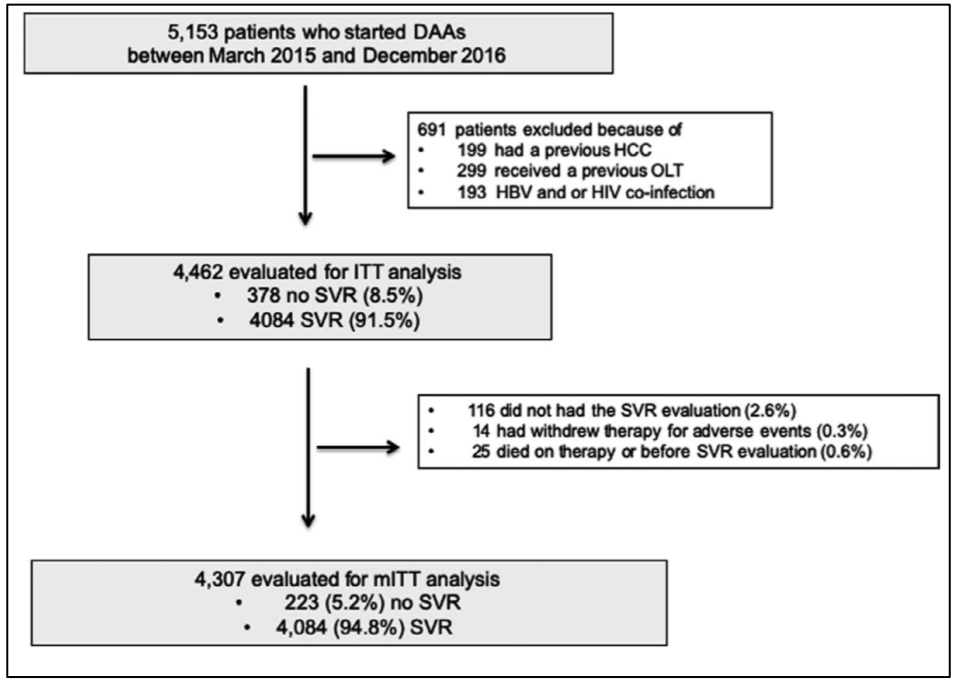

TABLE 3 Liver disease outcomes of 4307 patients included in RESIST-HCV cohort and treated with DAAs: mITT analysis

	Chronic Hepatitis 1064 patients (24.7%)			Child-Pugh A cirrhosis 2883 patients (66.9%)			Child-Pugh B cirrhosis 360 patients (8.4%)		
Disease events	SVR* 1027 pts (96.5%)	No SVR 37 pts (3.5%)	*p*	SVR* 2737 pts (94.9%)	No SVR 146 pts (5.1%)	*p*	SVR* 320 pts (88.9%)	No SVR 40 pts (11.1%)	*p*
Liver decompensation (%)	0	0	-	44 (1.6)	8 (5.5)	<.001	28 (9.0)	5 (12.5)	.44
de novo HCC (%)	3 (0.28)	0	.86	58 (2.1)	12 (8.2)	<.001	22 (6.9)	3 (7.5)	.69
Liver Transplant (%)	0	0	-	0	0	-	4 (1.3)	1 (2.5)	.56
Overall death (%)	5 (0.46)	3 (7.9)	<.001	18 (0.7)	12 (8.2)	<.001	15 (4.7)	6 (15.0)	.005
LR death (%)	0	0		9 (0.43)	6 (4.1)	<.001	9 (2.8)	3 (7.5)	.07
CV death (%)	3 (0.3)	2 (5.4)	<.001	3 (0.1)	3 (2.1)	<.001	5 (1.6)	2 (5.0)	.09

- Patients **HCV cirrhosis** risk per year of 2 to 5% and 3 to 6% per year to develop **hepatocellular carcinoma (HCC) and liver decompensation**, respectively.
- Liver **decompensation** increases the **risk of death to 15–20% per year.**
- Patients with HCV infection, especially those with diabetes, are also at increased **risk of death due to cardiovascular disease**

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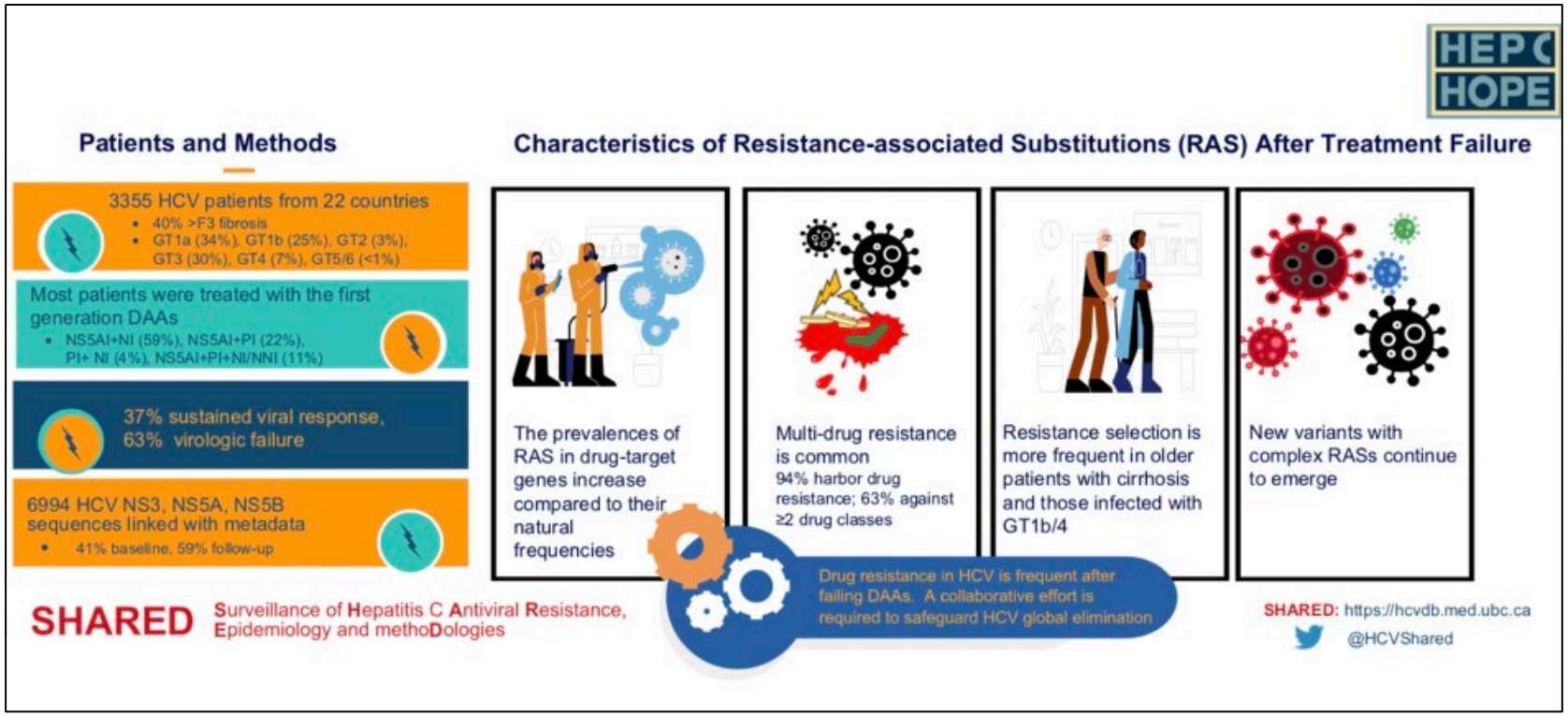
Characteristics of hepatitis C virus resistance in an international cohort after a decade of direct-acting antivirals

Anita Y.M. Howe, Francesca Ceccherini-Silberstein, JHEP Report 2022

JHEP Reports Innovation in Hepatology | EASL

International cohort 3,355 pts from 22 countries following DAA therapy.



Nearly all patients harbored drug-resistant variants after treatment failure, with over 2/3 having resistance against ≥2 drug classes.

Highly resistant variants and selection of **multiple resistant variants.**

Previously unrecognized variants in patients who failed **NS5A inhibitors**

Resistance selection was frequent **in older people with cirrhosis** and those infected with **genotypes 1b and 4** following DAA failure.

DRUG RESISTANCE IN HCV IS FREQUENT AFTER DAA TREATMENT FAILURE.
PREVIOUSLY UNRECOGNIZED SUBSTITUTIONS CONTINUE TO EMERGE AND REMAIN UNCHARACTERIZED

The European Prevalence of Resistance Associated Substitutions among Direct Acting Antiviral Failures

S. Popping, F. Ceccherini Silberstein and HepCare , *Viruses* 2022, *14*, 16.

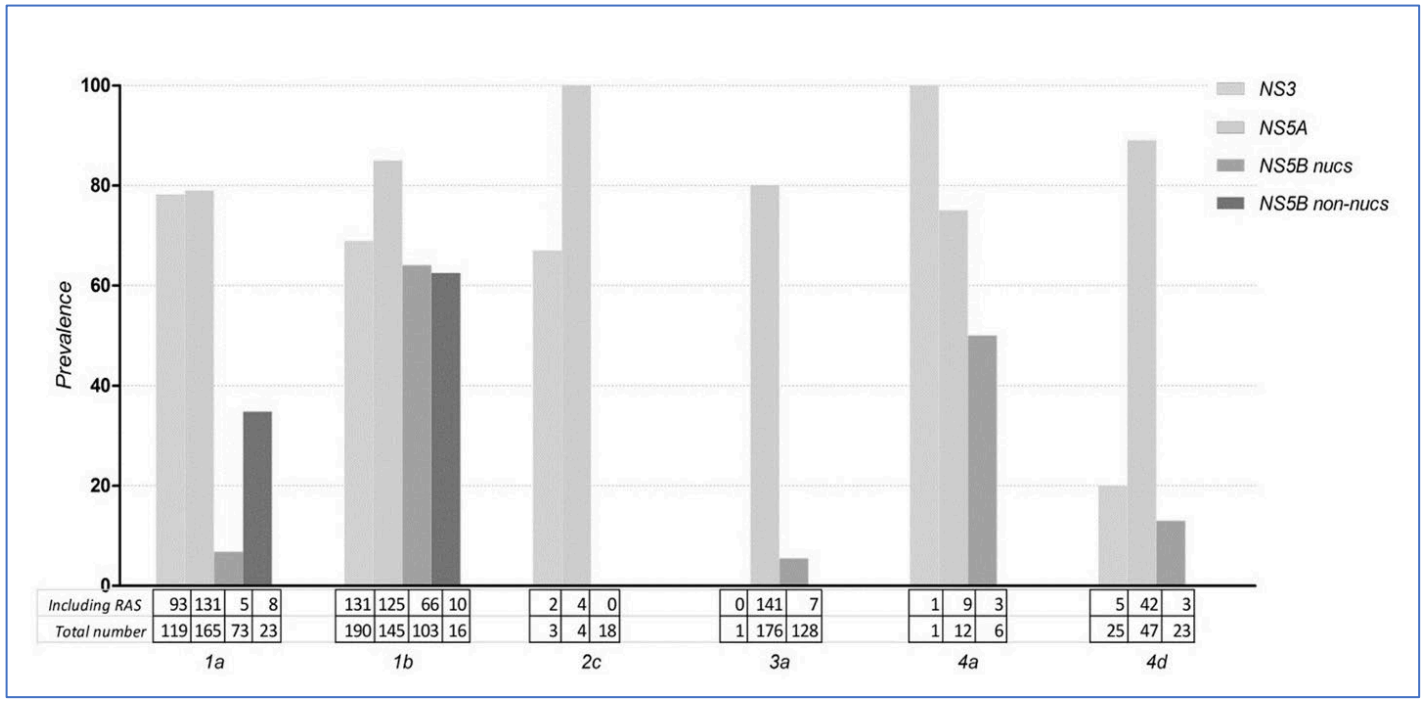


Table 1. Cohort description of clinical available data from patients who failed direct acting antiviral therapy.

Cohort		Failure (N = 938)
Sex (n = 895) (%)	Male	705 (79)
Age in years (mean(IQR)) (n = 460)	Sample taken	53.7 (48.3–59.7)
Type of failure, n (%)	Breakthrough	59 (6)
	Relapses	435 (46)
	Partial-responder	21 (2)
	Non-responder	30 (3)
	Unspecified	393 (42)
Fibrosis stage, (n = 615) (%)	F0	19 (3)
	F1	61 (10)
	F2	79 (13)
	F3	89 (14)
	F4 unspecified	73 (12)
	F4 compensated	283 (45)
	F4 decompensated	11 (2)
Previous therapy, n (%)	No	179 (19)
	Yes, not with DAAs	218 (23)
	Yes, with first generations protease inhibitors	64 (7)
	Unknown	477 (51)
Country of submission (%)	Denmark	14 (1)
	France	2 (0.2)
	Germany	15 (2)
	Italy	225 (24)
	Israel	102 (11)
	the Netherlands	32 (3)
	Romania	20 (2)
	Russia	168 (18)
	Spain	351 (37)
	Turkey	9 (1)

Lower RAS prevalence after failure was in GT 3 a

NS5A failures tend to have the highets number of RAS after falure

NS5B Prevalence was low across all genotypes

Cirrhotic patients F4 59%

(2% decompensated cirrhosis)

METAVIR F3 14%

49% of patients with Known therapy

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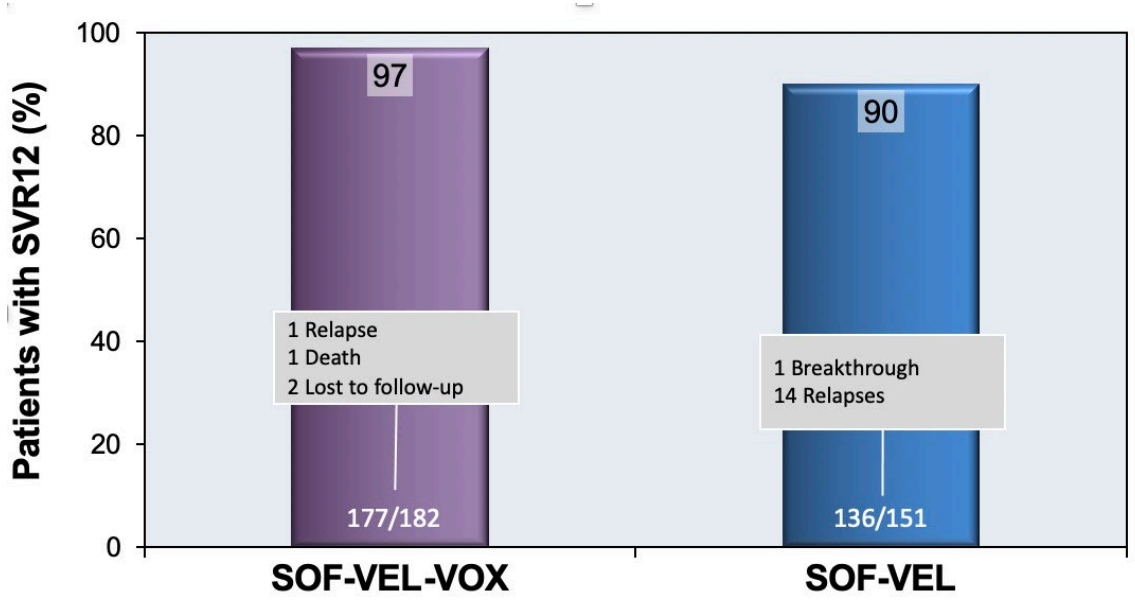
Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1-6

POLARIS-4: Study Features

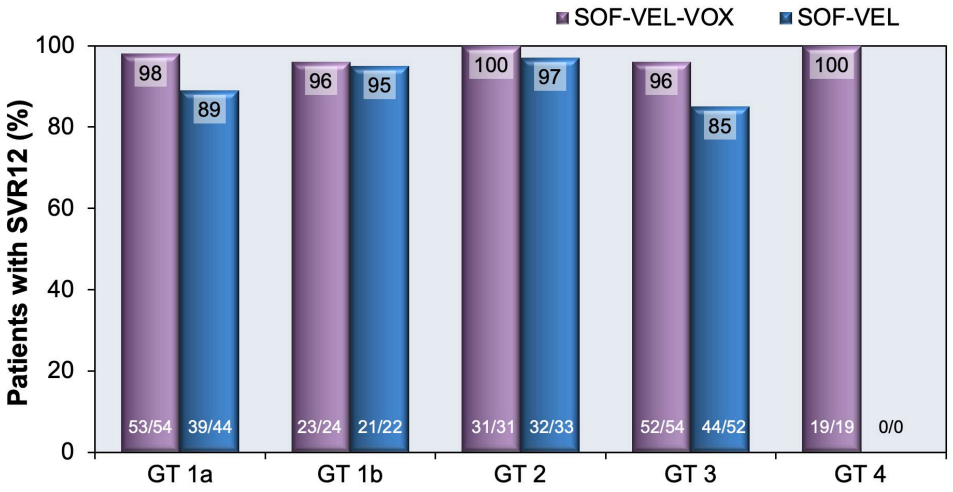
Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

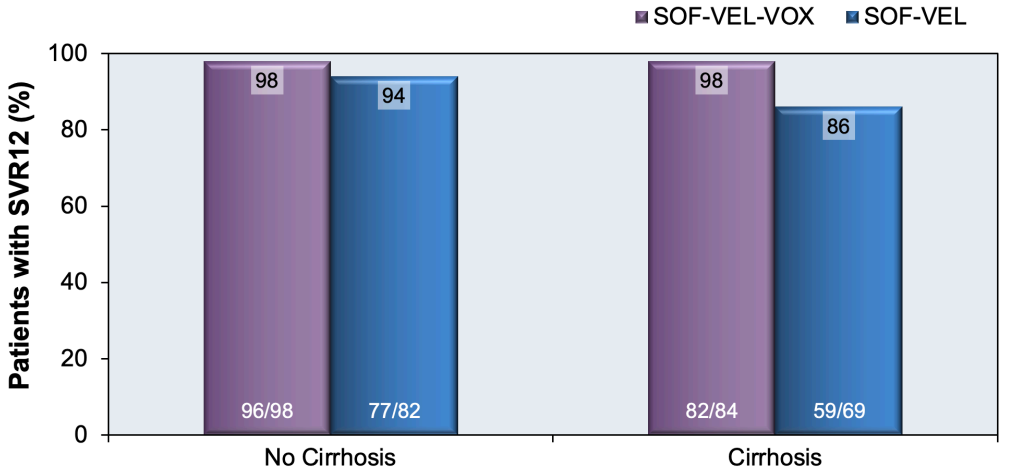
POLARIS-4 Trial

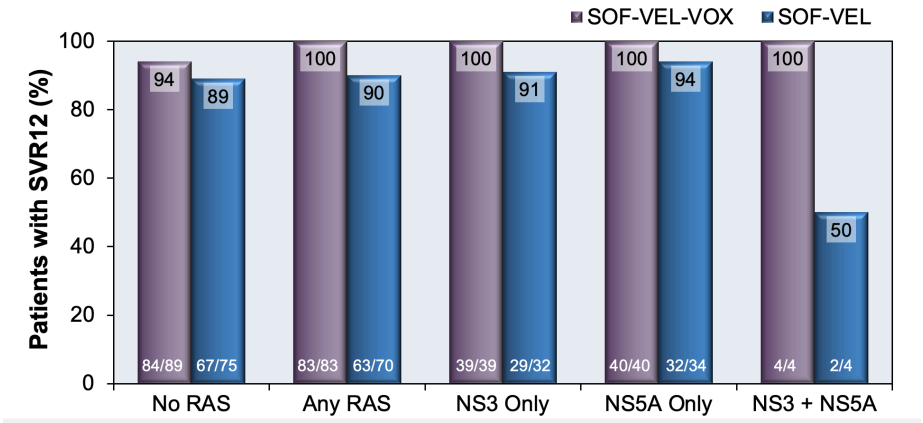
- **Design**: Open-label, randomized active-comparator, phase 3 trial to compare efficacy of a fixed-dose combination of **sofosbuvir-velpatasvir-voxilaprevir versus sofosbuvir-velpatasvir** for 12 weeks in DAA-experienced patients who had not received prior NS5A inhibitor.
- **Setting**: 102 sites in US, Canada, Europe, Australia & New Zealand
- **Entry Criteria**
  - Chronic HCV GT 1-6 (enrolled only **GT 1-4**)
  - HCV RNA ≥10,000 IU/mL at screening
  - DAA experienced (**excluding prior NS5A use**)
  - Patients with **compensated cirrhosis allowed**
- **Primary End-Point**: SVR12



Sofosbuvir-Velpatasvir-Voxilaprevir in DAA-Experienced GT 1-6 POLARIS-4: Results and Conclusions







SOF/VEL/VOX 12 w efficace (94-100%) :

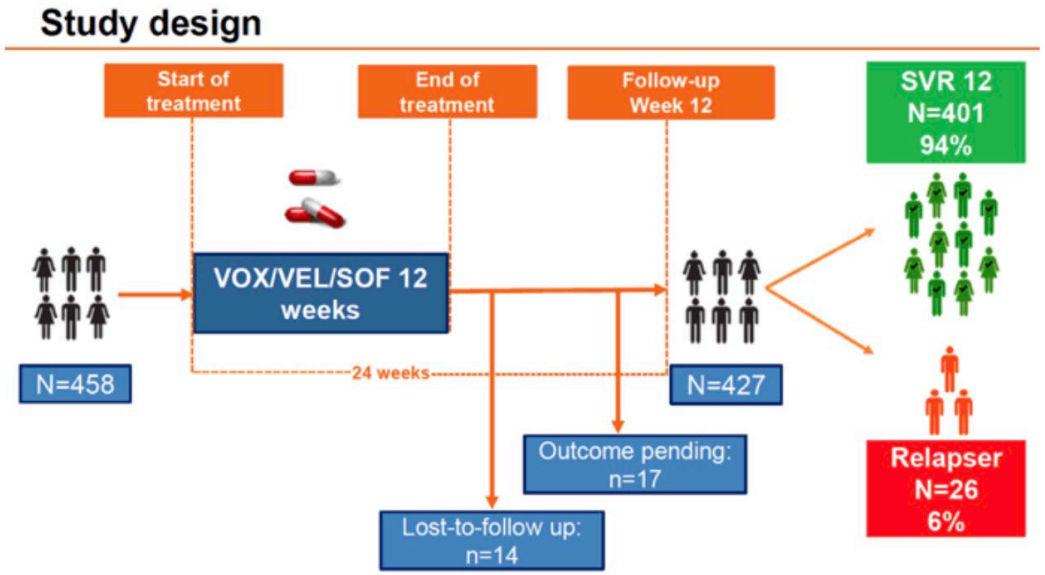
- **in tutti i genotipi**
- **anche nei cirrotici**
- **indipendentemente da documentazione RAS**

Source: Bourlière M, et al. N Engl J Med. 2017;376:2134-46.

Voxilaprevir/Velpatasvir/Sofosbuvir in Patients With HCV With Prior DAA Failure: SVR Rates

Graf. EASL 2022. Abstr OS003

Retrospective, longitudinal multicenter real-world study of adults with HCV in the European Resistance Database. 458 pts



Excellent overall effectiveness of VOX/VEL/SOF in patients with prior DAA failure treated **in a real-life setting (94 %)**

Identification of liver **cirrhosis** and **previous HCC** history as **main predictors of VOX/VEL/SOF failure**

RASs did not impact SVR

Excellent SVR rates in rare genotypes and chimera

SVR12 rates equivalent with vs without RBV (ribavirin was added in 4% of treatment schedules)

Glecaprevir/Pibrentasvir + Sofosbuvir as Retreatment After DAA Failure in Patients With HCV:

Gane. EASL 2022. Abstr OS004.

- Investigator initiated, open-label, single-arm trial in New Zealand
  - Ribavirin omitted due to poor tolerability

In patients with HCV, confirmed NS5A resistance, and previous DAA failure, GLE/PIB + SOF 16 wk safe and effective (ITT 93 % per protocol 98%)

ABSENCE OF RIBAVIRIN DID NOT AFFECT EFFICACY

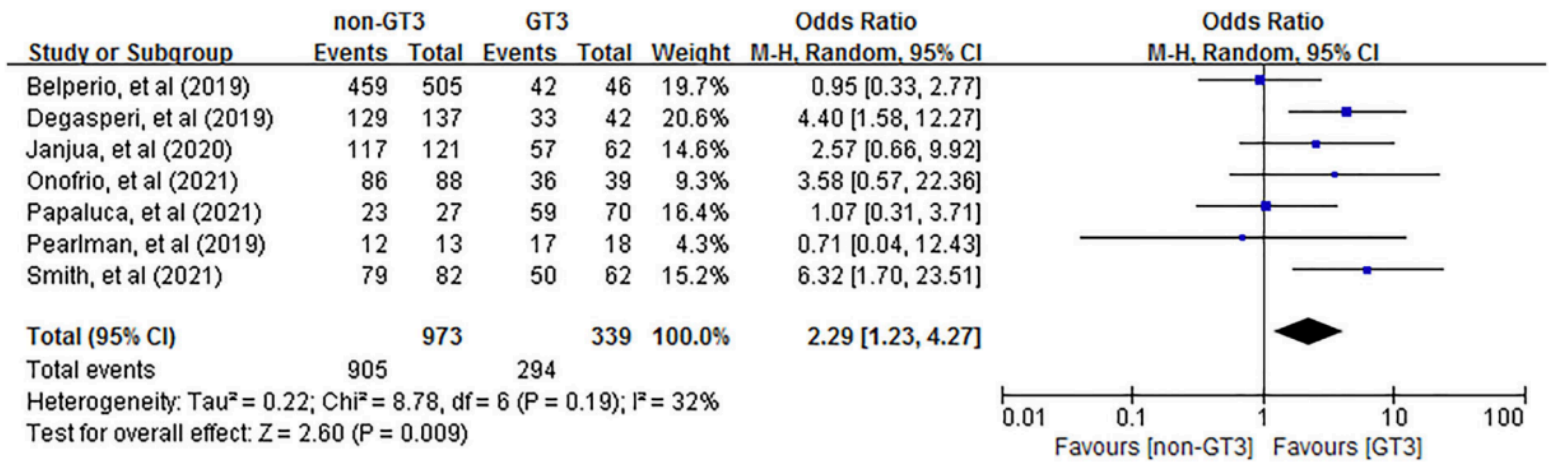
Slide credit: clinicaloptions.com

Effectiveness and Safety of Sofosbuvir/Velpatasvir/ Voxilaprevir as a Hepatitis C Virus Infection Salvage Therapy in the Real World: A Systematic Review and Meta-analysis

Jing Xie et al Infect Dis Ther (2022) 11:1661–1682

1796 HCV-infected patients were examined in 15 studies

Fig. 5 The overall SVR12 rate of different genotypes in ITT and PP population



Study or Subgroup	non-GT3 Events	non-GT3 Total	GT3 Events	GT3 Total	Weight	Odds Ratio M-H, Random, 95% CI
Belperio, et al (2019)	459	505	42	46	19.7%	0.95 [0.33, 2.77]
Degasperi, et al (2019)	129	137	33	42	20.6%	4.40 [1.58, 12.27]
Janjua, et al (2020)	117	121	57	62	14.6%	2.57 [0.66, 9.92]
Onofrio, et al (2021)	86	88	36	39	9.3%	3.58 [0.57, 22.36]
Papaluca, et al (2021)	23	27	59	70	16.4%	1.07 [0.31, 3.71]
Pearlman, et al (2019)	12	13	17	18	4.3%	0.71 [0.04, 12.43]
Smith, et al (2021)	79	82	50	62	15.2%	6.32 [1.70, 23.51]
Total (95% CI)		**973**		**339**	**100.0%**	**2.29 [1.23, 4.27]**
Total events	905		294			

Heterogeneity: Tau² = 0.22; Chi² = 8.78, df = 6 (P = 0.19); I² = 32%
Test for overall effect: Z = 2.60 (P = 0.009)

the overall SVR12 rates with SOF/VEL/VOX were 93% in the ITT population

SALVAGE THERAPY SOF/VEL/VOX in REAL WORLD

- I PAZIENTI DEGLI STUDI SONO DIVERSI E IN GENERE MENO ADERENTI
- POCHI DATI SU EFFICACY e SAFETY NELLA PRATICA CLINICA

IN QUESTA REVIEW:

- SVR 93 %

- **DATI DI EFFICACY E SAFETY SOVRAPPONIBILI A QUELLI DEGLI STUDI**

- **RISCHIO DI FAILURE DEL RITRATTAMENTO**
  - **GT3**
  - **Cirrosi**
  - **Sofosbuvir/ Velpatasvir experienced**

Retreatment of DAA failures

- Retreatment strategy depends on initial regimen

Recommendations	Grade of evidence	Grade of recommendation
After failure of PEG-IFNα + RBV, SOF + PEG-IFNα/RBV or SOF + RBV • Retreat according to recommendations for TE patients, by HCV genotype	A	1
HCV resistance testing after failure of any DAA-based regimen (excluding regimens with SOF as the only DAA) is a useful guide to retreatment	B	2
After failure of DAA (PI and/or NS5A inhibitor)-containing regimen		
• **First-line retreatment** – **SOF/VEL/VOX for 12 weeks (without cirrhosis/with compensated cirrhosis)** – **SOF/VEL + RBV* for 24 weeks (decompensated cirrhosis)**	A B	1 2
• **Patients with predictors of poor response**, **SOF + GLE/PIB for 12 weeks:** – Advanced liver disease – Multiple courses of DAA-based treatment – Complex NS5A RAS profile	B	2
• **Very difficult-to-cure patients**:† SOF/VEL/VOX + RBV or SOF + GLE/PIB + RBV (16 or 24 w)	C	2

*Daily weight-based RBV (1,000 mg or 1,200 mg in patients <75 kg or ≥75 kg, respectively); start RBV at a dose of 600 mg daily and adjust dose depending on tolerance;
†Patients with NS5A RASs who failed twice to achieve SVR after a combination regimen including a PI and/or an NS5A inhibitor
EASL CPG HCV. J Hepatol 2018;69:461–511.

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IDSA
Infectious Diseases Society of America

Last update:
October 24, 2022

Experienced a regimi con sofosbuvir

- **SOF/ VEL/ VOX per 12 settimane**
- **SOF/ VEL/ VOX plus RIBA in Gen 3 cirrotici non scompensati**

Regime alternativo:

- **GLE/ PIB per 16 settimane**
- **non raccomandato in Genotipo 3**

Recommended and alternative regimens listed by evidence level and alphabetically for:

Sofosbuvir-Based Treatment Failures, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)[b]	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) except for NS3/4 protease inhibitor inclusive combination DAA regimen failures[c] • **Not** recommended for genotype 3 infection with sofosbuvir/NS5A inhibitor experience.	16 weeks	I, A

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Genotype 3: Add weight-based ribavirin if cirrhosis is present and there are no contraindications.
[c] This regimen is not recommended for patients with prior exposure to an NS5A inhibitor plus NS3/4 PI regimens (e.g., elbasvir/grazoprevir).

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Last update:
October 24, 2022

Failure a multipli regimi con DAA

- **GLE/PIB plus SOF plus RIBA per 16 w ***
- **SOF/VEL/VOX plus RIBA per 24 w ****

Multiple DAA Treatment Failures (All Genotypes), Including Sofosbuvir/Velpatasvir/Voxilaprevir or Sofosbuvir Plus Glecaprevir/Pibrentasvir

Recommended regimens listed by evidence level and alphabetically for:

Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failures, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) plus daily sofosbuvir (400 mg) and weight-based ribavirin	16 weeks[b]	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) plus weight-based ribavirin	24 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Extension of treatment to 24 weeks should be considered in extremely difficult cases (e.g., genotype 3 with cirrhosis) or failure following sofosbuvir plus glecaprevir/pibrentasvir.

* Wyles D, Weiland O, Yao B, et al. **Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C virus infection**. *J Hepatol*. 2019;

** Bourliere M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, et al. **Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection**. N Engl J Med. 2017

** Gane EJ, Shiffman ML, Etzkorn K, et al, et al. **Sofosbuvir-velpatasvir with ribavirin for 24 weeks in hepatitis C virus patients previously treated with a direct-acting antiviral regimen**. Hepatology. 2017

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

IDSA
Infectious Diseases Society of America

Last update:
October 24, 2022

Decompensated Cirrhosis Genotype 1-6

Cirrosi scompensata con Genotipo 1-6

- **SOF/VEL plus RIBA 24 w**

- LED/SOF plus RIBA 24 w escluso Gen 3

Regimi con inibitori delle proteasi (glecaprevir, grazoprevir, paritaprevir, simeprevir, voxilaprevir) non raccomandati nei pazienti con cirrosi scompensata

Recommended regimens listed by pangenotypic, evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] and Genotype 1-6 Infection in Whom Prior Sofosbuvir- or NS5A Inhibitor-Based Treatment Failed

RECOMMENDED	DURATION	RATING
Genotype 1-6: Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin[b]	24 weeks	II, C[c]
Prior sofosbuvir-based treatment failure, genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg; increase as tolerated)	24 weeks	II, C[d]

[a] Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
[b] Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis.
[c] Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis.
[d] Only available data for genotype 6 are in patients with compensated cirrhosis.

IN SINTESI IN ITALIA

Epatite Cronica o Cirrosi Epatica Child A		
SOF/VEL/VOX 12 settimane	**Ottimale**	
Questo schema rappresenta l'opzione terapeutica di scelta in termini di efficacia ed effetti collaterali e può essere utilizzato in tutti i genotipi virali. Questo schema non è utilizzabile in pazienti con cirrosi Child-Pugh B o C.		

Cirrosi Epatica Child B		
SOF+ VEL + RBV 24 settimane	**Ottimale**	
Questo schema rappresenta l'opzione terapeutica di scelta in termini di efficacia ed effetti collaterali e può essere utilizzato in tutti i genotipi virali. La ribavirina va utilizzata se tollerata.		

Linee di indirizzo AISF – HCV

Aggiornamento del 14 Dicembre 2020

CONCLUSIONI

PERCHÉ SI FALLISCE

- SCARSA ADERENZA
- MALATTIA AVANZATA
- CO-MORBIDITÀ
- REGIME SUB-OTTIMALE (PER GENOTIPO O PER SEVERITÀ DI MALATTIA)

PLANNING DEL RITRATTAMENTO

- REINFEZIONE :
    - genotipo virale con test commerciali II generazione
- FAILURE
    - Test resistenze in tutti i geni (NS3, NS5A, NS5 indipendentemente dal regime fallito) ???
    - Attenta rivalutazione dei regimi precedenti!!!

Conclusioni

Dimensioni del problema: **late-relapse e non responder circa 3-3.5 %**
reinfezione meno del 2 % nei soggetti ad alto rischio

Perché trattare nuovamente: **scompenso, HCC, mortalità per cause epatiche ed extraepatiche**

Resistenze e failure: **poche evidenze sull'utilità nel planning del nuovo regime e scarsa disponibilità**

Come ritrattare: **SOF/VEL/VOX con poche eccezioni ; il valore aggiunto dell'uso di ribavirina è incerto.**