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# Il paziente fallito: strategie terapeutiche e discussione di casistica clinica

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- Dimensioni del fenomeno
- Determinanti del fallimento terapeutico nell'epoca dei DAA pangenotipici
- Trattamento del paziente fallito:
  - SOF/VEL/VOX: Risultati dei trials clinici
  - SOF/VEL/VOX: Dati real life
  - SOF+ G/P
  - Terza linea di terapia
- Linee guida
- Determinazione RAS nel pz fallito pros e cons

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JOURNAL OF HEPATOLOGY

# EASL recommendations on treatment of hepatitis C: Final update of the series☆

European Association for the Study of the Liver*

**Table 6A. Recommendations for simplified, genotyping/subtyping-free treatment of HCV-monoinfected or HCV-HIV coinfected adult (≥18 years) and adolescent (12–17 years) patients with chronic hepatitis C without cirrhosis or with compensated (Child-Pugh A) cirrhosis, including treatment-naïve patients (defined as patients who have never been treated for their HCV infection) and treatment-experienced patients (defined as patients who were previously treated with pegylated IFN-α and ribavirin; pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirin).**

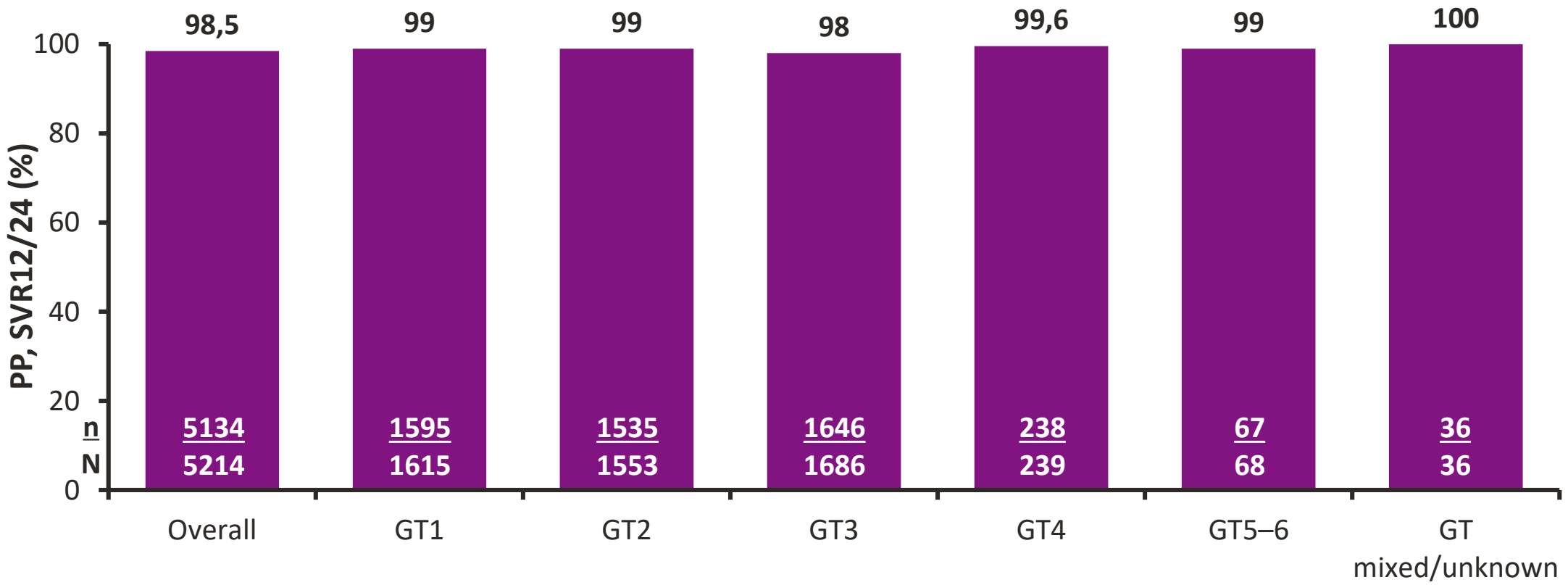
| Type of treatment | Genotype | Cirrhosis status | Prior treatment experience | Sofosbuvir/ velpatasvir | Glecaprevir/ pibrentasvir | Sofosbuvir/ velpatasvir/ voxilaprevir | Grazoprevir/ elbasvir |
|---|---|---|---|---|---|---|---|
| Simplified treatment, no genotype/subtype determination[a] | All genotypes | No cirrhosis | Treatment-naïve | 12 weeks | 8 weeks | No | No |
| | | | Treatment-experienced | | | | |
| | | Compensated (Child-Pugh A) cirrhosis) | Treatment-naïve | | | | |
| | | | Treatment-experienced | | 12 weeks | | |

IFN, interferon.

[a]Whenever HCV genotype and subtype determination is not available, not affordable and/or limits access to care.

# Real-World Effectiveness of 12-Week SOF/VEL in HCV GT1–6-Infected Patients

Integrated efficacy analysis of SOF/VEL for 12 weeks in HCV GT1–6-infected treatment-naive or -experienced patients with or without cirrhosis (N = 5541)[1]




PP, per protocol.

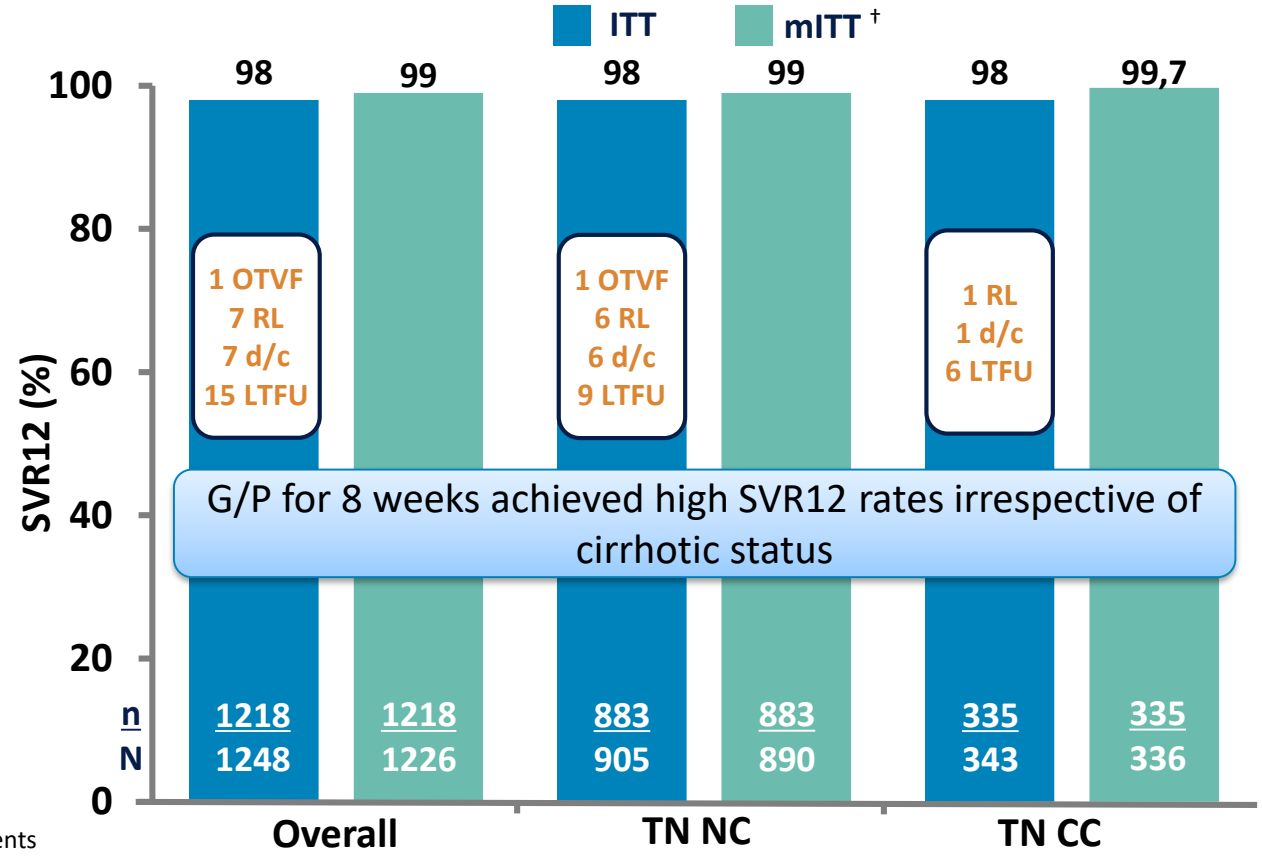
1.Mangia A, *et al.* Global real world evidence of sofosbuvir/velpatasvir as a simple, effective regimen for the treatment of chronic hepatitis C: Integrated analysis of 12 clinical practice cohorts. EASL 2019; oral presentation GS-03.

# G/P for 8 Weeks Achieved High SVR12 Rates in HCV GT1–6-Infected Treatment-Naive Patients

*Post hoc* analysis of data pooled from eight phase 2 or 3 clinical trials* to assess the safety and efficacy of G/P for 8 weeks in HCV GT1–6-infected treatment-naive patients without cirrhosis or with compensated cirrhosis (N = 1248)

**Baseline characteristics of the overall patient population (N = 1248)**

| Characteristic | n (%) |
|---|---|
| Male | 709 (57) |
| HCV GT | |
| GT1 | 583 (47) |
| GT2 | 228 (18) |
| GT3 | 280 (22) |
| GT4 | 66 (5) |
| GT5 | 20 (2) |
| GT6 | 71 (6) |




* SURVEYOR-1 and -2, ENDURANCE-1, -3, and -5,6, EXPEDITION-2, -5 and -8; † mITT population excluded patients who experienced non-virologic failure and those LTFU. CC, compensated cirrhosis; d/c, discontinuation; LTFU, lost to follow-up; mITT, modified intent-to-treat; NC, non-cirrhotic; OTVF, on-treatment virologic failure; RL, relapse; TN, treatment naive.


Zuckerman E, *et al. Clin Gastroenterol Hepatol* 2020 (ePub ahead of print). doi: 10.1016/j.cgh.2020.06.044.

AGENZIA ITALIANA DEL FARMACO

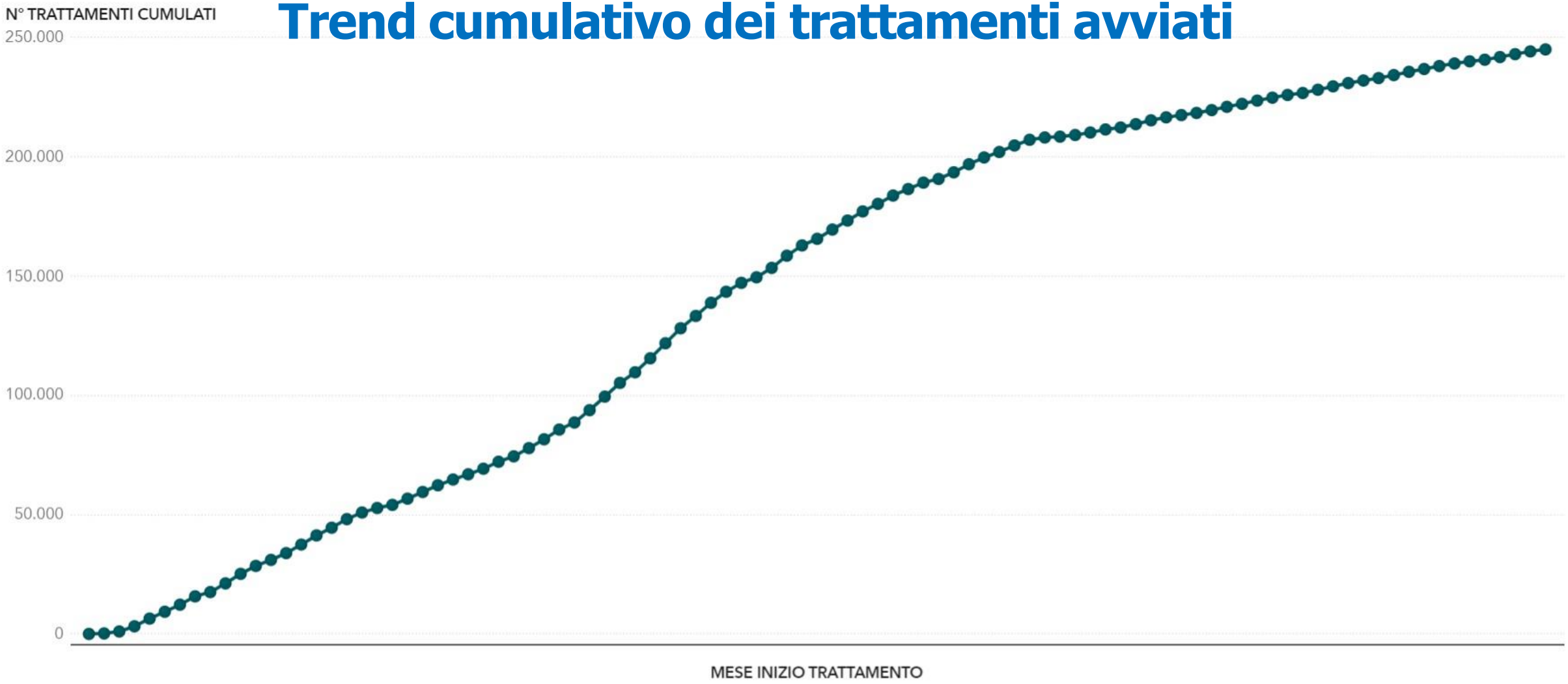
## Aggiornamento dati

# Registri AIFA DAAs - Epatite C cronica

2 Gennaio 2023

Ufficio Registri di Monitoraggio AIFA

# Trend cumulativo dei trattamenti avviati




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

**4902 - 9805 senza SVR**

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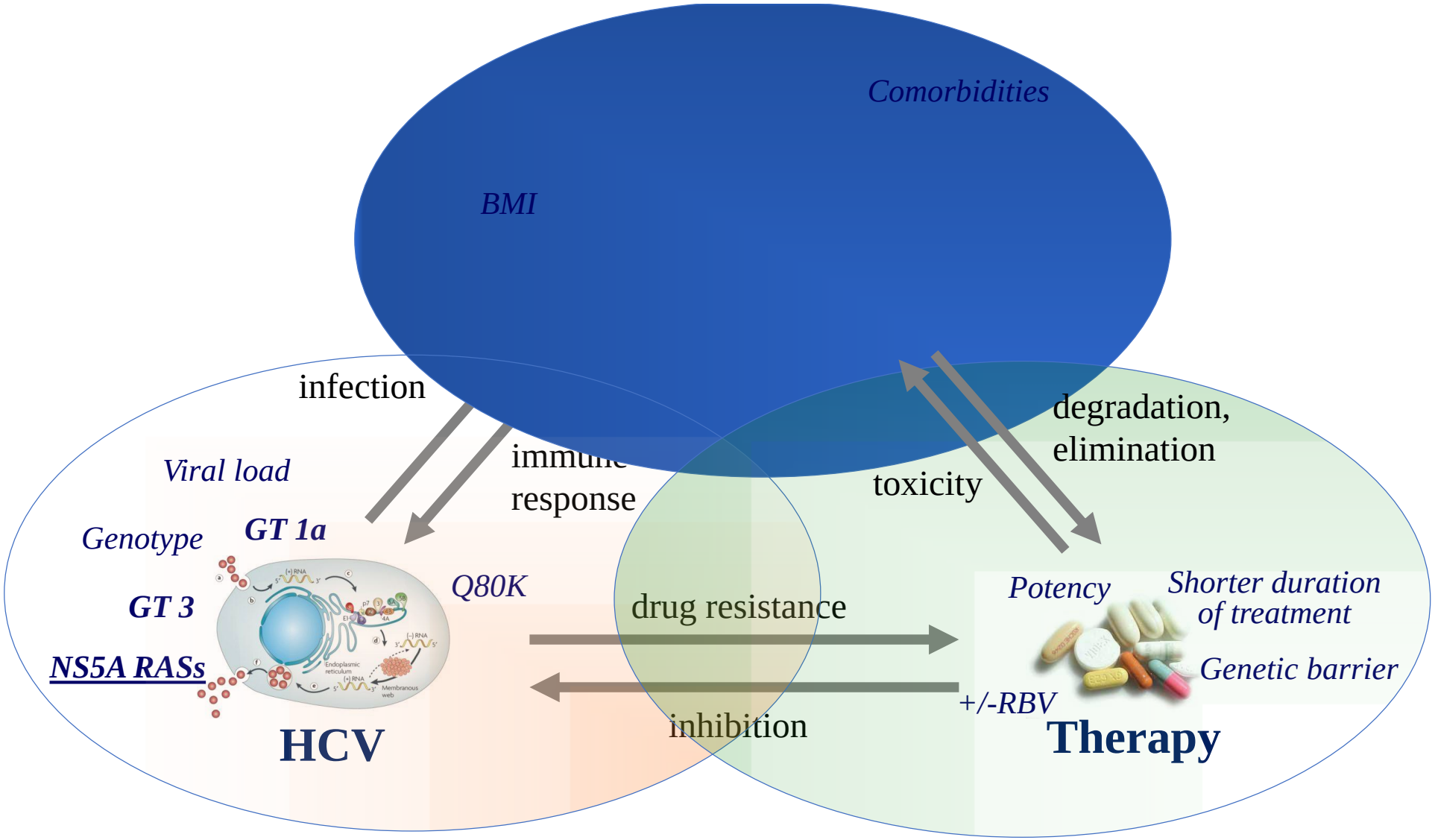
# Many factors contribute to viral response to DAA-treatment



**In a recent published French paper analyzing a total of 537 virological failures to DAA, 121 (22.5%) were infected with GT4 and 27 of them (22.3%) with GT4r; subtype-4r was thus over-represented as compared to its prevalence in the French general population, and all of individuals were of African origin**

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[1,2], Rodriguez C[1,2], Hézode C[2,3], Soulier A[1,2], Ruiz I[2,3], Poiteau L[1,2], Chevaliez S[1,2], Pawlotsky JM[1,2].

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.



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

# Suboptimal SVR rates in African patients with atypical genotype 1 subtypes: Implications for global elimination of hepatitis C

**Background & Aims:** HCV subtypes which are unusual in Europe are more prevalent in the African region, but little is known of their response to direct-acting antivirals (DAAs). These include non-1a/1b/ non-subtypeable genotype 1 (G1) or non-4a/4d (G4). In this report we aimed to describe the genotype distribution and treatment outcome in a south London cohortof African patients.

**Methods:** We identified all patients born in Africa who attendedour clinic from 2010-2018. Information on HCV genotype, treatment regimen and outcome were obtained. Non-subtypeable samples were analysed using Glasgow NimbleGen nextgeneration sequencing (NGS). Phylogenetic analysis was carried out by generating an uncorrected nucleotide p-distance tree from the complete coding regions of our sequences.

**Results:** Of 91 African patients, 47 (52%) were infected with an unusual subtype. Fourteen novel, as yet undesignated subtypes (G1*), were identified by NGS. Three individuals were infected with the same subtype, now designated as subtype 1p. Baseline sequences were available for 22 patients; 18/22 (82%) had baseline NS5A resistance-associated substitutions (RASs). Sustained virological response (SVR) was achieved in 56/63 (89%) overall, yet only in 21/28 (75%) of those with unusual G1 subtypes, with failure in 3/16 G1*, 1/2 G1p and 3/3 in G1l. Six treatment failures occurred with sofosbuvir/ledipasvir compared to 1 failure on a PI-based regimen. The SVR rate for all other genotypes and subtypes was 35/35 (100%).

**Conclusions:** Most individuals in an unselected cohort of African patients were infected with an unusual genotype, including novel subtype 1p. The SVR rate of those with unusual G1 subtypes was 75%, raising concern about expansion of DAAs across Africa. Depending on the regimen used, higher failure rates in African cohorts could jeopardise HCV elimination.

*Childs K et al., J Hepatol 2019*

SHARED

Surveillance of Hepatitis-C Antiviral Resistance, Epidemiology and methoDologies

*An international collaboration of viral sequences, treatment histories, and health outcomes related to the hepatitis C virus*

# The global prevalence of resistance-associated substitutions (RAS) in "unusual" HCV subtypes

HEP C HOPE

S. Popping*, S. Fourati*, AYM Howe , A. de Salazar, VC Di Maio, ESE Tay, C. Rodrigo, E. Cunningham, M. Kjellin, J. Sfalcin, P. Gomes, M. Poljak, M. Lunar, M. Sayan, O. Mor, D. Salmon, R. Usubillaga, C. Seguin-Devaux, A. Soulier , A. Lloyd , J. Grebely, J. Lennerstrand, R. Kaiser, P. Zhigalkina, V. Chulanov, RJ de Knegt, M. Douglas, F. Ceccherini-Silberstein, R. Harrigan, F. Garcia ,C. Boucher, JM Pawlotsky

*On behalf of the contributing members of the SHARED database*

- "Unusual" subtypes
  - GT1 non 1a/b,
  - GT2 non 2a/b,
  - GT3 non 3a
  - GT4 non 4a/d
  - GT5, GT6, GT-7 and GT-8

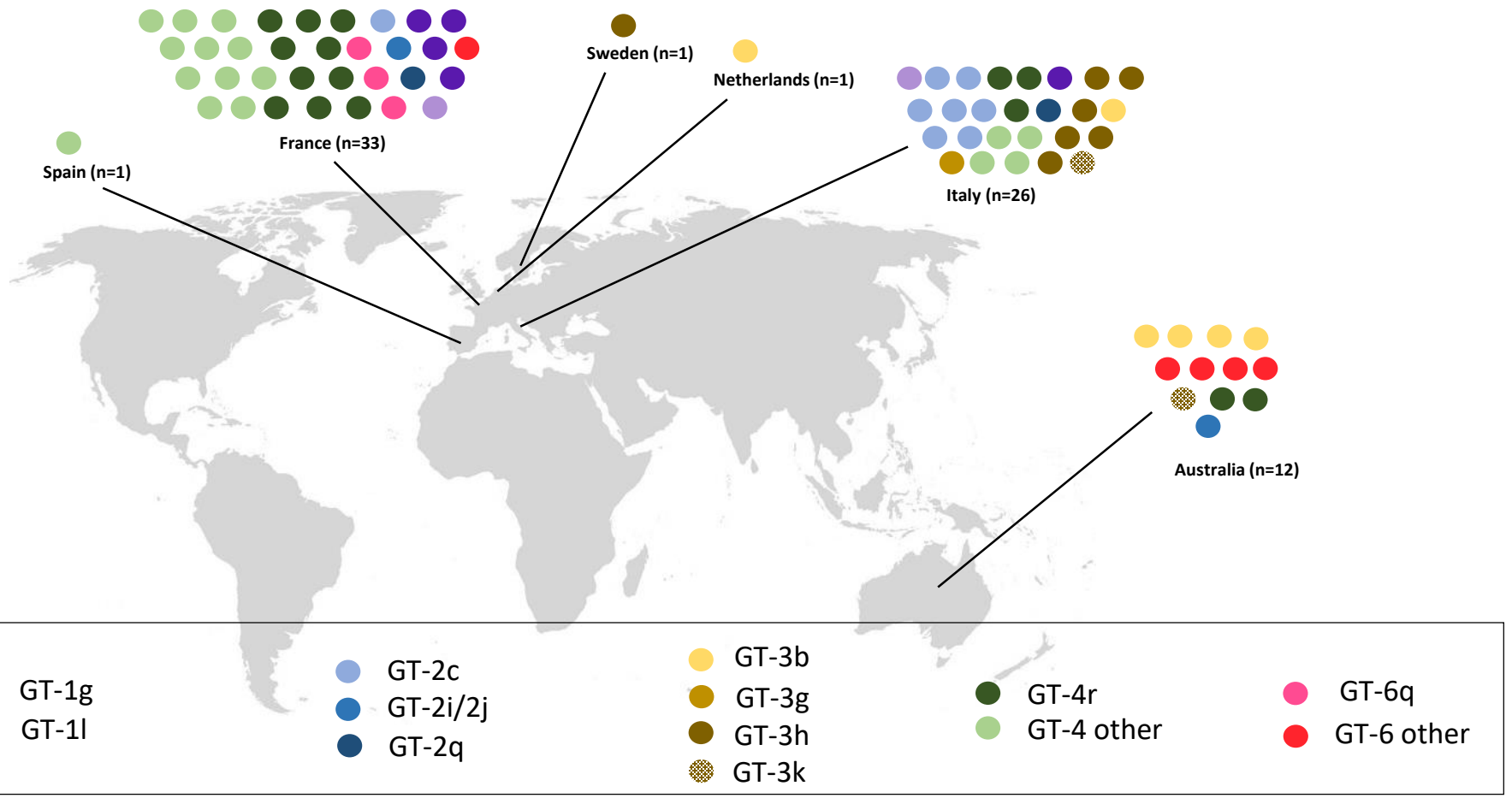
- "Unusual" subtypes
  - Mostly originating from Africa and Asia
  - Multiple polymorphisms in NS5A
  - Lower SVR rates than "usual" subtypes

*Fourati S, et al AASLD 2019*

# **From 1176** patients who failed NS5A-inhibitor based therapy

- 74 "unusual" subtypes from GT-1 to GT-6

**Countries where the diagnosis of "unusual" subtype has been performed**




*SHARED database*

*Fourati S, et al AASLD 2019*

# Low Risk of Failing Direct-Acting Antivirals in People With Human Immunodeficiency Virus/Hepatitis C Virus From Sub-Saharan Africa or Southeastern Asia: A European Cross-Sectional Study

**Table 1. Demographic and Clinical Description of Individuals With Human Immunodeficiency Virus/Hepatitis C Virus From Sub-Saharan Africa or Southeastern Asia Treated With Interferon-Free Direct-Acting Antivirals and With Available Data on Sustained Virological Response at Least 12 Weeks After the End of Treatment**

| Characteristic | (N = 142) |
|---|---|
| Age, y, mean (SD) | 47 (10) |
| Female sex | 44 (31) |
| Route of HIV acquisition | |
| Men who have sex with men | 51 (36) |
| Injection drug use | 25 (18) |
| Heterosexual contact | 52 (37) |
| Other | 6 (4) |
| Unknown | 8 (6) |
| Advanced fibrosis or cirrhosis | |
| No | 94 (66) |
| Yes | 28 (20) |
| Missing | 20 (14) |
| Region of origin | |
| Eastern Africa | 19 (13) |
| Western Africa | 11 (8) |
| Southern Africa | 7 (5) |
| Middle Africa | 27 (19) |
| Eastern Asia | 7 (5) |
| Southeastern Asia | 53 (37) |
| Southern Asia | 18 (13) |
| Undetectable HIV RNA (<50 copies/mL) | |
| No | 6 (4) |
| Yes | 134 (94) |
| Missing | 2 (1) |
| $CD4^+$ count, cells/μL, mean (SD) | 633 (286) |
| DAA regimen | |
| Sofosbuvir/ledipasvir | 64 (45) |
| Sofosbuvir/daclatasvir | 28 (20) |
| Sofosbuvir/velpatasvir | 13 (9) |
| Elbasvir/grazoprevir | 13 (9) |
| Glecaprevir/pibrentasvir | 10 (7) |
| Sofosbuvir/simeprevir | 9 (6) |
| Sofosbuvir/ribavirin | 3 (2) |
| Dasabuvir/ombitasvir/paritaprevir/ritonavir | 2 (1) |

Data are presented as No. (%) unless otherwise indicated. All characteristics are reported for the time at which the first interferon-free DAA treatment regimen was commenced, or until 1 year after for laboratory values. Data were obtained from EuroSIDA (including data from clinics from Southern, Western, Northern, Central, and Eastern Europe) [14], AIDS Therapy Evaluation in the Netherlands (ATHENA) [15] (the Netherlands), and Swiss HIV Cohort Study [13] (Switzerland).

Abbreviations: DAA, direct-acting antiviral; HIV, human immunodeficiency virus; SD, standard deviation.

**Table 2. Distribution of Hepatitis C Virus Genotypes of Individuals With Human Immunodeficiency Virus/Hepatitis C Virus From Sub-Saharan Africa or Southeastern Asia Treated With Interferon-Free Direct-Acting Antivirals and With Available Data on Sustained Virological Response at Least 12 Weeks After the End of Treatment**

| Genotype and Subtype | Sub-Saharan Africa (n = 64), No. (%) | Southeastern Asia (n = 78), No. (%) |
|---|---|---|
| Genotype 1 | 23 (36%) | 58 (74%) |
| a | 18 | 42 |
| b | 2 | 10 |
| c | 1 | 0 |
| Unknown | 2 | 6 |
| Genotype 2 | 8 (13%) | 1 (1%) |
| a | 2 | 0 |
| c | 2 | 0 |
| Unknown | 4 | 1 |
| Genotype 3 | 2 (3%) | 10 (13%) |
| a | 1 | 7 |
| h | 1 | 0 |
| Unknown | 0 | 3 |
| Genotype 4 | 26 (41%) | 3 (4%) |
| a | 2 | 1 |
| c | 2 | 0 |
| d | 1 | 2 |
| e | 2 | 0 |
| f | 2 | 0 |
| g | 1 | 0 |
| v | 1 | 0 |
| Unknown | 15 | 0 |
| Genotype 5 | 1 (2%) | 0 |
| Genotype 6 | 0 | 3 (4%) |
| a | 0 | 2 |
| j | 0 | 1 |
| Unknown | 4 (6%) | 3 (4%) |

**Table 3. Rates of Sustained Virological Response at Least 12 Weeks After the End of Treatment, by Treatment Regimen**

| DAA Regimen | Included, No. | Achieved $SVR_{12}$, No. | $SVR_{12}$ Rate |
|---|---|---|---|
| Sofosbuvir/ledipasvir | 64 | 62 | 97% |
| Sofosbuvir/daclatasvir | 28 | 26 | 93% |
| Sofosbuvir/velpatasvir | 13 | 12 | 92% |
| Elbasvir/grazoprevir | 13 | 12 | 92% |
| Glecaprevir/pibrentasvir | 10 | 10 | 100% |
| Sofosbuvir/simeprevir | 9 | 9 | 100% |
| Sofosbuvir/ribavirin | 3 | 3 | 100% |
| Dasabuvir/ombitasvir/ paritaprevir/ritonavir | 2 | 2 | 100% |

Abbreviations: DAA, direct-acting antiviral; $SVR_{12}$, sustained virological response at least 12 weeks after the end of treatment.

**Table 4. Individuals With Human Immunodeficiency Virus/Hepatitis C Virus From Sub-Saharan Africa or Southeastern Asia Failing Interferon-Free Direct-Acting Antiviral Treatment**

| Characteristic | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Region of origin | Middle Africa | Southeastern Asia | East Africa | South East Asia | Middle Africa | East Africa |
| HCV treatment history | No | No | 1 treatment | 1 treatment | No | 1 treatment |
| Cirrhosis | No | Unknown | No | Yes | No | Yes |
| eGFR <30 mL/min/1.73 $m^2$ | No | Unknown | No | No | No | No |
| Genotype/subtype | 4c | 6j | 3h | 3a | 2[a] | 4a |
| Failed DAA regimen | SOF/LDV | ELB/GRZ | SOF/VEL | SOF/DAC | SOF/LDV | SOF/DAC |
| Treatment adherence[b] | NA | 100% | Good | Good | Good | Good |
| Pre-DAA RAS | NA | NA | NA | NA | NA | NA |
| Post-DAA RAS | NS5A: 30R, 93S | NS3: 170V NS5A: 31M | NS3: 166S, 175M NS5A, NS5B: None[c] | NS3, NS5A, NS5B: None | NA | NA |
| Successful retreatment | Yes | Yes | Yes | No | Yes | Not retreated |
| DAA regimen used for retreatment | GLE/PIB | SOF/VEL/VOX | SOF/VEL/VOX | SOF/GLE/PIB | SOF/DAC/ RBV | … |

Isfordink C et al OFID https://doi.org/10.1093/ofid/ofac508

# Frequent NS5A and multiclass resistance in almost all HCV genotypes at DAA failures: What are the chances for second-line regimens?

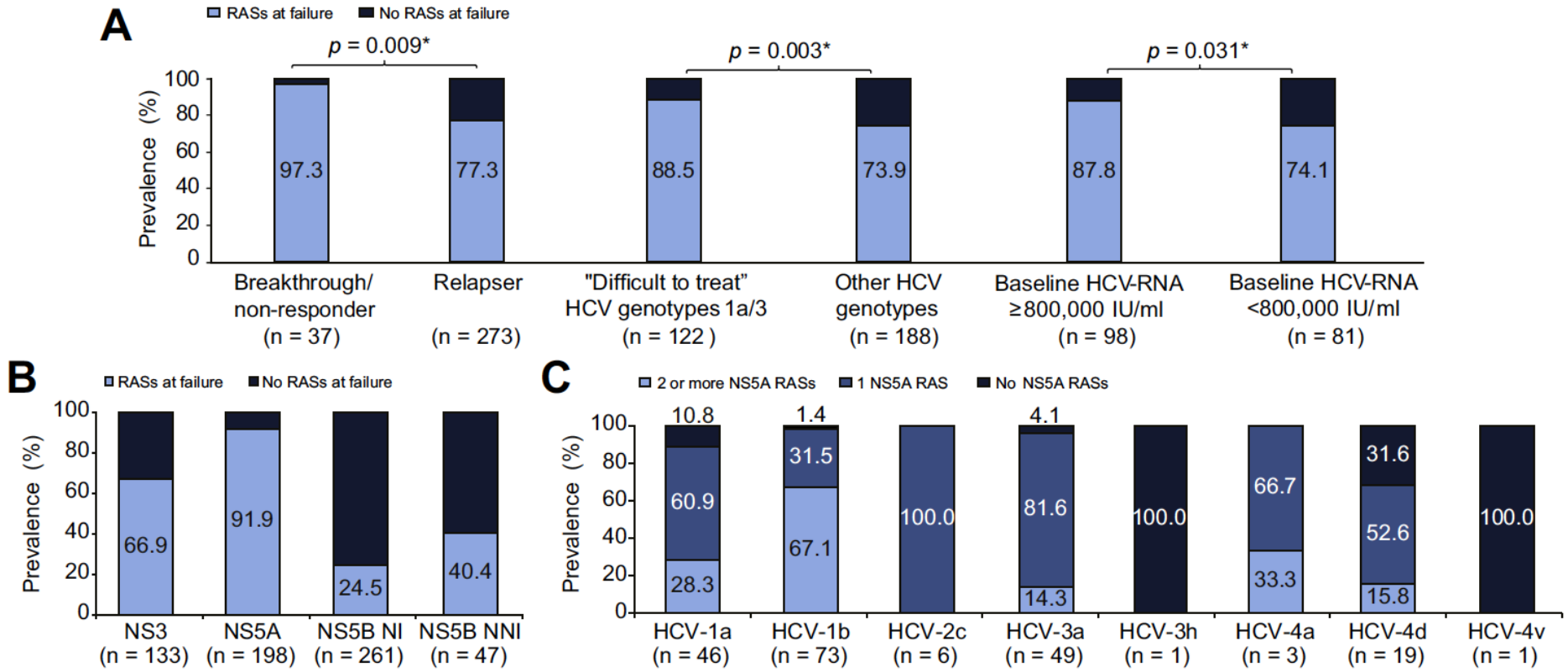
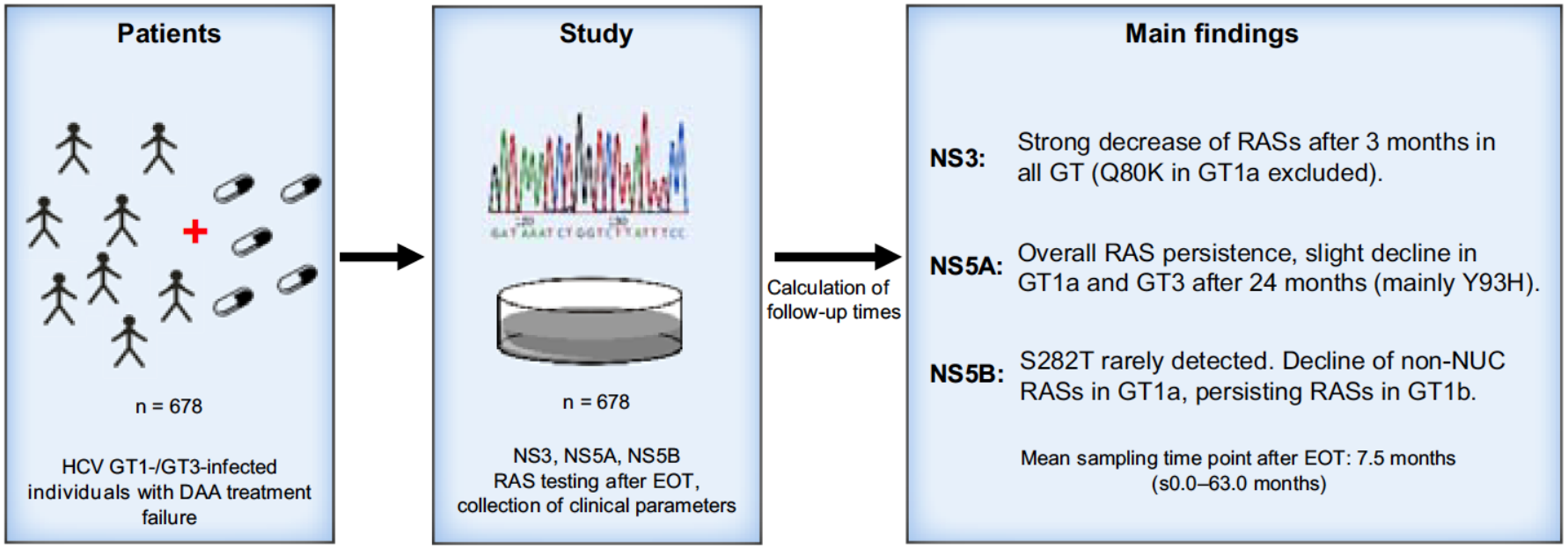
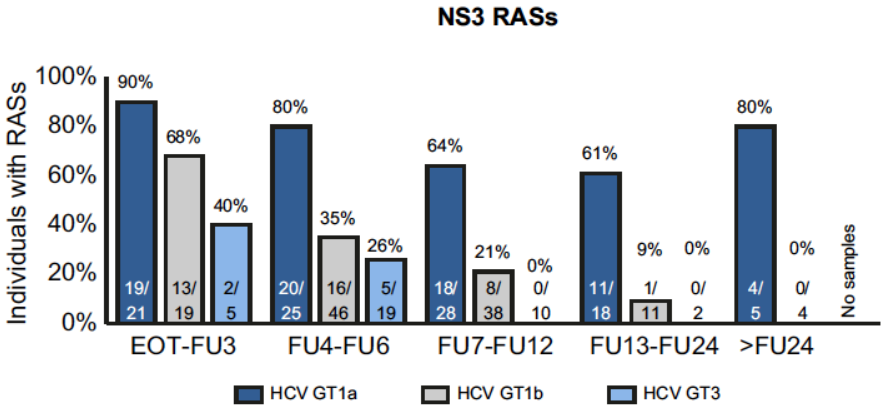


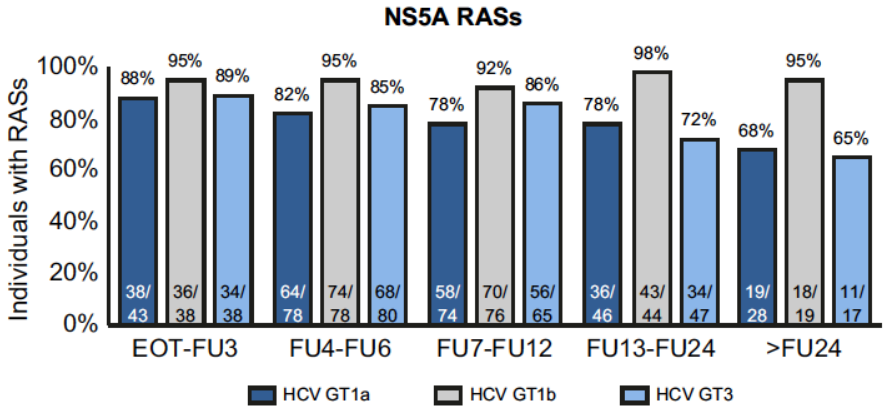

**Fig. 1. Distribution of RASs at failure.** (A) shows the distribution of RASs according to DAA response, HCV genotype infection and baseline HCV-RNA levels. (*) *p* value was calculated by Chi-squared test. (B) shows the prevalence of RASs related to each DAA-class. NS5B NI, nucleotide inhibitor; NS5B NNI, non-nucleoside inhibitor. (C) shows the prevalence of single and multiple NS5A RASs detected among NS5A-failing patients. DAA, direct-acting antivirals; RASs, resistance-associated-substitutions.

Di Maio VC et al Journal of Hepatology 2018 vol. 68 j 595–629

# Long-term persistence of HCV resistance-associated substitutions after DAA treatment failure




Dietz J et al Journal of Hepatology, January 2023. vol. 78 j 57–66

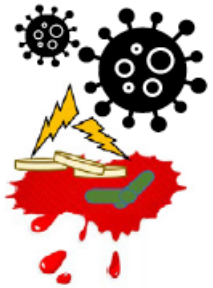
# Characteristics of hepatitis C virus resistance in an international cohort after a decade of direct-acting antivirals

## Patients and Methods

- 3355 HCV patients from 22 countries
  - 40% >F3 fibrosis
  - GT1a (34%), GT1b (25%), GT2 (3%), GT3 (30%), GT4 (7%), GT5/6 (<1%)
- Most patients were treated with the first generation DAAs
  - NS5AI+NI (59%), NS5AI+PI (22%), PI+ NI (4%), NS5AI+PI+NI/NNI (11%)
- 37% sustained viral response, 63% virologic failure
- 6994 HCV NS3, NS5A, NS5B sequences linked with metadata
  - 41% baseline, 59% follow-up

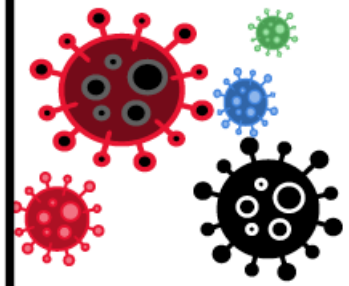
## Characteristics of Resistance-associated Substitutions (RAS) After Treatment Failure

The prevalences of RAS in drug-target genes increase compared to their natural frequencies



Multi-drug resistance is common
94% harbor drug resistance; 63% against ≥2 drug classes

Resistance selection is more frequent in older patients with cirrhosis and those infected with GT1b/4



New variants with complex RASs continue to emerge

Drug resistance in HCV is frequent after failing DAAs. A collaborative effort is required to safeguard HCV global elimination

**SHARED** Surveillance of Hepatitis C Antiviral Resistance, Epidemiology and methoDologies

**SHARED:** https://hcvdb.med.ubc.ca
@HCVShared

Howe AYM et al JHEP Reports 2022 vol. 4 j 100462

# Evaluation of machine learning algorithms for predicting direct-acting antiviral treatment failure among patients with chronic hepatitis C infection

- Among 6525 HCV-infected adults, 308 patients (4.7%) experienced DAA treatment failure.
- Machine Learning  models performed similarly in predicting DAA treatment failure (C statistic [95% CI]: Elastic Network , 0.74 [0.69–0.79 used the fewest predictors (n = 27).
- With Youden index, the EN had 58.4% sensitivity and 77.8% specificity, and nine patients were needed to evaluate to identify 1 DAA treatment failure.
- Over 60% treatment failure were classified in top three risk decile subgroups.
- EN-identified predictors included male sex, treatment < 8 weeks, treatment discontinuation due to adverse events, albumin level < 3.5 g/dL, total bilirubin level > 1.2 g/ dL, advanced liver disease and use of tobacco, alcohol or vitamins

Park H et al Sci Rep (2022) 12:18094

# Evaluation of machine learning algorithms for predicting direct-acting antiviral treatment failure among patients with chronic hepatitis C infection

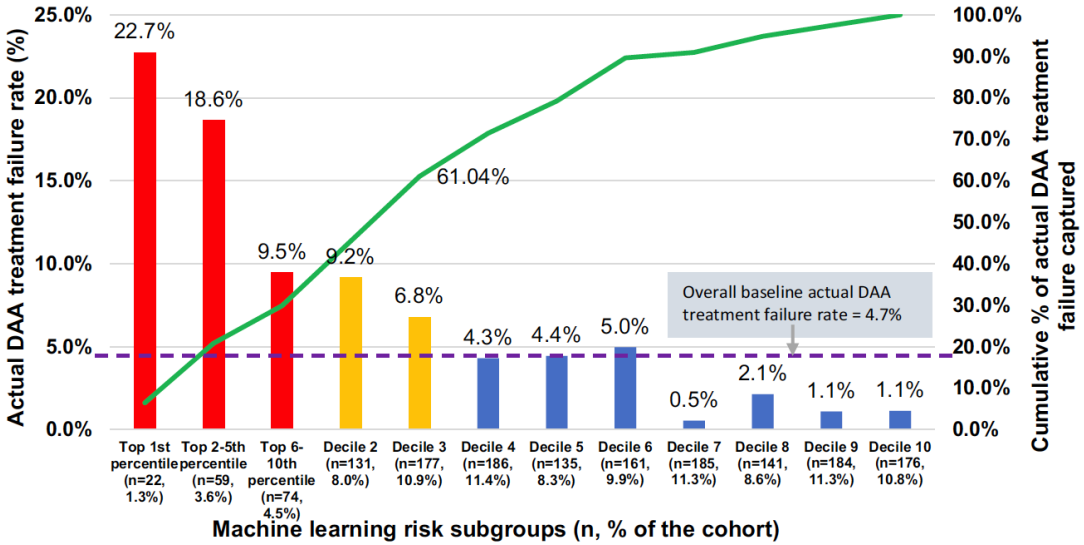



**Figure 2.** Electric net model assessment of direct-acting antiviral (DAA) treatment failure rates for each decile risk subgroup. Data were derived using the validation sample.

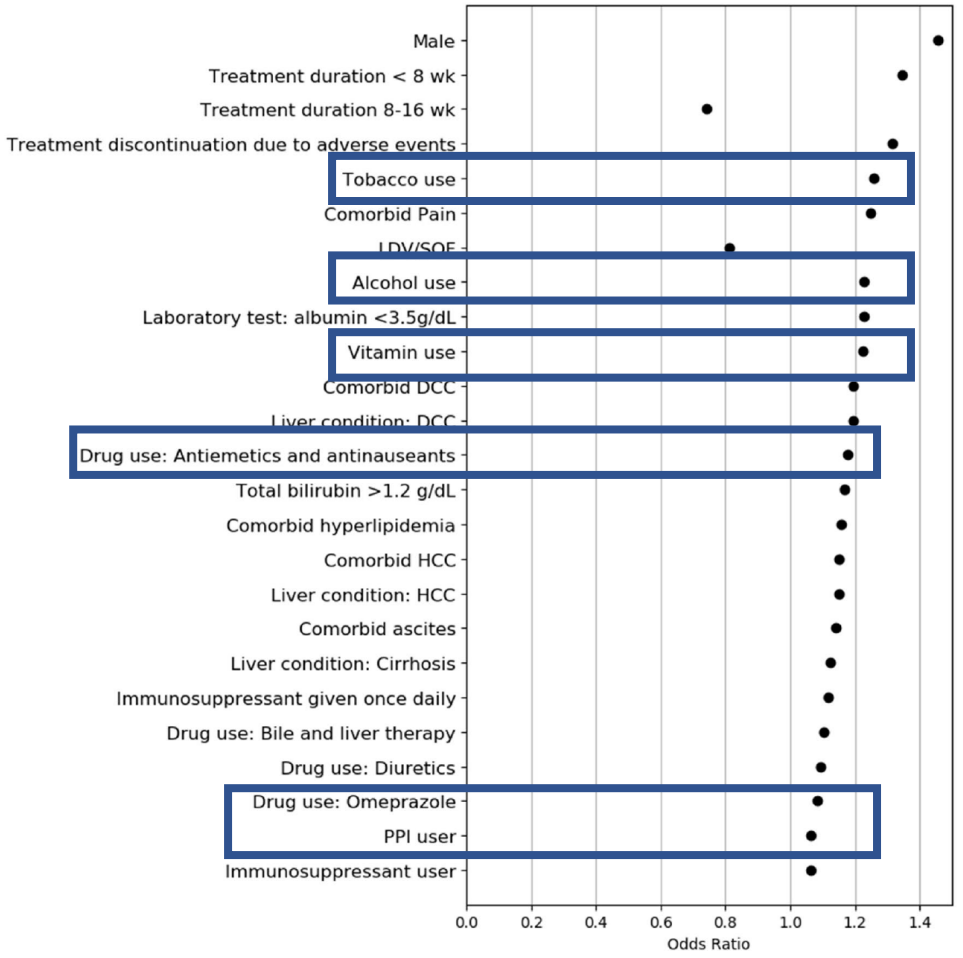



**Figure 3.** Elastic net model identification of 25 key prediction factors associated with direct-acting antiviral treatment failure[a]. *DCC* decompensated cirrhosis, *HCC* hepatocellular carcinoma, *LDV/SOF* ledipasvir/sofosbuvir, *PPI* proton pump inhibitor. [a]Predictors are ordered by factor importance based on odds ratios. Elastic net regularization does not provide an estimate of precision; therefore, 95% CIs are not given.

Park H et al Sci Rep (2022) 12:18094

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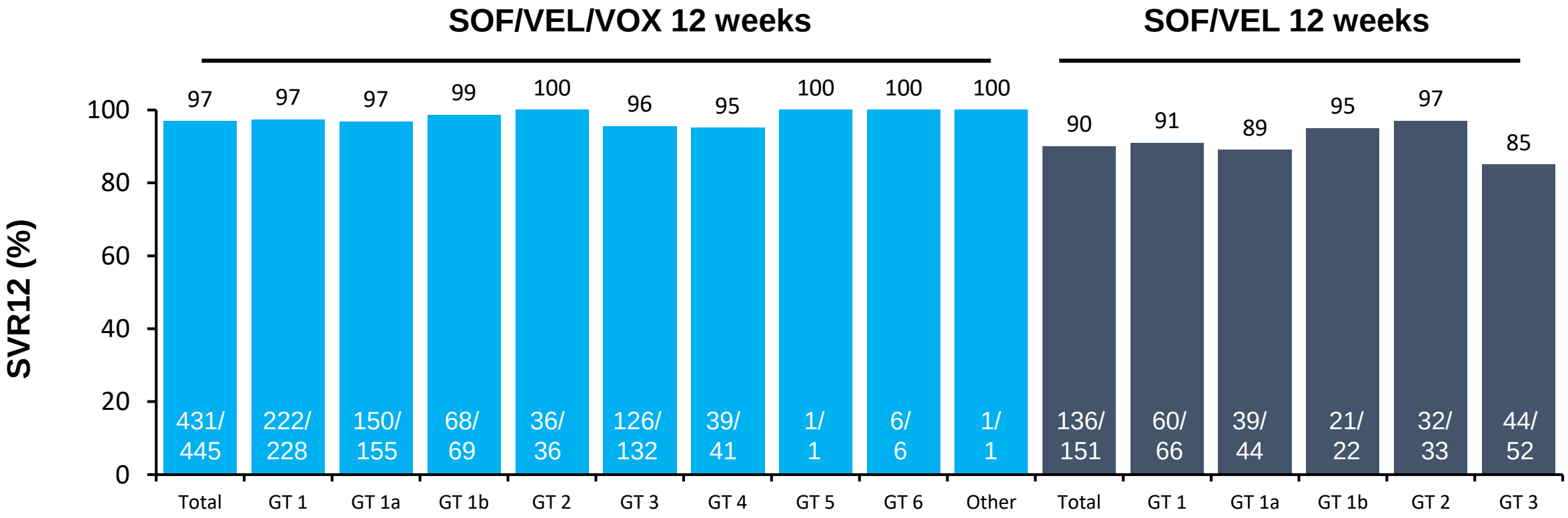
# SOF/VEL/VOX for 12 weeks is effective in GT 1–6 DAA-experienced patients

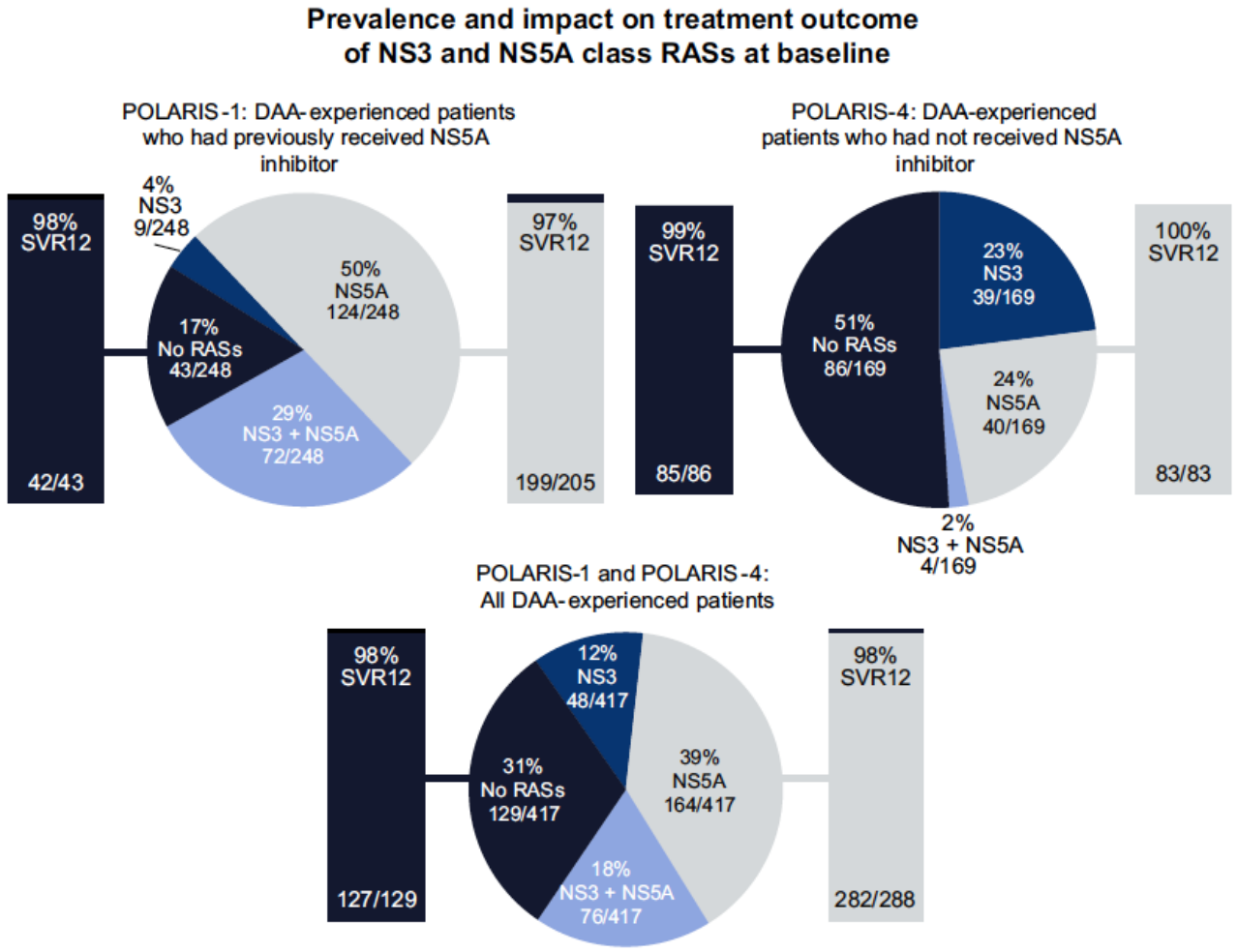



**Tolerability of SOF/VEL/VOX for 12 weeks**

- SAEs were reported in 9 (2%) patients receiving SOF/VEL/VOX for 12 weeks, none were considered treatment-related
- 1 patient died 2 days after completing treatment from an illicit drug overdose

Bourliere M, et al. N Engl J Med 2017;376:2134–46

# No impact of resistance-associated substitutions on the efficacy of sofosbuvir, velpatasvir, and voxilaprevir for 12 weeks in HCV DAA-experienced patients

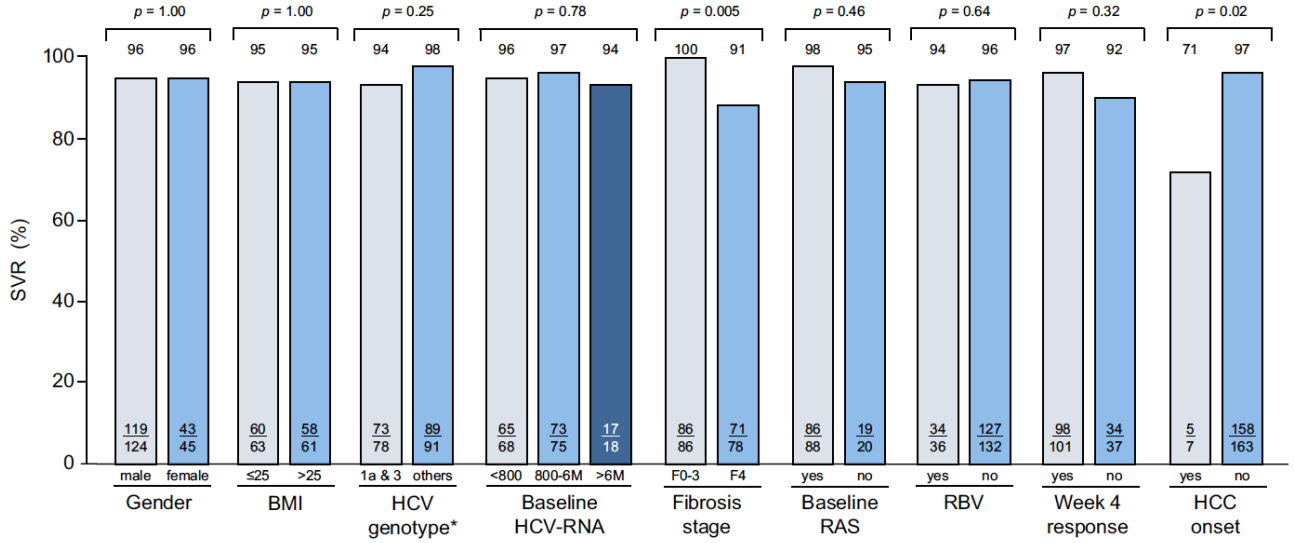



Sarrazin C et al Journal of Hepatology 2018 vol. 69 j 1221–1230

# Real-life effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in hepatitis C patients with previous DAA failure

**Table 1. Baseline characteristics of the 179 patients included in the study.**

| Characteristics | n = 179 |
|---|---|
| Age, years | 57 (18–88) |
| Males | 132 (74%) |
| BMI, kg/m$^2$ | 25 (16–45) |
| IFN experienced | 52 (29%) |
| LSM, kPa | 10.2 (3.5–63.9) |
| Fibrosis | |
| F0-F2 | 57 (32%) |
| F3 | 38 (21%) |
| F4 | 79 (44%) |
| n.a. | 5 (3%) |
| CPT score A* | 78 (99%)§ |
| A5 | 64 (81%) |
| A6 | 14 (18%) |
| Oesophageal varices | 25 (32%)§ |
| Previous HCC | 16 (9%) |
| HCV genotype | |
| 1 | 103 (58%)* |
| 2 | 18 (10%) |
| 3 | 42 (23%) |
| 4 | 16 (9%) |
| HCV-RNA, IU/ml | 1,081,817 (482–25,590,000) |
| ALT, U/L | 54 (10–538) |
| GGT, U/L | 53 (9–428) |
| PLT, 10$^3$/mm$^3$ | 154 (35–539) |
| Bilirubin, mg/dl | 0.7 (0.3–5.7) |
| Albumin, g/dl | 4.2 (2.8–5.1) |
| INR | 1.0 (0.9–3.5) |
| Creatinine, mg/dl | 0.8 (0.4–1.7) |
| eGFR (MDRD), ml/min/1.73 m$^2$ | 93 (41–150) |
| HIV positive | 27 (15%) |
| HBsAg positive | 2 (1%) |
| Diabetes | 25 (14%) |
| Arterial hypertension | 47 (26%) |




| | Patient #1 | Patient #2 | Patient #3 | Patient #4 | Patient #5 | Patient #6 | Patient #7 |
|---|---|---|---|---|---|---|---|
| Age, years | 73 | 61 | 54 | 50 | 55 | 67 | 55 |
| Gender | female | male | female | male | male | male | male |
| BMI, kg/m$^2$ | 26 | 29 | 33 | 25 | 22 | 25 | 25 |
| HCV genotype | 1b | 1a | 4 | 1a | 3 | 3 | 3 |
| HBV/HIV co–infection | no | no | HIV | HBV | HIV | no | no |
| Fibrosis stage | F4 | F4 | F4 | F4 | F4 | F4 | F4 |
| Previous treatments | BOC + PR OBT/PTV–r + DSV | TVR + PR SOF/LDV | – SOF/LDV | SOF/LDV SOF/VEL | SOF + DCV | SOF/VEL | SOF + DCV |
| HCC history | no | no | no | no | no | no | no |
| Adherence | yes | yes | yes | yes | yes | yes | yes |
| RBV use | yes | yes | no | no | no | no | no |
| HCV–RNA, IU/ml | | | | | | | |
| Baseline | 547,066 | 1,536,215 | 455,000 | 1,165,000 | 8,020,000 | 102,546 | 30,022 |
| Week 4 | 72,284 | 15 | 57 | undetected | undetected | undetected | n.a. |
| EOT | – | undetected | undetected | undetected | undetected | undetected | n.a. |
| SVR4 | – | undetected | 3,800 | 1,160,000 | undetected | undetected | |
| SVR12 | – | 387,675 | – | – | 4,741,000 | 198,300 | undetected |
| NS3 RAS | | | | | | | |
| Baseline | none | 176S | n.a. | n.a. | n.a. | none | n.a. |
| At failure | none | 176S | n.a. | n.a. | n.a. | n.a. | n.a. |
| NS5A RAS | | | | | | | |
| Baseline | none | 30R, 31 M | n.a. | n.a. | n.a. | Y93H | n.a. |
| At failure | none | 30R, 31 M | n.a. | n.a. | n.a. | n.a. | n.a. |
| HCC after EOT | no | yes | no | no | no | no | yes |

BMI, body mass index; BOC, boceprevir; DCV, daclatasvir; DSV, dasabuvir; EOT, end-of-treatment; HCC, hepatocellular carcinoma; LDV, ledipasvir; n.a., not available; NS, non-structural; OBV/PTV-r, ombitasvir/paritaprevir-ritonavir; PR, pegylated-interferon + ribavirin; RAS, resistance-associated substitutions; RBV, ribavirin; SOF, sofosbuvir; TVR, telaprevir; VEL, velpatasvir.

Degasperi E et al Journal of Hepatology 2019 vol. 71 j 1106–1115

# Effectiveness of SOF/VEL/VOX in real-life reports

| Study | Patients | Males | Diabetes | HCV Genotypes | HIV | Cirrhosis | NS5A-exposed | RBV | SVR12 (PP) |
|---|---|---|---|---|---|---|---|---|---|
| Belperio et al. | 573 | 567 (99%) | 208 (36%) | 490 HCV-1 (86%)<br>51 HCV-3 (9%) | 16 (3%) | 198 (35%) | 567 (99%) | - | 480/506 (95%) |
| Llaneras et al. | 173 | 103 (75%) | NA | 86 HCV-1 (63%)<br>30 HCV-3 (22%) | 6 (4%) | 46 (34%) | 131 (96%) | - | 128/135 (95%) |
| Saxena et al. | 277* | 209 (75%) | 63 (23%) | 209 HCV-1 (75%)<br>47 HCV-3 (15%) | 8 (3%) | 125 (45%) | 210 (89%) | 9% | 208/214 (97%) |
| Bacon et al. | 196 | 144 (76%) | 41 (21%) | 151 HCV-1 (77%)<br>32 HCV-3 (16%) | 6 (3%) | 82 (42%) | 143 (83%) | 4% | 182/184 (98%) |
| Vermehren et al. | 110 | 94 (86%) | NA | 71 HCV-1 (65%)<br>34 HCV-3 (31%) | NA | 30 (27%) | 83 (75%) | 4% | 74/74 (100%) |
| Hezode et al. | 46 | 33 (72%) | NA | 15 HCV-1 (33%)<br>18 HCV-3 (39%) | 5 (11%) | 46 (100%) | 46 (100%) | 22% | 42/44 (95%) |
| Boyle et al. | 16 | 13 (81%) | NA | 9 HCV-1 (56%)<br>7 HCV-3 (44%) | 3 (19%) | 5 (31%) | 16 (100%) | - | 11/12 (92%) |

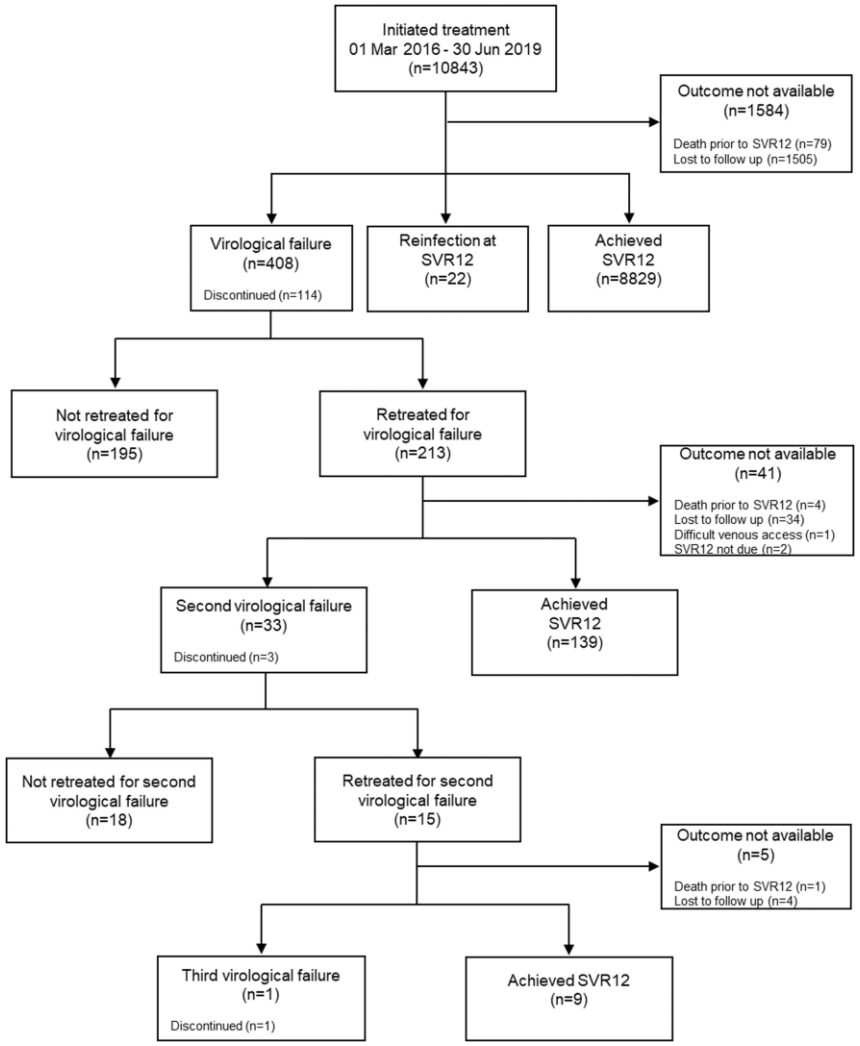
Belperio PS, J Viral Hepat 2019. https://doi.org/ 10.1111/jvh.13115, Llaneras J, Hepatol 2019;71:666–672; Saxena V, Hepatology 2018;68:S418–419A
Bacon BR . J Hepatol 2019;70 e209. Vermehren J, J Hepatol 2019;70 e241. Hezode C, Hepatol 2019;70 e224. Boyle A, J Hepatol 2019;70 e212

Safety and efficacy of sofosbuvir–velpatasvir–voxilaprevir for re-treatment of chronic hepatitis C virus infection in patients with previous direct-acting antiviral treatment failure in Rwanda (SHARED-3): a single-arm trial

- 49 individuals were screened and 40 participants were enrolled.
- 20 (50%) were female, 20 (50%) were male, median age was 63 years (IQR 56–68), and median HCV viral load was 6·2 log10 IU/mL (5·8–6·5) at baseline. The genotype subtypes identified were 4r (18 [45%] participants), 4k (six [15%]), 4b (five [13%]), 4q (four [10%]), 4l (two [5%]), 4a (one [3%]), 4m (one [3%]), and 3h (one [3%]). One (3%) genotype 4 isolate could not be subtyped, and one (3%) isolate was of unknown genotype.
- All successfully sequenced isolates (33 [83%]) had at least two NS5A resistance-associated substitutions and 25 (63%) had three or more.
- 39 (98% [95% CI 87–100]) participants had SVR12.

Gupta N et al Lancet Gastroenterol Hepatol 2022; 7: 542–51

# Retreatment for hepatitis C virus direct-acting antiviral therapy virological failure in primary and tertiary settings: The REACH-C cohort



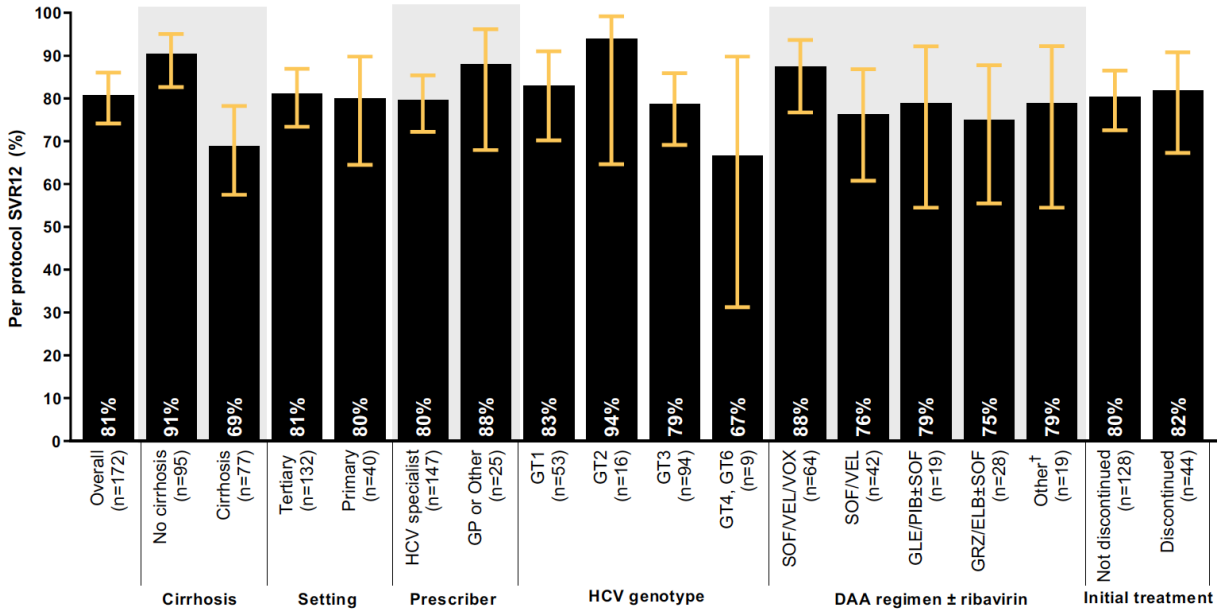
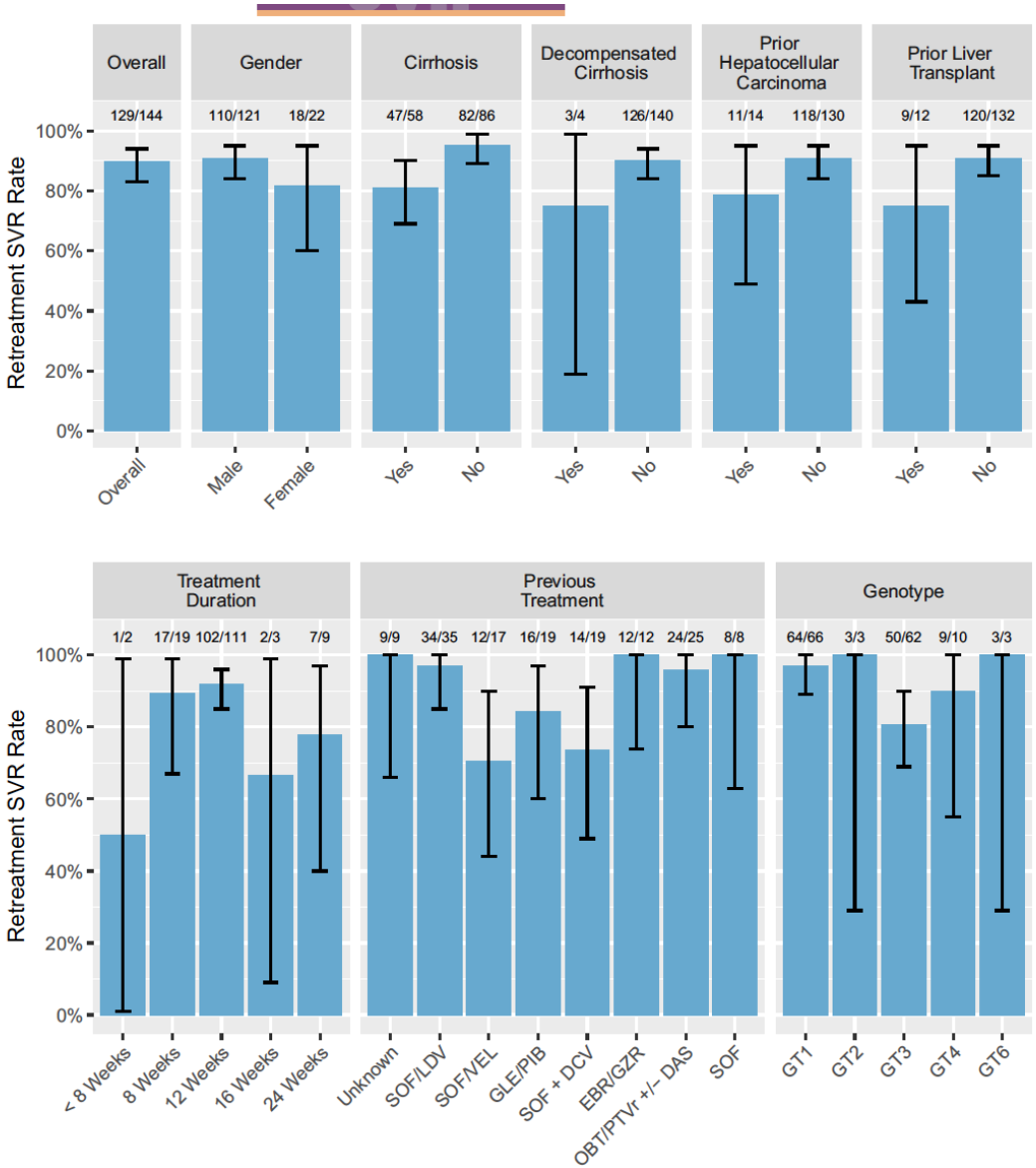



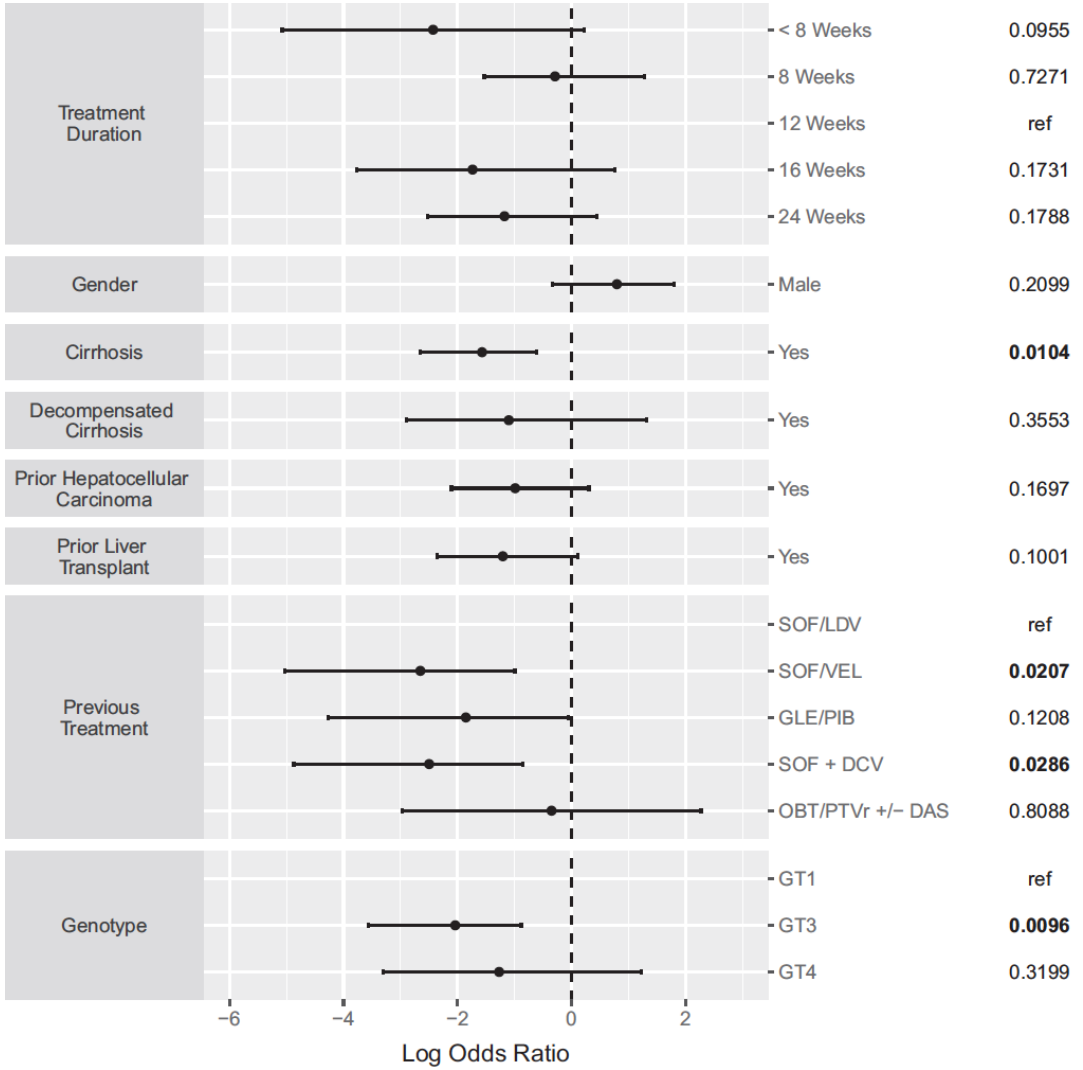

TABLE 4 Logistic regression of factors associated with second virological failure

| Characteristic | Achieved retreatment SVR12 (*n* = 139) | Second virological failure (*n* = 33) | Total (*n* = 172) | Unadjusted OR (95% CI) | Unadjusted *p*-value | Adjusted AOR (95% CI) | Adjusted *p*-value |
|---|---|---|---|---|---|---|---|
| Cirrhosis, *n* (%) | | | | | | | |
| No (ref.) | 86 (62) | 9 (27) | 95 (55) | 1.00 | – | 1.00 | – |
| Yes | 53 (38) | 24 (73) | 77 (45) | 4.33 (1.87–10.01) | .001 | 4.26 (1.64–11.09) | .003 |
| Retreatment setting, *n* (%) | | | | | | | |
| Tertiary (ref.) | 107 (77) | 25 (76) | 132 (76) | 1.00 | – | | |
| Primary | 32 (23) | 24 (8) | 40 (23) | 1.07 (0.44–2.60) | .881 | | |
| Prescriber type, *n* (%) | | | | | | | |
| HCV specialist (ref.) | 117 (84) | 30 (91) | 147 (85) | 1.00 | – | | |
| Other specialist or GP | 22 (16) | 3 (9) | 25 (15) | 0.53 (0.15–1.90) | .330 | | |

Carson J et al J Viral Hepat. 2022;29:661–676.

# Real world SOF/VEL/VOX retreatment outcomes and viral resistance analysis for HCV patients with prior failure to DAA therapy



# Real world SOF/VEL/VOX retreatment outcomes and viral resistance analysis for HCV patients with prior failure to DAA therapy

| Protein | RAS | SVR Rate % (*n*) | *p* | log Odds ratio | Standard error |
|---|---|---|---|---|---|
| NS3 | V55A | 100 (4/4) | .99 | 14.446 | 1199.772 |
| | K/Q80K | 100 (14/14) | .992 | 16.331 | 1638.472 |
| | K/Q80L | 100 (2/2) | .993 | 14.43 | 1696.734 |
| | Q80R | 100 (1/1) | .993 | 13.422 | 1455.398 |
| | A156T | 100 (1/1) | .993 | 13.422 | 1455.398 |
| | L175M | 100 (1/1) | .993 | 13.422 | 1455.398 |
| NS5A | M28T | 100 (5/5) | .993 | 15.454 | 1769.258 |
| | A30K | 71 (10/14) | **.029** | −1.465 | 0.67 |
| | K/R30K | 100 (1/1) | .993 | 13.422 | 1455.398 |
| | L/M31M | 100 (2/2) | .993 | 14.43 | 1696.734 |
| | L31M | 100 (16/16) | .992 | 16.373 | 1543.764 |
| | L31V | 100 (3/3) | .992 | 14.438 | 1385.378 |
| | H58D | 100 (9/9) | .99 | 15.183 | 1201.731 |
| | Y93C | 100 (4/4) | .99 | 14.446 | 1199.772 |
| | Y93H | 78 (29/37) | **.014** | −1.371 | 0.559 |
| | Y93N | 100 (2/2) | .993 | 14.43 | 1696.734 |
| NS5B | A/T/V150V | 93 (26/28) | .531 | 0.495 | 0.791 |
| | F/L159F | 67 (2/3) | .229 | −1.512 | 1.257 |
| | L159F | 100 (2/2) | .993 | 14.43 | 1696.734 |
| | E/K206E | 80 (16/20) | .142 | −0.943 | 0.642 |
| | E237G | 100 (1/1) | .993 | 13.422 | 1455.398 |
| | D/N244I | 100 (1/1) | .993 | 13.422 | 1455.398 |
| | C/N316H | 100 (1/1) | .993 | 13.422 | 1455.398 |
| | C/N316N | 75 (3/4) | .355 | −1.099 | 1.189 |
| | I/V321I | 50 (1/2) | .125 | −2.213 | 1.442 |
| | V321I | 100 (1/1) | .993 | 13.422 | 1455.398 |

Logistic regression was used to test the association between the presence of RAS with outcome in the whole cohort. Bold values indicates $p<0.05$.

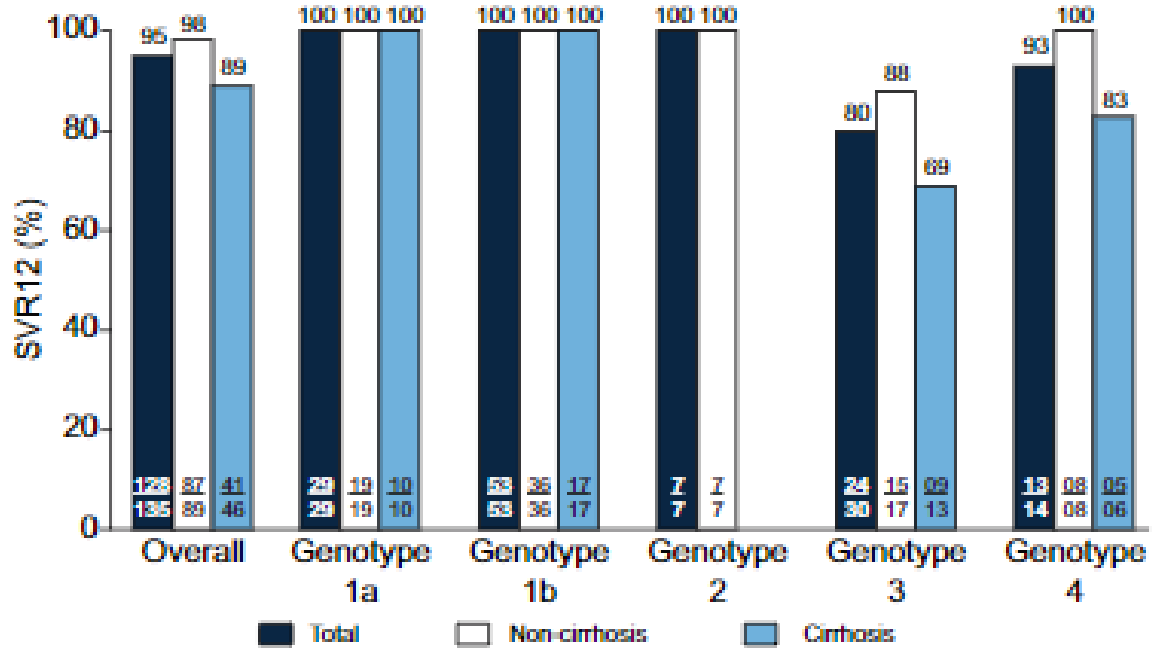
Smith DA et al J Viral Hepat. 2021;28:1256–1264.

# Previous DAA combination treatments by HCV genotype

| | Overall (N = 137) | GT1a (n = 30) | GT1b (n = 54) | GT2 (n = 7) | GT3 (n = 30) | GT4 (n = 14) |
|---|---|---|---|---|---|---|
| Sofosbuvir-based regimen | | | | | | |
| Sofosbuvir plus simeprevir | 3 (2) | 1 (3) | 1 (2) | – | – | 1 (7) |
| Sofosbuvir plus daclatasvir | 25 (18) | – | 2 (4) | 1 (14) | 22 (73) | – |
| Sofosbuvir/ledipasvir | 52 (38)* | 20 (67) | 20 (37) | – | 3 (10) | 7 (50) |
| Sofosbuvir/velpatasvir | 8 (6) | – | – | 3 (43) | 4 (14) | 1 (7) |
| NS5A plus NS3/4A | | | | | | |
| Simeprevir plus daclatasvir | 1 (1) | – | 1 (2) | – | – | – |
| Ombitasvir/paritaprevir/r | 4 (3) | 2 (7) | 1 (2) | – | – | 1 (7) |
| Elbasvir/grazoprevir | 9 (7) | 1 (3) | 5 (9) | – | – | 3 (21) |
| Glecaprevir/pibrentasvir | 1 (1) | 1 (3) | – | – | – | – |
| NS5A plus NS5B plus NS3/4A | | | | | | |
| Dasabuvir plus ombitasvir/paritaprevir/r | 28 (20) | 4 (13) | 24 (44) | – | – | – |
| Experimental combination | 6 (4) | 1 (3) | – | 3 (43) | 1 (3) | 1 (7) |

Data presented are: n (%).
DAA, direct-acting antiviral; GT, genotype; HCV, hepatitis C virus.
*Two patients were genotype 1 non-subtipable previously treated with a sofosbuvir plus ledipasvir.

## SVR12 achieved in 95% (128/135)




SVR12 rates by HCV genotype were 100% (29/29) in patients with GT1a, 100% (53/53) in GT1b, 80% (24/30) in GT3, 100% (7/7) in GT2 and 93% (13/14) in GT4. The SVR12 rate was 89% (41/46) in cirrhotic patients and 98% (87/89) in non-cirrhotic patients (p = 0.05)

*Llaneras J. et al., J. Hepatol., 2019*

# GT3 patients with cirrhosis showed the lowest SVR12 rates: only 69% compared to 97% in non-GT3 cirrhotic patients (OR 24; 95% CI 2.7–213)

*GT3 was the only factor associated with low SVR12 in retreatment with SOF/VEL/VOX*

| | SVR12 rates | Univariate *p* value | Multivariate | |
|---|---|---|---|---|
| | | | OR (95% CI) | *p* value |
| Gender | | 0.44 | | |
| Males | 95/101 (94) | | | |
| Females | 33/34 (97) | | | |
| Age (years) | 56 (52–64) | 0.45 | | |
| HIV coinfection | 6/6 (100) | 0.72 | | |
| Previous HCC | 7/9 (78) | 0.07 | | |
| Liver transplant | 8/8 (100) | 0.66 | | |
| ALT level (IU/L) | 52 (37–84) | 0.014 | | 0.12 |
| CTP score | | 0.19 | | |
| A (5–6) | 125/131 (95) | | | |
| B (7–8) | 3/4 (75) | | | |
| Cirrhosis | 41/46 (89) | 0.05 | | 0.21 |
| Genotype | | <0.001 | 16 (1.7–152) | 0.02 |
| Non-GT3 | 104/105 (99) | | | |
| GT3 | 24/30 (80) | | | |
| Previous DAA combination | | 0.62 | | |
| Sofosbuvir-based | 81/87 (93) | | | |
| NS5A + NS3/4A | 14/15 (93) | | | |
| NS5A + NS5B + NS3/4A | 27/27 (100) | | | |
| EASL 2014 guidelines recommendation (24) | 102/109 (96) | 0.26 | | |

Data presented are: n of patients/total N (%), or median (range).
ALT, alanine aminotransferase; CTP, Child-Turcotte-Pugh score; DAA, direct-acting antiviral; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus

| Gender | Age (yr) | Genotype | Fibrosis | CTP* | Previous DAA treatment | Resistance-associated substitutions** |
|---|---|---|---|---|---|---|
| Male | 55 | 3 | F4 | 5 | Sofosbuvir + daclatasvir + ribavirin/24w | L28S, M31L, D168G |
| Male | 47 | 3 | F4 | 5 | Sofosbuvir + daclatasvir + ribavirin/24w | Not available |
| Male | 62 | 3 | F2 | – | Sofosbuvir + daclatasvir/12w | Y93H |
| Male | 54 | 3 | F0-F1 | – | Sofosbuvir + daclatasvir/12w | Not substitutions detected |
| Male | 63 | 3 | F4 | 7 | Sofosbuvir + daclatasvir/12w | Not substitutions detected |
| Male | 53 | 3 | F4 | 5 | Sofosbuvir/velpatasvir/12w | Not available |
| Female | 50 | 4 | F4 | 5 | Elbasvir/grazoprevir/12w | Y93H |

*CTP, Child-Turcotte-Pugh score.
**Analysis performed prior to receiving treatment with SOF/VEL/VOX for 8 weeks, 12 weeks or 24 weeks: Treatment for 8,12 or 24 weeks.

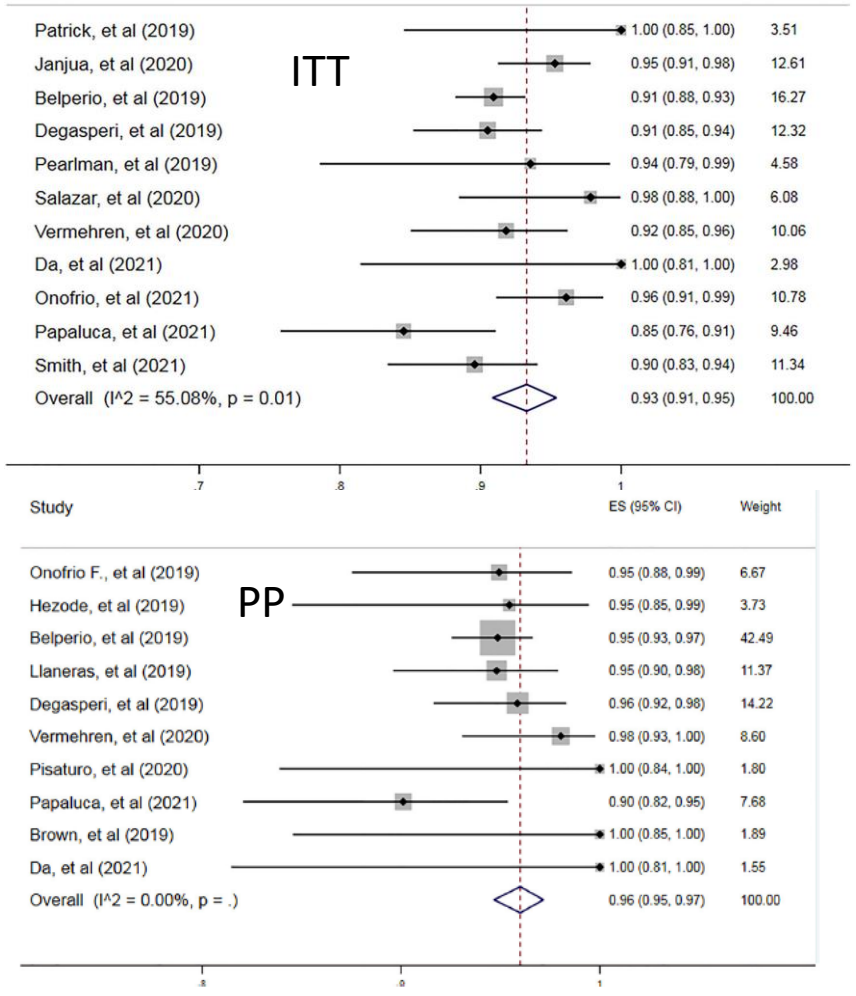
*Llaneras J. et al., J. Hepatol., 2019*

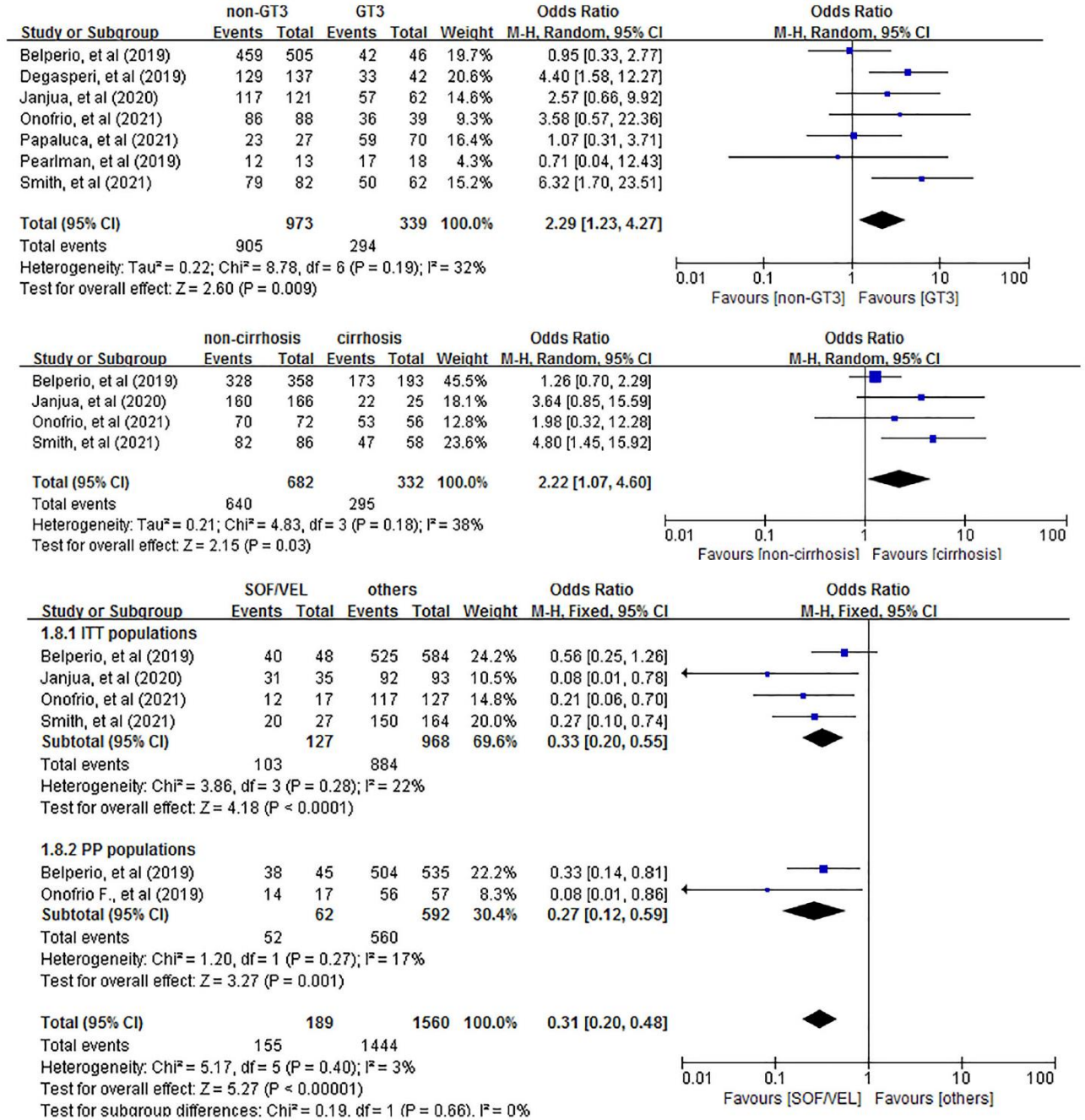
Resistance analysis and treatment outcomes in hepatitis C virus genotype 3-infected patients within the Italian network VIRONET-C

- 34 failure to first line recommended regimen
  - 4 G/P
  - 6 SOF/VEL
  - 24 SOF + DAC ± RBV
  - 30/34 any RAS
    - 2 NS3
    - 30 NS5A
- Re – treatment
  - 22 SOF/VEL/VOX 100% (22/22)SVR
  - 4 G/P+SOF ± RBV 100%  (4/4) SVR
  - 10 SOF/VEL ± RBV 80% (8/10) SVR

Di Maio VC et al Liver International. 2021;41:1802–1814.

# 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




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

# Retreatment of patients failing SOF/VEL

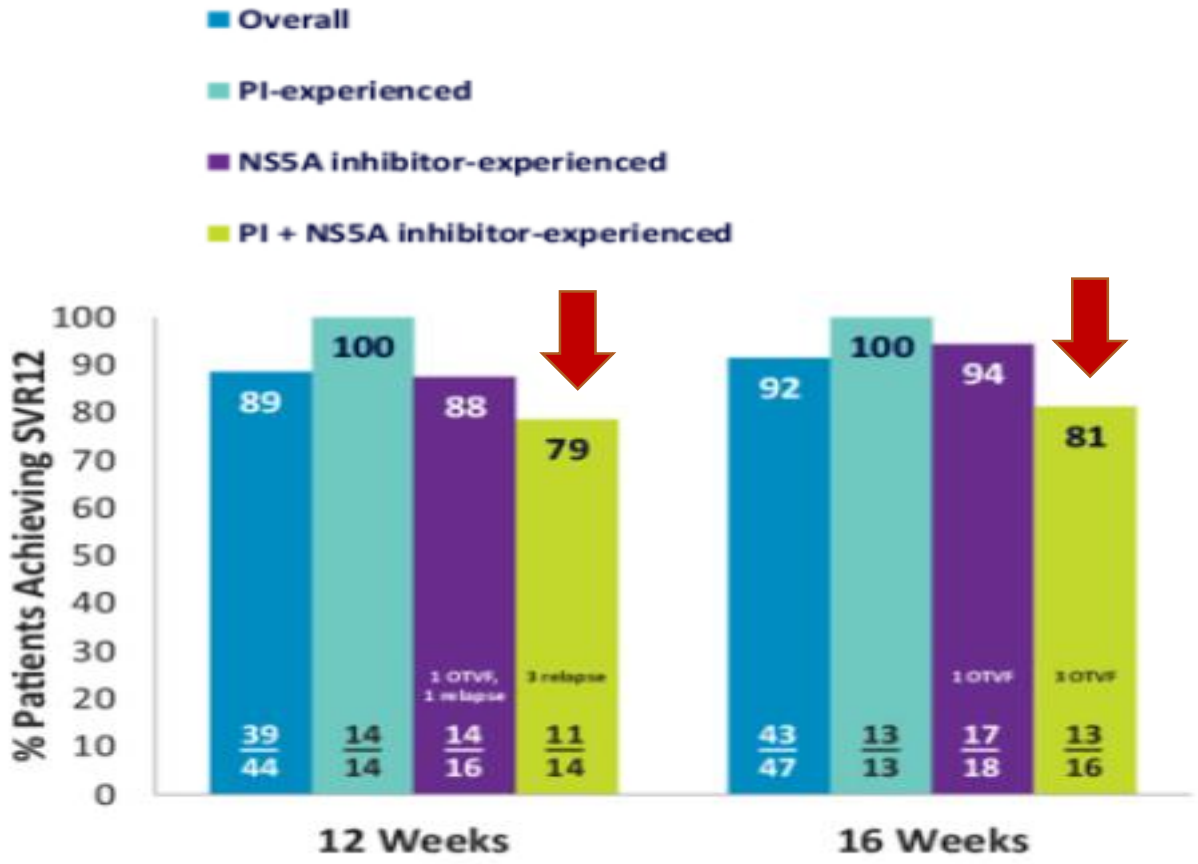
| Author (year) | Treatment | SVR | Cumulative SVR |
|---|---|---|---|
| Degasperi (2019) | SOF/VEL/VOX | 94% (29/31) | 85% (95% CI 79-91%) (107/126) |
| Di Maio (2020) HCV G3 | SOF/VEL/VOX | 100% (6/6) | |
| Smith (2021) | SOF/VEL/VOX | 70% (12/17) | |
| Papaluca (2021) | SOF/VEL/VOX | 95% (18/19) | |
| Llaneras ( 2019) | SOF/VEL/VOX | 87% (7/8) | |
| Belperio (2019) | SOF/VEL/VOX | 84% (38/45) | |

# Il paziente fallito: strategie terapeutiche e discussione di casistica clinica

- Dimensioni del fenomeno
- Determinanti del fallimento terapeutico nell'epoca dei DAA pangenotipici
- Trattamento del paziente fallito:
  - SOF/VEL/VOX: Risultati dei trials clinici
  - SOF/VEL/VOX: Dati real life
  - SOF+ G/P
  - Terza linea di terapia
- Linee guida
- Determinazione RAS nel pz fallito pros e cons

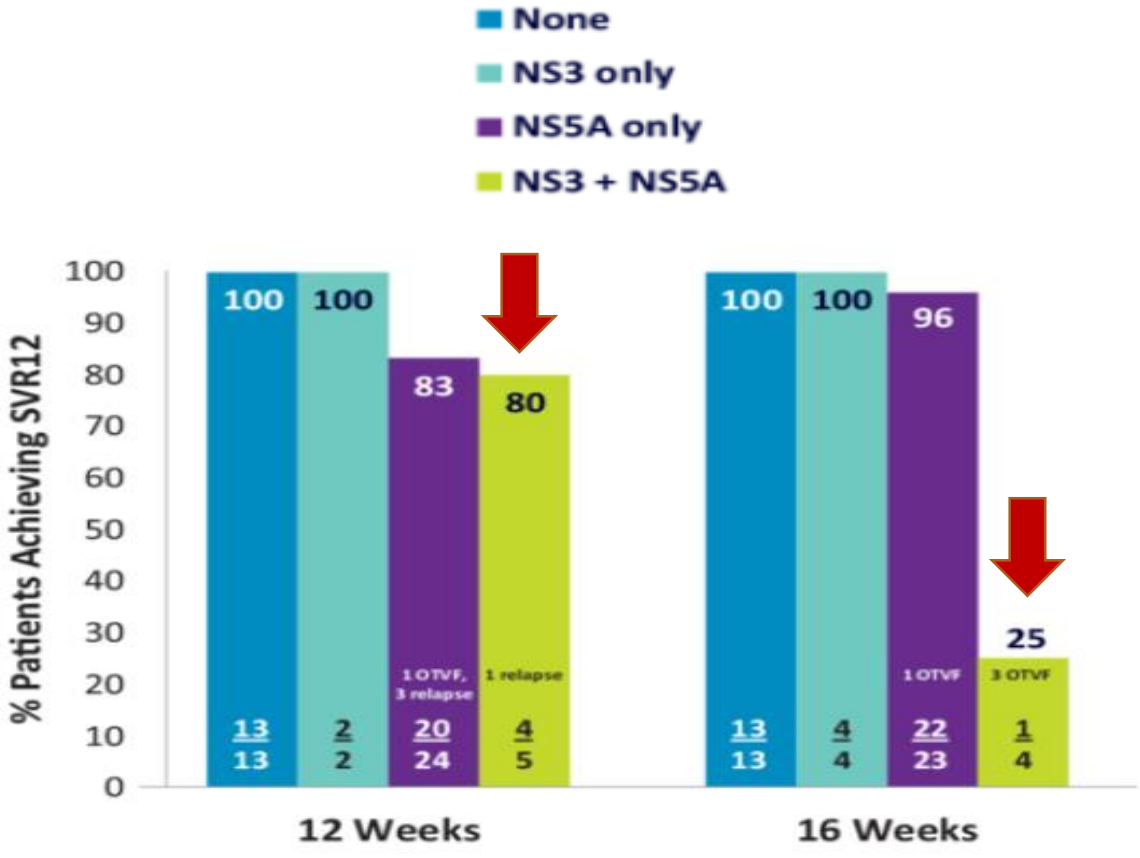
**MAGELLAN-I**: efficacy of glecaprevir/pibrentasvir in DAA-experienced patients can be reduced by double-class RASs

## $SVR_{12}$ rate by prior DAA-experience




OTVF = on-treatment virologic failure.

## $SVR_{12}$ rate by baseline RASs




*Pilot-Matias T. et al., EASL 2017 poster #SAT-204*

# Glecaprevir/Pibrentasvir for Hepatitis C Virus Genotype 3 Patients With Cirrhosis and/or Prior Treatment Experience: A Partially Randomized Phase 3 Clinical Trial

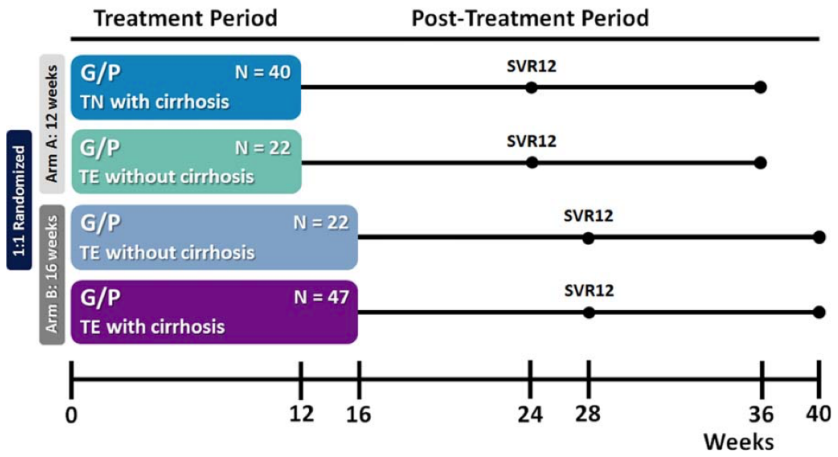



**FIG. 1.** SURVEYOR-II, Part 3 study design. Patients were enrolled into two arms to be treated with either 12 weeks (arm A) or 16 weeks (arm B) of G/P. Treatment-naive patients with cirrhosis received 12 weeks of treatment, while those with prior treatment experience and cirrhosis received 16 weeks. Patients with prior treatment experience but without cirrhosis were randomized 1:1 for treatment with either 12 or 16 weeks of G/P. Patients were followed for 24 weeks posttreatment to monitor safety and sustained virologic response. Abbreviations: TE, treatment-experienced; TN, treatment-naive.

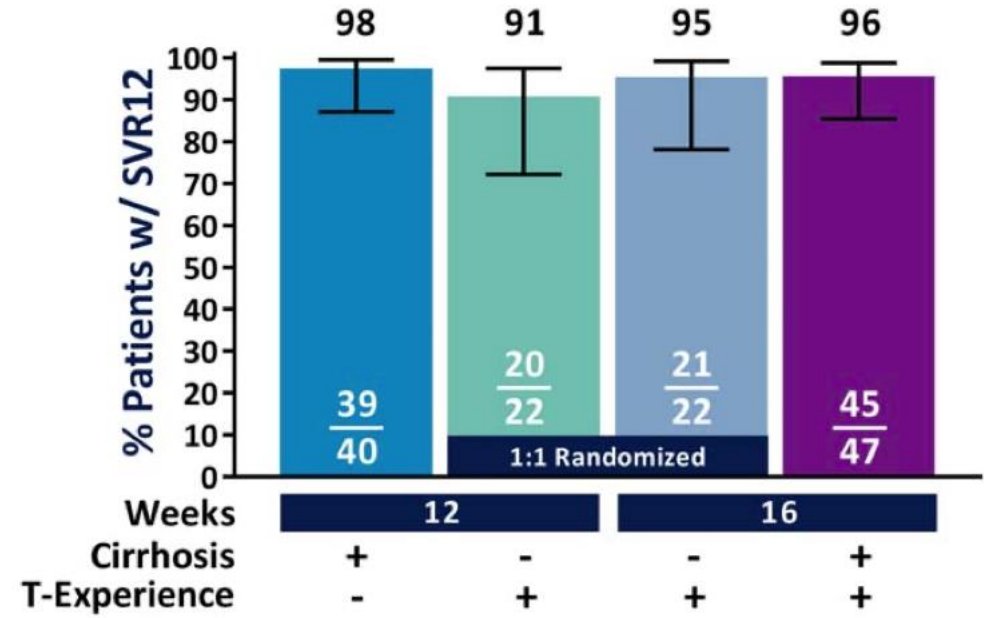



**FIG. 2.** The numbers and percentages of patients who achieved SVR12 in each treatment arm are summarized. Treatment-naive patients with compensated cirrhosis were treated with G/P for 12 weeks, and patients with both compensated cirrhosis and prior treatment experience were treated for 16 weeks. Patients without cirrhosis who had prior treatment experience were randomized 1:1 to receive either 12 or 16 weeks of G/P. Two-sided 95% CIs were calculated using the Wilson score method for binomial proportions. Abbreviation: TE, treatment.

Wyles T et al HEPATOLOGY, 2018; 67: 514-523

# Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C virus infection

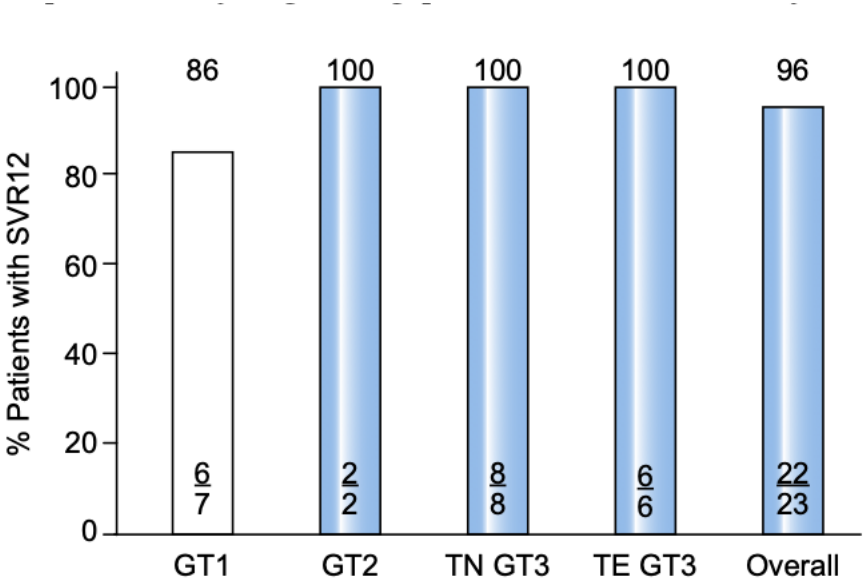



**Fig. 1. Efficacy of G/P + SOF + RBV.** Percentage of patients with sustained virologic response at post-treatment week 12 (SVR12), by genotype and overall, are shown; n/N inside bars.

**Table 1. Treatment and Resistance History of Patients.**

| Genotype/ Subtype | Cirrhosis | Treatment prior to G/P parent study | Type of VF in parent study | NS3 RASs at G/P failure in parent study* | NS5A RASs at G/P failure in parent study* | Time from failure in parent study to retreatment in Magellan-3 (months) | NS3 RASs at BL in MAGELLAN-3* | NS5A RASs at BL in MAGELLAN-3* |
|---|---|---|---|---|---|---|---|---|
| 1b | No | DCV + ASV | Relapse | None | L28M + P32del | 10.3 | None | L28M + P32del |
| 1a | No | OBV/PTV/r + DSV + RBV; pegIFN + RBV + DCV | OTVF | A156G + D168A | Q30R + L31M + H58D | 7.5 | A156G, D168A/T | Q30R + L31M + H58D |
| 1a | No | TVR, DCV; pegIFN/ RBV | Relapse | A156V | Q30R + L31M + H58D | 12.6 | None | Q30R + L31M + H58D |
| 1a§ | Yes | SOF + LDV | OTVF | A156V | Q30K + Y93H | 8.6 | None | Q30K + Y93H |
| 1a | Yes | SOF + SMV; SOF + LDV | Relapse | R155K + A156T | M28G + Q30R | 6.7 | R155K | M28G + Q30R |
| 1a | Yes | OBV/PTV/r + DSV | OTVF | D168A | M28G + Q30R | 14 | None | M28G + Q30R |
| 1a | Yes | pegIFN + RBV | Relapse | None | Q30R + Y93N | 9 | None | Q30R + Y93N |
| 2a | No | SOF + RBV | Relapse | None | None | 5.2 | None | None |
| 2a | No | IFN + RBV | Relapse | None | None | 11.3 | None | None |
| 3a | No | Naïve | Relapse | None | Y93H | 7.0 | None | Y93H |
| 3a | No | Naïve | Relapse | None | Y93H | 4.6 | None | Y93H |
| 3a | No | Naïve | OTVF | Q168R | A30K + Y93H | 11.7 | Q168R | A30K + Y93H |
| 3a | No | Naïve | Relapse | None | A30K + Y93H | 6.0 | None | A30K |
| 3a | No | Naïve | Relapse | Q168L | A30K + Y93H | 11.8 | Q168L | A30K + Y93H |
| 3b | No | Naïve | Relapse | None | (A30K + V31M) + Y93H† | 13.2 | None | A30K + V31M + Y93H |
| 3a | Yes | Naïve | OTVF | A156G | A30K + Y93H | 10.3 | Q168R | A30K + Y93H |
| 3a | Yes | Naïve | Relapse | Q168L | A30K + Y93H | 11.4 | None | A30K, Y93H |
| 3a | No | IFN + RBV | Relapse | None | Y93H | 7.0 | None | Y93H |
| 3a | No | IFN + RBV | Relapse | None | L31F + Y93H | 18.9 | None | Y93H |
| 3a | No | IFN + RBV | Relapse | Q168R | A30K + Y93H | 8.1 | None | A30K |
| 3a | No | IFN + RBV | Relapse | None | A30K + Y93H | 6.2 | None | A30K + Y93H |
| 3a | No | IFN + RBV | OTVF | Q168L | A30K + Y93H | 21.8 | None | A30K |
| 3a | Yes | IFN + RBV | OTVF | A156G | A30K + Y93H | 14.0 | None | A30K + Y93H |

ASV, asunaprevir; BL, baseline; DCV, daclatasvir; DSV, dasabuvir; G/P, glecaprevir/pibrentasvir; LDV, ledipasvir; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir; OTVF, on-treatment VF; RAS, resistance-associated substitution; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; VF, virologic failure.
'+'indicates that at least 1 of the substitutions was present at >90% prevalence and all others were present at >50% prevalence
*The detection threshold was 15%. NS3 resistance-associated substitution (RAS) positions included in analyses were: 155, 156 and 168. NS5A RAS positions included in analyses were: 24, 28, 30, 31, 32, 58, 92, and 93.
§Patient with virologic failure
†GT3b wild-type NS5A sequence has K30 and M31; in addition, Y93H was present.

Wyles D et al Journal of Hepatology 2019 vol. 70 j 1019–1038

# Re-treatment of patients failing GP

| Author (year ) | Treatment | SVR | Cumulative SVR |
|---|---|---|---|
| Wyles (2019) | SOF + GP + RBV (12-16w) | 96% (22/23) | 96%(23/24) |
| Di Maio (2021) G3 | SOF+G/P+RBV | 100% 1 | |
| | SOF/VEL/VOX | 100% (4/4) | 94% (95% CI 90-98%) (103/109) |
| Degasperi (2019) | SOF/VEL/VOX | 100% (9/9) | |
| Pearlman (2019) | SOF/VEL/VOX 12 w | 94% (29/31) | |
| De Salazar (2020) | SOF/VEL/VOX 12-16 w (3) + RBV (9) | 98% (45/46) | |
| Smith (2021) | SOF/VEL/VOX | 84% (16/19) | |
| De Salazar (2020) | SOF/VEL | 75% (3/4) | |

Wyles D, et al. J Hepatol 2019; 70: 1019–23; Pearlman B et al AmJ Gastroenterol 2019; 114: 1550–2.
De Salazar et al J Antimicrob Chemother 2020; 75: 3349–3358

# Prevalence of resistance-associated substitutions and retreatment of patients failing a glecaprevir/pibrentasvir regimen

**Table 1.** Demographics and clinical characteristics of the population studied

| Characteristic | |
|---|---|
| Study population, *n* | 90 |
| Sex (male), *n* (%) | 71/90 (78.9) |
| Age (years), median (IQR) | 54 (45–63) |
| Clinical characteristics | |
| viral load ($log_{10}$ IU/mL), median (IQR) | 6.11 (5.34–6.57) |
| genotype, *n* (%) | |
| 1a | 23 (25.6) |
| 1b | 10 (11.1) |
| 2a + 2c | 3 + 17 (22.2) |
| 3a | 36 (40.0) |
| 4d | 1 (1.1) |
| outcome of G/P treatment, *n* (%) | |
| relapse | 76/85 (89.4) |
| breakthrough | 7/85 (8.2) |
| non-compliance | 1/85 (1.2) |
| discontinuation | 1/85 (1.2) |
| fibrosis score, *n* (%)[a] | |
| F0–F1 | 30 (33.3) |
| F2 | 5 (5.6) |
| F3 | 5 (5.6) |
| F4 | 5 (5.6) |
| unavailable | 45 (50) |
| cirrhosis (>12.5 kPa), *n* (%) | 10/90 (11.1) |
| HIV coinfected, *n* (%) | 7/90 (7.8) |
| previous HCV treatment experience, *n* (%) | 2/90 (2.2) |
| 8 weeks duration G/P, *n* (%) | 80/90 (88.9) |

G/P, glecaprevir/pibrentasvir.
[a]Measured using FibroScan.

**Table 2.** Patients with RASs in NS5A, NS3 or NS5B after failing glecaprevir/pibrentasvir therapy

| Patient no. | Genotype | NS5A | NS3 | NS5B |
|---|---|---|---|---|
| 1 | 1a | L31M + H58D + Y93C | A156V | WT |
| 2 | 1a | Q30D + Y93H | Q80K[a] | WT |
| 3 | 1a | Q30R + H58D | A156V | WT |
| 4 | 1a | Q30R + H58D | Q80K | WT |
| 5 | 1b | L31M | WT | C316N[a] |
| 6 | 3a | A30K + Y93H | Q168L + A156G | WT |
| 7 | 3a | A30K + L31V + Y93H | A156T | WT |
| 8 | 3a | A30K + Y93H | Q168R + Y56H | WT |
| 9 | 3a | A30K + Y93H | A156G | WT |
| 10 | 3a | L31F + Y93H | Q168L | WT |

[a]Prevalent baseline polymorphisms unlikely to be selected during glecaprevir/pibrentasvir therapy.

**Table 3.** Prevalence and profile of RASs in NS5A and NS3 after failing glecaprevir/pibrentasvir according to the viral genotype

| Genotype | Any RAS, *n* (%) | NS5A RASs, *n* (%) | NS3 RASs, *n* (%) | Without RASs, *n* (%) | *P* |
|---|---|---|---|---|---|
| 1a | 21/23 (91.3) | 20/23 (87.0) | 5/21[a] (23.8) | 2/23 (8.7) | any RAS: <0.05 |
| 1b | 5/10 (50.0) | 4/10 (10.0) | 1/10 (10.0) | 5/10 (50.0) | NS5A RASs: <0.05 |
| 2a/2c | 4/18 (22.2) | 4/18[a] (22.2) | 0 | 14/18[a] (77.8) | NS3 RASs: NS |
| 3a | 27/34 (79.4) | 25/33[a] (75.8) | 7/33[a] (21.2) | 6/34[a] (17.6) | NS5B RASs: <0.05 |

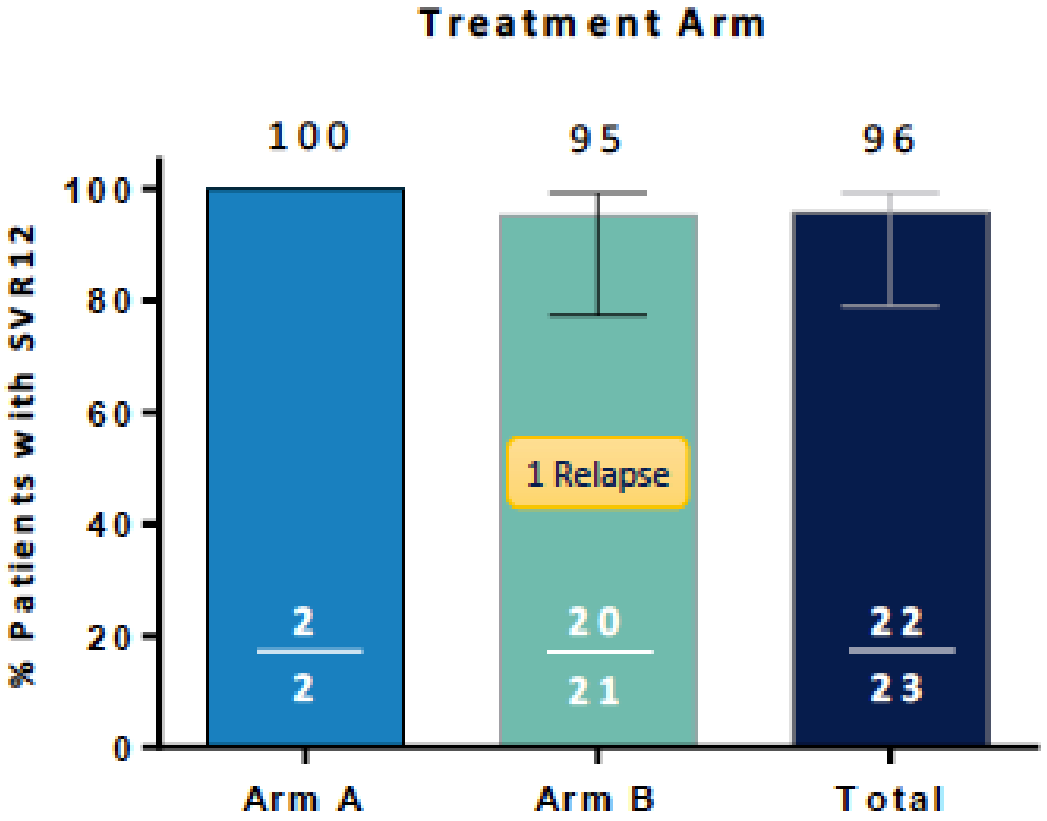
NS, not significant.
[a]In patients with available data.

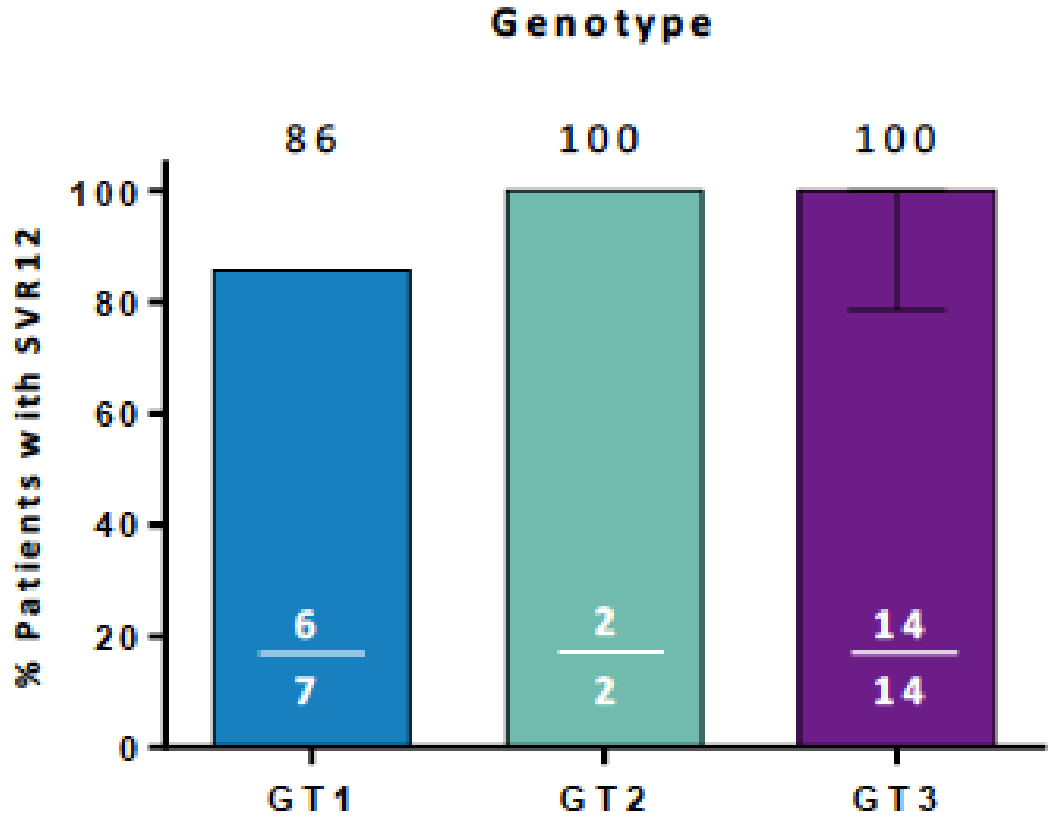
Data on retreatment 56 patients.
52 retreated with SOF/VEL/VOX (9 RBV; 3 for 16-24 w) → 45/46 SVR12 Failure cirrhotic, infected with genotype 3a RAS NS5B A30K + Y93H NS3 Y56H + Q168R
4 retreated with SOF/VEL 3/4 SVR12 ; Failure NS3 WT NS5A Q30R + H58D NS3 A156V

De Salazar et al J Antimicrob Chemother 2020; 75: 3349–3358

# Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C. Magallen-3 study

Phase 3 ongoing study evaluating the efficacy and safety of G/P +SOF+ RBV patients who previously failed G/P treatment.




- 30% had cirrhosis, 26% failed PI and/or NS5Ai before G/P treatment failure, and 65% had ≥2 NS5A RAS at baseline

Arm A: Non GT 3, Non Cirrhosis G/P+SOF+RBV 12 wks

Arm B: Any GT with or without Cirrhosis G/P+SOF+RBV 16 weeks

Wyles D et al. ILC 2018

# Il paziente fallito: strategie terapeutiche e discussione di casistica clinica

- Dimensioni del fenomeno
- Determinanti del fallimento terapeutico nell'epoca dei DAA pangenotipici
- Trattamento del paziente fallito:
  - SOF/VEL/VOX: Risultati dei trials clinici
  - SOF/VEL/VOX: Dati real life
  - SOF+ G/P
  - Terza linea di terapia
- Linee guida
- Determinazione RAS nel pz fallito pros e cons

# Failure on voxilaprevir, velpatasvir, sofosbuvir and efficacy of rescue therapy

**Table 1. Clinical characteristics of VOX/VEL/SOF failure patients (n = 40).**

| | |
|---|---|
| **Male gender** | **30 (75)** |
| Mean age (years) | 59 (31-76) |
| Sampling country | |
| Germany | 13 (33) |
| Italy | 10 (25) |
| Spain | 12 (30) |
| Austria | 3 (8) |
| Switzerland | 1 (2) |
| Belgium | 1 (2) |
| HCV genotype: | |
| Genotype 1a | 11 (28) |
| Genotype 1b | 9 (23) |
| Genotype 3a | 18 (45) |
| Genotype 3b | 1 (2) |
| Genotype 4d | 1 (2) |
| HIV coinfection | 6 (15) |
| Past HBV infection* | 6 (15) |
| Fibrosis stage (in patients w/o cirrhosis) | |
| F0/F1 | 2/7** (29) |
| F2 | 3/7** (42) |
| F3 | 2/7** (29) |
| Cirrhosis | 28 (70) |
| Child grade A | 20/23** (87) |
| Child grade B | 3/23** (13) |
| Child grade C | - |
| Pre-treatment history | |
| P/R ± BOC/TVR | 15 (38) |
| DAA treatment history | |
| One DAA treatment | 31 (78) |
| Two DAA treatments | 5 (12) |
| Three DAA treatments | 4 (10) |
| Pre-treatment regimens | |
| Any SOF-based regimen | 34 (85) |
| Any PI-based regimen | 12 (30) |
| NS5Ai-based regimen | 40 (100) |
| HCC | 11 (28) |
| Liver Transplantation | 6 (15) |
| SOF/VEL/VOX retreatment | |
| RBV added | - |
| 12 weeks duration | 39 (98) |
| Discontinuation week 4 | 1 (3) |
| Virologic Treatment Failure | 39 (98) |

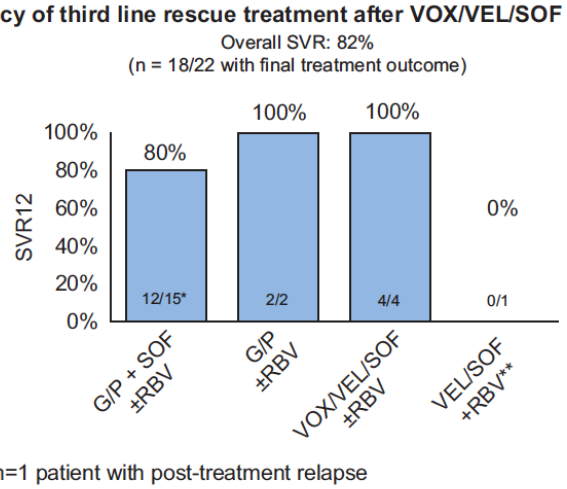



**Fig. 1. Updated rescue treatment efficacies in patients with VOX/VEL/SOF retreatment failure.** *n = 1 patient with post-treatment relapse, n = 2 patients died after end of treatment or after reaching SVR4.

| | | RASs at VOX/VEL/SOF failure | | | | Rescue treatment | | | |
|---|---|---|---|---|---|---|---|---|---|
| PAT. | HCV GT | NS3 | NS5A | NS5B | Comorbidities | Initiation (month/year) | Regimen | Duration (weeks) | Response |
| 5 | 1a | Q80K | L31M | No RASs | Cirrhosis Child A, HIV coinfection | 11/18 | G/P+SOF | 12 | SVR12 |
| 9 | 1a | No RASs | M28V | No RASs | Cirrhosis Child B, LTX, HCC | 03/19 | G/P+SOF | 16 | Death |
| 34 | 3a | Q168R | Y93H | No RASs | Cirrhosis Child A, HCC | 12/19 | G/P+SOF | 12 | SVR12 |
| 20 | 1b | Y56H, D168V | L31V, Y93H | L159F, C316N | 3 previous DAA treatments | 09/19 | G/P+SOF+RBV | 24 | SVR12 |
| 24 | 3a | No RASs | Y93H | No RASs | Cirrhosis, LTX, HCC | 02/19 | G/P+SOF+RBV | 12 | SVR12 |
| 28 | 3a | Q168K | Y93H | No RASs | Cirrhosis Child A, portal hypertension, diabetes | 01/19 | G/P+SOF+RBV | 24 | SVR12 |
| 33 | 3a | No RASs | Y93H | No RASs | Cirrhosis Child A | 11/19 | G/P+SOF | 12 | SVR12 |
| 27 | 3a | No RASs | Y93H | No RASs | Cirrhosis Child A, LTX | 12/19 | G/P+SOF | 12 | SVR4, death |
| 22 | 3a | No RASs | Y93H | No RASs | Cirrhosis, HCC# | 01/19 | G/P+SOF+RBV | 16 | Relapse* |
| 35 | 3a | Q168K | Y93H | A150V, V321A | Fibrosis F3 | 09/19 | G/P+SOF+RBV | 16 | SVR12 |
| 2 | 1a | No RASs | Q30H, L31V, Y93H | No RASs | Cirrhosis, Child A | 01/20 | G/P+SOF | 24 | SVR12 |
| 4 | 1a | No RASs | Q30R, L31M | No RASs | Cirrhosis, Child A, LTX, HCC | 12/19 | G/P+SOF+RBV | 16 | SVR12 |
| 38 | 3a | No RASs | A30K, Y93H | No RASs | Cirrhosis | 05/20 | G/P+SOF+RBV | 16 | FU pending |
| 40 | 4d | D168V, A156S | M31V, Y93H | No RASs | Obesity | 03/20 | G/P+SOF | 24 | SVR12 |
| 1 | 1a | Q80K | No RASs | No RASs | - | 04/20 | G/P+SOF+RBV | 12 | SVR12 |
| 8 | 1a | Q80K | No RASs | No RASs | HIV coinfection | 02/20 | G/P+RBV | 12 | SVR12 |
| 15 | 1b | No RASs | Y93H | No RASs | Cirrhosis, Child A, Diabetes | 12/18 | G/P | 12 | SVR12 |
| 13 | 1b | No RASs | L31I | No RASs | LTX, chronic kidney disease | 06/19 | VOX/VEL/SOF | 24 | SVR12 |
| 23 | 3a | Q168R | A30K, Y93H | No RASs | - | 01/19 | VOX/VEL/SOF+RBV | 24 | SVR12 |
| 26 | 3a | No RASs | No RASs | No RASs | Cirrhosis Child A, HCC, Obesity, HIV coinfection | 09/19 | VOX/VEL/SOF | 24 | SVR12 |
| 29 | 3a | No RASs | No RASs | No RASs | Cirrhosis Child A, HIV coinfection | 03/20 | VOX/VEL/SOF | 24 | SVR12 |
| 32 | 3a | No RASs | Y93H | No RASs | Cirrhosis, Child B | 03/19 | VEL/SOF+RBV | 24 | Relapse** |

- VOX/VEL/SOF failure was mainly observed in HCV GT3- and GT1a-infected patients with cirrhosis.
- Rescue treatment with multiple targeted therapies was effective in most patients

Dietz J et al. Journal of Hepatology 2021 vol. 74 j 801–810 & 2021 vol. 75 j 221–255

# Failure on voxilaprevir, velpatasvir, sofosbuvir and efficacy of rescue therapy

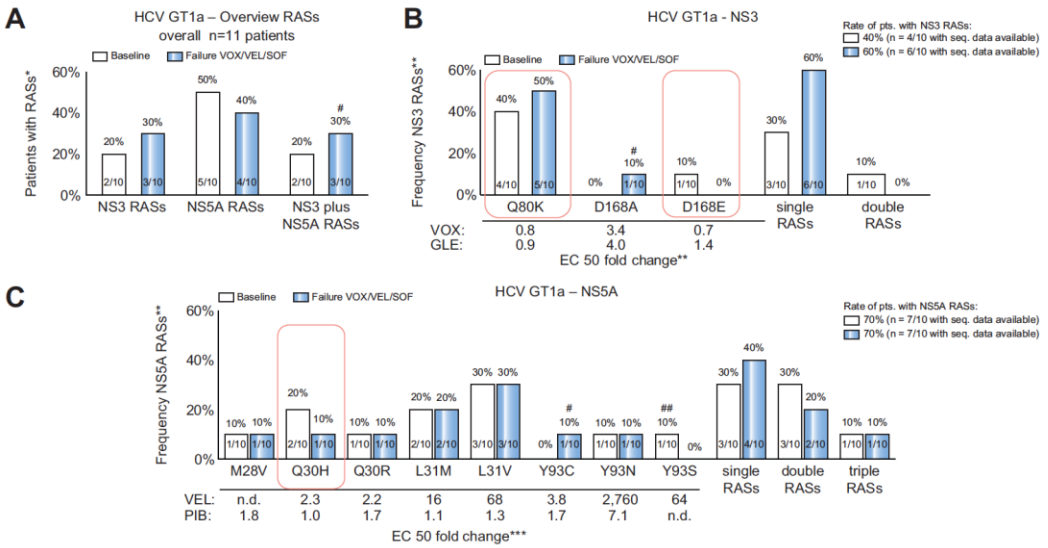



**Fig. 1. RASs in patients infected with HCV GT1a in whom VOX/VEL/SOF retreatment failed.** (A) Overall NS3 and NS5A RAS frequencies, (B) frequencies of NS3

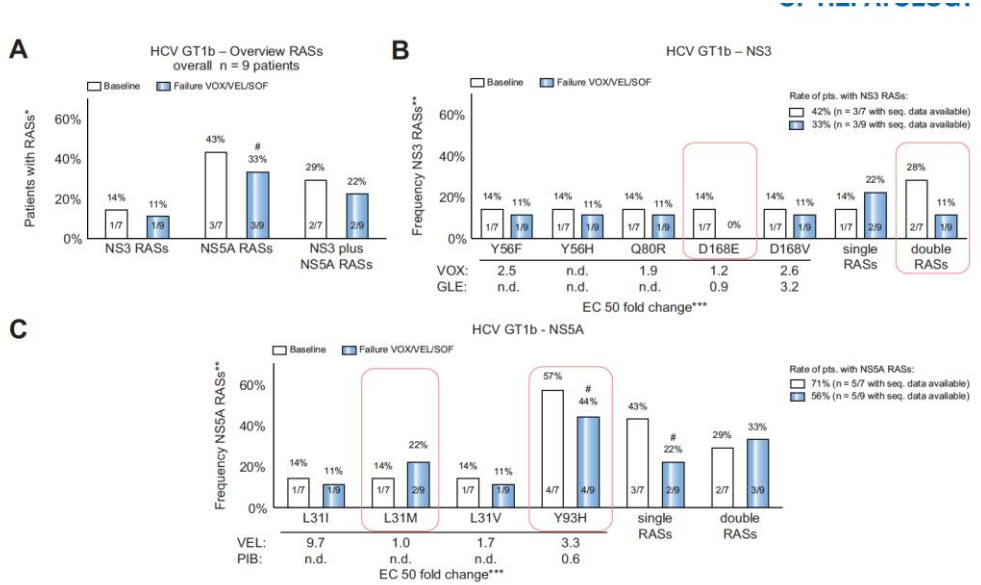



**Fig. 2. RAS patterns in patients infected with HCV GT1b in whom VOX/VEL/SOF retreatment failed.** (A) Overall NS3 and NS5A RAS frequencies, (B) frequencies

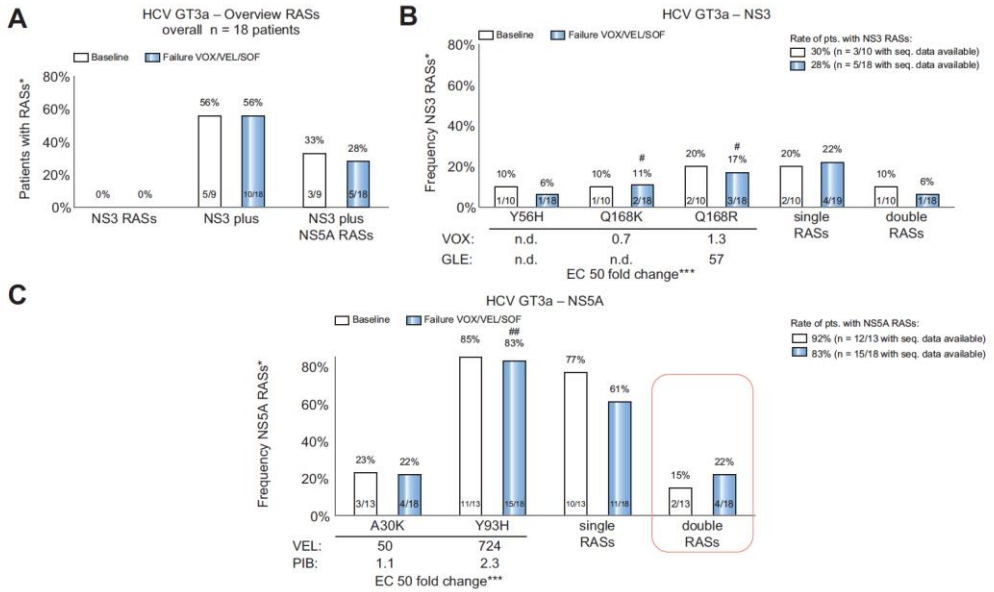



**Fig. 3. Frequencies of RASs in patients with VOX/VEL/SOF retreatment failure and HCV GT3a infection.** (A) Overall NS3 and NS5A RAS frequencies, (B) fre-

Baseline RAS data from a subgroup of patients before VOX/VEL/SOF retreatment (78%) showed few NS3 RASs apart from Q80K in GT1a (40%), typical NS5A RAS patterns in most patients (74%) and no S282T in NS5B.
Sequencing after VOX/VEL/SOF failure was available in 98% of patients and showed only minor changes for NS3 and NS5A RASs.
VOX/VEL/SOF failure was not associated with specific RAS patterns within NS3, NS5A or NS5B target regions.

Dietz J et al. Journal of Hepatology 2021 vol. 74 j 801–810

# Glecaprevir/pibrentasvir + sofosbuvir + ribavirin offers 100% cure rate for hepatitis C virus retreatment in 6 patients after SOF/VEL/VOX failure in real-world settings

**Table 1. Patient characteristics.**

| Patient | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Age | 67 | 60 | 61 | 68 | 68 | 58 |
| Gender | Male | Male | Female | Male | Male | Male |
| Genotype | 1b | 3a | 3 | 1a | 1b | 1a |
| Stage | Cirrhosis (CTP A) | Cirrhosis (CTP A) | Cirrhosis (CTP A) | Cirrhosis (CTP A) | Cirrhosis (CTP A) | Cirrhosis (CTP B) |
| Baseline history of HCC | No | Indeterminate liver lesions[1] | No | Yes; received Y90 radioembolization | Yes; received Y90 radioembolization | No |
| Baseline NS5A resistance | T17S, T79A, Q288R, R311P, A347T, S396P, D403S | Y93H, S62T | No resistance panel available | K24K/E, M28T/M, Q30R, Y93N | R30Q, L31V, Q54H, Y93H | L31V |
| Baseline NS3 resistance | Q80K | No resistance panel available | No resistance panel available | No mutations or resistance predicted | Q80K/Q, D168V | V36M |
| Baseline HCV RNA (IU/ml) | 2,299,631 | 1,038,041 | 705,684 | 667,144 | 1,960,000 | 886,538 |
| Regimen (length in weeks)[2] | G/P + SOF + RBV (16) | G/P + SOF + RBV (16) | G/P + SOF + RBV (16) | G/P + SOF + RBV; then G/P (24)[3] | G/P + SOF + RBV (24) | G/P + SOF + RBV (16) |
| Week 4 HCV RNA | – | Detected, <15 IU/ml | – | Not detected | Not detected | Not detected |
| End of Treatment HCV RNA | Not detected | – | Not detected | Not detected | Not detected | Not detected |
| ≥12 weeks after treatment HCV RNA | Not detected | Not detected | Not detected | Not detected | Not detected | Not detected |
| Failed previous regimens (length in weeks) | | | | | | |
| Course 1: | LDV/SOF (12) | PegIFN + RBV (48) | SOF/VEL (12) | PegIFN + RBV + SOF (12) | PegIFN + RBV (48) | SOF/VEL (12) |
| Course 2: | SOF/VEL/VOX (12) | SOF/VEL + RBV (12) | SOF/VEL/VOX + RBV (12) | LDV/SOF (24) | SOF + SMV (12) | SOF/VEL/VOX (12) |
| Course 3: | – | SOF/VEL/VOX (12) | – | G/P (16) | LDV/SOF + RBV (24) | – |
| Course 4: | – | – | – | SOF/VEL/VOX + RBV (12) | SOF/VEL/VOX (12) | – |

CTP, Child-Turcotte-Pugh; G/P, glecaprevir/pibrentasvir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LDV/SOF, ledipasvir/sofosbuvir; PegIFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SOF/VEL, sofosbuvir/velpatasvir; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir.

[1]Patient 2 was diagnosed with HCC during HCV treatment.

[2]Ribavirin dose = 1,200 mg/day (dosed 600 mg twice daily); all patients weighed > 75 kg.

[3]Patient 4 received G/P + SOF + RBV for 13 weeks 4 days, then had a 14-day interruption due to orthotopic liver transplantation. SOF + RBV were discontinued after day 95 due to acute kidney injury post-transplant, but the patient received G/P through 24 weeks.

Martin M et al. Journal of Hepatology 2021 vol. 75 j 221–255

# Il paziente fallito: strategie terapeutiche e discussione di casistica clinica

- Dimensioni del fenomeno
- Determinanti del fallimento terapeutico nell'epoca dei DAA pangenotipici
- Trattamento del paziente fallito:
  - SOF/VEL/VOX: Risultati dei trials clinici
  - SOF/VEL/VOX: Dati real life
  - SOF+ G/P
  - Terza linea di terapia
- Linee guida
- Determinazione RAS nel pz fallito pros e cons

# 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<br>• 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) | A | 1 |
| – SOF/VEL + RBV* for 24 weeks (decompensated cirrhosis) | B | 2 |
| • Patients with predictors of poor response, SOF + GLE/PIB for 12 weeks:<br>– Advanced liver disease<br>– Multiple courses of DAA-based treatment<br>– Complex NS5A RAS profile | B | 2 |
| • Very difficult-to-cure patients:† SOF/VEL/VOX + RBV or SOF + GLE/PIB + RBV for 12 weeks or for 16 or 24 weeks | 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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AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

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

IDSA
Infectious Diseases Society of America

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]<br>• **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).

Recommended regimens listed by evidence level and alphabetically for:

## Glecaprevir/Pibrentasvir Treatment Failures (All Genotypes), 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 | IIa, B |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) | 12 weeks | IIa, B |
| For patients with compensated cirrhosis, addition of weight-based ribavirin is recommended. | 12 weeks | IIa, C |

[a] For decompensated cirrhosis, please refer to the appropriate section.

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 |

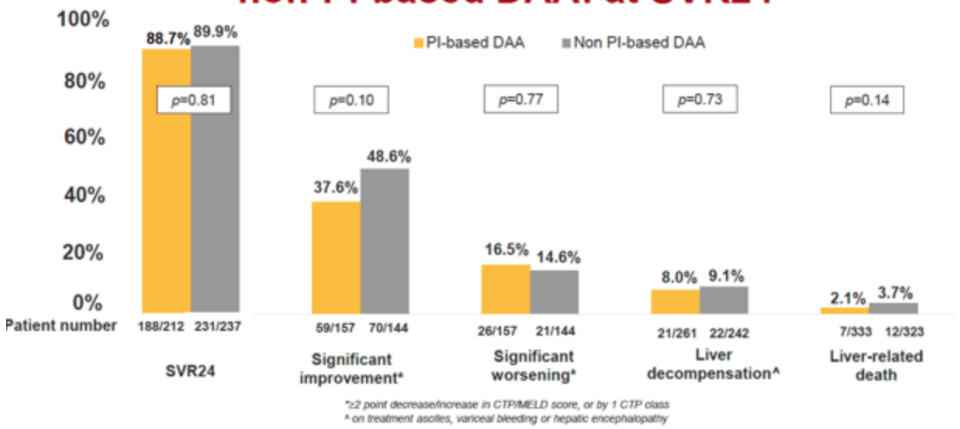
[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Extension of treatment to 24 weeks should be considered in extremely difficult cases (e.g., genotype 3 with cirrhosis) or failure following sofosbuvir plus glecaprevir/pibrentasvir.

# HCV PI vs Non-PI DAA in Advanced Cirrhosis - Outcomes Real-World REAL-C study

## Baseline characteristics (IPTW-Matched)

| Baseline characteristics (n=681) | | PI-based DAA (n=338) | Non PI-based DAA (n=343) | p-value |
|---|---|---|---|---|
| Child-Turcott-Pugh class | A | 180 (60.2) | 168 (55.6) | 0.09 |
| | B | 111 (36.9) | 112 (37.2) | |
| | C | 9 (2.7) | 22 (6.4) | |
| MELD score | <10 | 129 (32.6) | 81 (19.4) | <0.001 |
| | 10-15 | 185 (54.7) | 238 (69.2) | |
| | 16-20 | 13 (3.8) | 22 (6.6) | |
| | >20 | 30 (8.9) | 17 (4.8) | |
| Clinical decomp | Variceal bleeding | 36 (9.4) | 45 (13.1) | 0.28 |
| | Ascites | 88 (27.9) | 79 (25.4) | 0.60 |
| | HE | 28 (9.1) | 44 (14.6) | 0.07 |
| Albumin (g/L) | | 3.4 ± 0.7 | 3.5 ± 0.6 | 0.47 |
| INR (mean, SD) | | 1.2 ± 0.3 | 1.3 ± 0.3 | 0.04 |
| Platelets (x $10^9$/L) | | 111 ± 61 | 112 ± 93 | 0.97 |

## Clinical outcomes between PI versus non-PI-based DAA: at SVR24




## DAA regiments

| DAA regiments# (n, %) | PI-based DAA (n=456) | Non PI-based DAA (n=621) |
|---|---|---|
| Ombitasvir, Paritaprevir & Ritonavir +/- Dasabuvir | 140 (30.7) | 0 (0.0) |
| Daclatasvir/Asunaprevir | 133 (29.2) | 0 (0.0) |
| Glecaprevir/Pibrentasvir | 71 (15.4) | 0 (0.0) |
| Elbasvir/Grazoprevir | 70 (15.4) | 0 (0.0) |
| Sofosbuvir/Velpatasvir/Voxilaprevir | 11 (2.4) | 0 (0.0) |
| Sofosbuvir/Ledipasvir | 0 (0.0) | 284 (45.7) |
| Sofosbuvir/Velpatasvir | 0 (0.0) | 169 (27.2) |
| Sofosbuvir/Daclatasvir | 0 (0.0) | 59 (9.5) |
| Sofosbuvir/Ribavirin | 0 (0.0) | 109 (17.6) |

## Clinical outcomes Stratified by CTP-class

| Study outcomes, n (%) | Child's class B | | | Child's class C | | |
|---|---|---|---|---|---|---|
| | PI-based DAA | Non-PI-based DAA | P-value | PI-based DAA | Non-PI-based DAA | P-value |
| SVR12 | 89/99 (89.9) | 86/99 (86.9) | 0.42 | 5/8 (62.5) | 15/19 (78.9) | 0.49 |
| New Liver decompensation | 9/93 (9.7) | 7/83 (8.4) | 0.83 | 0/5 (0) | 1/14 (7.1) | 0.17 |
| Significant improvement | 41/78 (52.6) | 37/72 (51.4) | 0.99 | 1/3 (33.3) | 7/10 (70.0) | 0.52 |
| Significant worsening | 26/78 (33.3) | 11/72 (15.3) | 0.16 | 0/3 | 2/10 (20.0) | 0.05 |
| SAE | 0/86 | 0/108 | - | 0/7 | 0/19 | - |
| Death | 1/111 (0.9) | 7/110 (6.4) | 0.02 | 1/9 (11.1) | 3/22 (13.6) | 0.97 |

Wong YJ AASLD 2022

# Hepatitis C Resistance after 1st line treatment :

## Cons

Need to simplify treatment

Limited availability of RAS testing → VIRONET

The presence of RAS per se is not predictive of SVR to second line treatment

High response to to SOF/VEL/VOX in RCT and real life data (in Italy)

Third line treatment in case of SOF/VEL/VOX failure seems to be effective .

## Pros

It is necessary to verify all possible causes of virologic failure, including: incorrect GT, natural resistance, poor compliance, suboptimal treatment, potential drug-drug interactions.

HCV genotypic resistance test prior to retreatment can be helpful to make a decision. HCV resistance test at failure should be considered for all 3 HCV genes (NS3, NS5A, NS5B).

In DAA-failing patients, RASs prevalence is generally remarkably high, particularly in NS5A and may persist for long time of follow up.

**The frequent NS5A complex resistance and multi-class resistance advocate for tailored administration of drugs with different mechanisms of action based on expert guidance.**

In difficult-to-cure patients, (HCV G3 Cirrhotics failure to SOFVEL) the use of the two recommended regimens (sofosbuvir/velpatasvir/voxilaprevir, and glecaprevir/pibrentasvir + sofosbuvir) in combination with ribavirin and/or the extension of treatment to 16-24 weeks can increase the probability of achieving SVR.

**Resistance test can help to personalize the treatment by increasing probabilities of response according to the resistance profile observed in the context of an experienced multidisciplinary team (complexity: virus, host, clinical aspects, previous treatment outcome, DAAs available, comorbidity)**

# Il paziente fallito: strategie terapeutiche e discussione di casistica clinica – Messaggi Chiave

- Dimensioni del fenomeno: 2-4% → circa 5-10.000 pz in Italia
- Determinanti del fallimento terapeutico nell'epoca dei DAA pangenotipici : cirrosi HCV G3, RAS complesse
- Trattamento del paziente fallito:
  - SOF/VEL/VOX: Risultati dei trials clinici > 95% SVR
  - SOF/VEL/VOX: Dati real life
    - Identificazione di pazienti difficult to treat: HCV G3, Cirrosi, prima linea con SOF-VEL
  - SOF+ G/P possible terapia in casi selezionati ma dati da trials aneddotici
  - Terza linea di terapia dopo fallimento SOF/VEL/VOX → SOF/G/P + RBV x 12-24 settimane → dati aneddotici ma efficacia > 95%
- Linee guida
  - SOF/VEL/VOX seconda linea , SOF/G/P terza linea
  - RAS guided therapy → EASL si se disponibile AASLD no
- Cirrosi scompensata → se fallimento seconda linea SOF/VEL → triplice nei pz non candidabili a trapianto

- Determinazione RAS nel pz fallito più pros che cons se disponibile