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ORIGINAL ARTICLE

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

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Abstract

Sustained viral response (SVR) rates for direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) infection routinely exceed 95%. However, a small number of patients require retreatment. Sofosbuvir, velpatasvir and voxilaprevir (SOF/VEL/VOX) is a potent DAA combination primarily used for the retreatment of patients who failed by DAA therapies. Here we evaluate retreatment outcomes and the effects of resistance-associated substitutions (RAS) in a real-world cohort, including a large number of genotype (GT)3 infected patients. 144 patients from the UK were retreated with SOF/VEL/VOX following virologic failure with first-line DAA treatment regimens. Full-length HCV genome sequencing was performed prior to retreatment with SOF/VEL/VOX. HCV subtypes were assigned and RAS relevant to each genotype were identified. GT1a and GT3a each made up 38% (GT1a n = 55, GT3a n = 54) of the cohort. 40% (n = 58) of patients had liver cirrhosis of whom 7% (n = 4) were decompensated, 10% (n = 14) had hepatocellular carcinoma (HCC) and 8% (n = 12) had received a liver transplant prior to retreatment. The overall retreatment SVR12 rate was 90% (129/144). On univariate analysis, GT3 infection (50/62; SVR = 81%, p = .009), cirrhosis (47/58; SVR = 81%, p = .01) and prior treatment with SOF/VEL (12/17; SVR = 71%, p = .02) or SOF+DCV (14/19; SVR = 74%, p = .012) were significantly associated with retreatment failure, but existence of pre-retreatment RAS was not when viral genotype was taken into account. Retreatment with SOF/VEL/VOX is very successful for non-GT3-infected patients. However, for GT3-infected patients,

Abbreviations: SVR, sustained virological response; HCV, hepatitis C virus; DAA, direct-acting antiviral; RAS, resistance-associated substitutions; EASL, European Association for the Study of the Liver; AASLD, American Association for the Study of Liver Disease; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir; HCC, hepatocellular carcinoma; WGS, whole-genome sequencing; PHE, Public Health England; CVR, centre for virus research; GLUE, genes linked by underlying evolution; DCV, daclatasvir; GLE, glecaprevir; PIB, pibrentasvir.

particularly those with cirrhosis and failed by initial SOF/VEL treatment, SVR rates were significantly lower and alternative retreatment regimens should be considered.

KEYWORDS
direct-acting antivirals, hepatitis C virus, resistance-associated substitutions, retreatment

1 | INTRODUCTION

Sustained virological response (SVR) rates for patients chronically infected with hepatitis C virus (HCV) and treated with direct-acting antiviral (DAA) therapies in clinical trials and real-world cohorts are often >95%.[1-3] Treatment failure is associated with multiple host and viral factors including advanced fibrosis or cirrhosis, HCV subtype[4-6] and the presence of resistance-associated substitutions (RAS) in HCV-encoded proteins that are targeted by DAA.[7] This leaves a small percentage of HCV-infected patients who have been failed by first-line therapies and are therefore by definition "difficult to treat". For patients who have been failed by pan-genotypic regimens such as SOF/VEL and glecaprevir and pibrentasvir, (GLE/PIB) retreatment options are limited. Currently the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Disease (AASLD), recommend a combination of sofosbuvir, velpatasvir and voxilaprevir (SOF/VEL/VOX) for these patients.[8,9]

Retreatment of patients previously failed by predominantly first-generation NS5A inhibitor-containing DAA therapy with SOF/VEL/VOX has been evaluated in both the POLARIS-1 and POLARIS-4 phase-II and III studies.[10] In these studies, SOF/VEL/VOX showed a very high SVR rate in GT1-infected patients (222/228; 97% SVR); however, a slightly lower SVR rate was observed in GT3 patients (126/132; 95% SVR). In addition, a number of studies have evaluated the observed real-world outcomes of SOF/VEL/VOX retreatment. The largest cohort (n = 573) reported by Belperio et al,[11] showed lower SVR rates than in the POLARIS 1 and 4 studies for all genotypes (GT1: 429/473; 91% SVR, GT2: 18/20; 90% SVR, GT3: 42/46; 91% SVR, GT4: 12/12; 100% SVR). This study also showed that the SVR rate for those who had received SOF/VEL as first-line therapy, was reduced for GTs 1–3 (GT1: 15/19; 79% SVR, GT2: 13/15; 87% SVR, GT3: 11/13; 85% SVR). In an Italian cohort,[12] the SVR rate was 95% (162/169) with cirrhosis and hepatocellular carcinoma (HCC) being associated with treatment failure, however, there was no significant difference between the SVR rates of patients with different genotypes (GT1: 98/101; 97% SVR, GT2: 17/17; 100% SVR, GT3: 33/36; 91% SVR, GT4: 14/15; 93% SVR). Finally, Llaneras et al[13] reported an overall SVR rate of 95% (128/135) with 100% in patients with GT1 (82/82) and GT2 (7/7) infection, 80% (24/30) in GT3 and 93% (13/14) in GT4. SVR rates were significantly lower in patients with cirrhosis (89%, p = .05), or those with GT3 infection (80%, p < .001), whilst patients with GT3 infection and cirrhosis had the lowest SVR rate (69%).

Despite these studies there remains limited data on SOF/VEL/VOX retreatment from the real-world setting, particularly for patients with GT3 infection following unsuccessful therapy with pan-genotypic DAA regimens. These data are required to inform optimal retreatment strategies. In this paper, we report the outcomes of 144 patients failed by first-line DAA therapy and retreated with SOF/VEL/VOX. We then analyse the effect of clinical characteristics and RAS on SOF/VEL/VOX retreatment.

2 | METHODS

2.1 | Patients and samples

This study included 215 individuals from across England who did not achieve SVR with previous interferon-free DAA treatment. Blood samples were taken prior to retreatment and samples sent to Oxford and Glasgow for HCV whole-genome sequencing (WGS). Clinical, demographical and treatment outcome data were collected from patients, who were enrolled in HCV Research UK (n = 37), following informed consent and ethical approval.[14] For patients not enrolled in HCV Research UK, whole-genome HCV sequences and anonymised clinical data were provided by Public Health England (PHE), collected as part of the Virus Reference Department's HCV antiviral resistance testing service. This provides a clinical service for National Health Service Trusts, which send patients' blood samples for HCV genotyping and resistance testing by WGS and receive results in real time to inform clinical management. Approval for the use of data from this service was granted under Regulation 3 of the Health Service (Control of Patient Information) Regulations 2002. For retreatment, SVR has defined a minimum of 12 weeks after the end of treatment.

This project has been supported by the Hepatitis C Trust an organisation which campaigns for issues affecting patients with HCV in the UK. A patient representative was present at all STOP-HCV steering group committee meetings where the plans for this study were discussed in detail with direct patient involvement in the planning at all stages. In addition, both HCV Research UK and Public Health England have a Patient and Public Involvement Strategy and engage with patients and the public about how the data collected by them is used.

2.2 | Whole genome sequencing of HCV

Whole HCV genome sequencing was conducted at three sites to define HCV subtype and identify RAS: (i) The MRC-University of

Glasgow Centre for Virus Research (CVR), (ii) The Peter Medawar Building for Pathogen Research, University of Oxford, and (iii) The Virus Reference Department, National Infection Service, Public Health England. These sites have previously collaborated to ensure uniform standards for HCV sequencing.[15] Briefly, RNA was isolated from patient plasma samples and reverse transcribed to produce cDNA. An Illumina sequencing library was generated and enriched for HCV viral sequences using specific oligonucleotide probes. Illumina sequencing reads were then processed and mapped to the closest HCV reference genome. Precise details of how the sequencing was performed at each site are described in the supplementary materials.

2.3 | Resistance-associated substitution calling using HCV-GLUE

HCV subtypes were assigned and NS3, NS5A and NS5B RAS relevant to each genotype were identified (15% of reads cut off) using HCV-GLUE and RAS definitions provided by PHE[16] (Supplementary Table 3). A RAS was considered relevant if there is in-vitro evidence of a >50 Fold change in EC50 and/or in-vivo evidence that the RAS is treatment emergent or associated with treatment failure. HCV-GLUE is a resource created as part of the STOP-HCV consortium based on the GLUE (Genes Linked by Underlying Evolution) platform.[17] HCV-GLUE uses the ICCT HCV reference sequences and collates publicly available HCV sequences, to construct phylogenies using RAxML to assign sequences to HCV clades. It also contains a database of HCV RAS created by PHE[16] and this is used to identify RAS relevant to the HCV genotype and subtype.[18]

2.4 | Statistical analysis

All statistical analysis was performed using custom code and R version 3.6.2. Logistic regression was used for the analysis of association between categorical variables.

3 | RESULTS

3.1 | Baseline characteristics of patients

Outcomes were available for 144 patients who were retreated with SOF/VEL/VOX. The mean age was 56 years (49–63 IQR) with 84% (*n* = 121) of the cohort being male. Overall, 40% (*n* = 58) had cirrhosis, with 7% (*n* = 4) decompensated. Of 10% (*n* = 14) had HCC and 8% (*n* = 12) had received a liver transplant prior to retreatment (Table 1). The median time from the end of previous treatment to pre-retreatment sequencing analysis was 13 months (2–32 Range).

TABLE 1 Clinical characteristics of 144 patients prior to retreatment with SOF/VEL/VOX split by genotype

	GT1 (*n* = 66)	GT2 (*n* = 3)	GT3 (*n* = 62)	GT4 (*n* = 10)	GT6 (*n* = 3)
Demographics					
Median age (IQR), years	54 (48-60)	64 (56-67)	57 (51-62)	62 (57-75)	27 (27-44)
Sex: Male	86% (56/65)[a]	67% (2/3)	85% (53/62)	70% (7/10)	100% (3/3)
Liver disease State					
Cirrhosis	24% (16/66)	67% (2/3)	60% (37/62)	30% (3/10)	0% (0/3)
Decompensated cirrhosis	0% (0/16)	0% (0/2)	11% (4/37)	0% (0/3)	0% (0/0)
Hepatocellular carcinoma	9% (6/66)	0% (0/3)	13% (8/62)	0% (0/10)	0% (0/3)
Prior liver transplant	3% (2/66)	33% (1/3)	15% (9/62)	0% (0/10)	0% (0/3)
Mean baseline viral load, log10 IU/ml (IQR)	6.6 (6.0-6.7)	6.0 (5.9-6.2)	6.4 (5.5-6.5)	7.1 (5.6-6.7)	6.2 (6.0-6.3)
Previous DAA treatment regimen[b]					
SOF/LDV	38% (25/66)	-	10% (6/62)	40% (4/10)	-
SOF/VEL	2% (1/66)	-	26% (16/62)	-	-
GLE/PIB	2% (1/66)	-	24% (15/62)	-	100% (3/3)
SOF + DCV	-	-	31% (19/62)	-	-
EBR/GZR	15% (10/66)	-	-	20% (2/10)	-
OBV/PTVr +/- DAS	32% (21/66)	-	2% (1/62)	30% (3/10)	-
SOF	2% (1/66)	100% (3/3)	6% (4/62)	-	-
Unknown	11% (7/66)	-	2% (1/62)	10% (1/10)	-

Abbreviations: DAS, Dasabuvir; DCV, Daclatasvir; EBR, Elbasvir; GLE, Glecaprevir; GZR, Grazoprevir; LDV, Ledipasvir; OBV, Ombitasvir; PIB, Pibrentasvir; PTV, Paritaprevir; r, Ritonavir; SOF, Sofosbuvir; VEL, Velpatasvir.

[a]Data missing for one patient.

[b]Full breakdown of previous treatment regimens including ribavirin and interferon use are in Supplementary Table 1.

GT1a and GT3a were the two most common subtypes, each making up 38% (GT1a *n* = 55, GT3a *n* = 54) of the cohort, 17 other subtypes were identified from genotypes 1, 2, 3, 4 and 6, with GT1b, GT4r and GT3b making up 6% (*n* = 9), 4% (*n* = 6), and 3% (*n* = 5) of the cohort respectively (Figure 1).

3.2 | Effectiveness of retreatment with SOF/VEL/VOX

The overall SVR12 rate for patients retreated with SOF/VEL/VOX was 91% (*n* = 129) (Figure 2). The majority of patients who did not achieve an SVR (*n* = 15) experienced a post-treatment relapse (*n* = 10). One patient experienced an on-treatment breakthrough (patient's HCV RNA was undetectable during treatment and then became detectable again during treatment.) and two were non-responders (patients who never achieve undetectable HCV RNA). Relapse/breakthrough/non-response was not reported by the treating clinician for the remaining two patients. Poor adherence to retreatment was not reported for any of the patients who did not achieve an SVR.

Evaluating the factors associated with outcome using univariable logistic regression, GT3 infection (52/64; SVR = 81%, *p* = .009) and cirrhosis (47/58; SVR = 81%, *p* = .01) were both significantly associated with treatment outcome (Figure 3). Patients whose initial regimen was either SOF/VEL or SOF +DAC were also less likely to achieve SVR on retreatment (12/17, 71% = 0.02 and 14/19, 74%, *p* = .012 respectively). Patients with GT3 infection, cirrhosis and prior treatment with SOF/VEL had the lowest SVR rate of 42% (3/7). However, one of these patients only received 4 weeks of SOF/VEL/VOX (Supplementary Table 2). Multivariable analysis using logistic regression with SVR as the response variable and GT, presence/absence of cirrhosis and previous treatment regimen included as explanatory variables, revealed that prior treatment with SOF/VEL had the largest effect on SVR and remained the only variable significantly associated with outcome (*p* = .03) (Supplementary Figure 1). However, with the exception of one GT1 patient previously treated with SOF/VEL, all patients with prior SOF/VEL or SOF +DCV treatment had GT3 infection which confounded this result (Table 1). When GT3-infected patients were analysed separately, cirrhosis and prior treatment regimen were no longer significantly associated with outcome, in both the univariable and multivariable analysis.

3.3 | Effect of resistance-associated substitutions on retreatment outcome

Among the 144 patients retreated with SOF/VEL/VOX and with available outcomes, 70% (101/144) had detectable RAS prior to retreatment. 16% had NS3 inhibitor RAS, 51% NS5A inhibitor RAS and 34% SOF RAS. However, the majority of SOF RAS were detected in GT3a sequences (Supplementary Figure 2). Of the viral sequences in 15 patients failed by SOF/VEL/VOX retreatment, 12/15 (80%) had detectable RAS prior to retreatment compared to 89/129 (68%) in those subsequently achieving SVR. However, despite the high prevalence of RAS, the presence of a RAS in a particular protein or

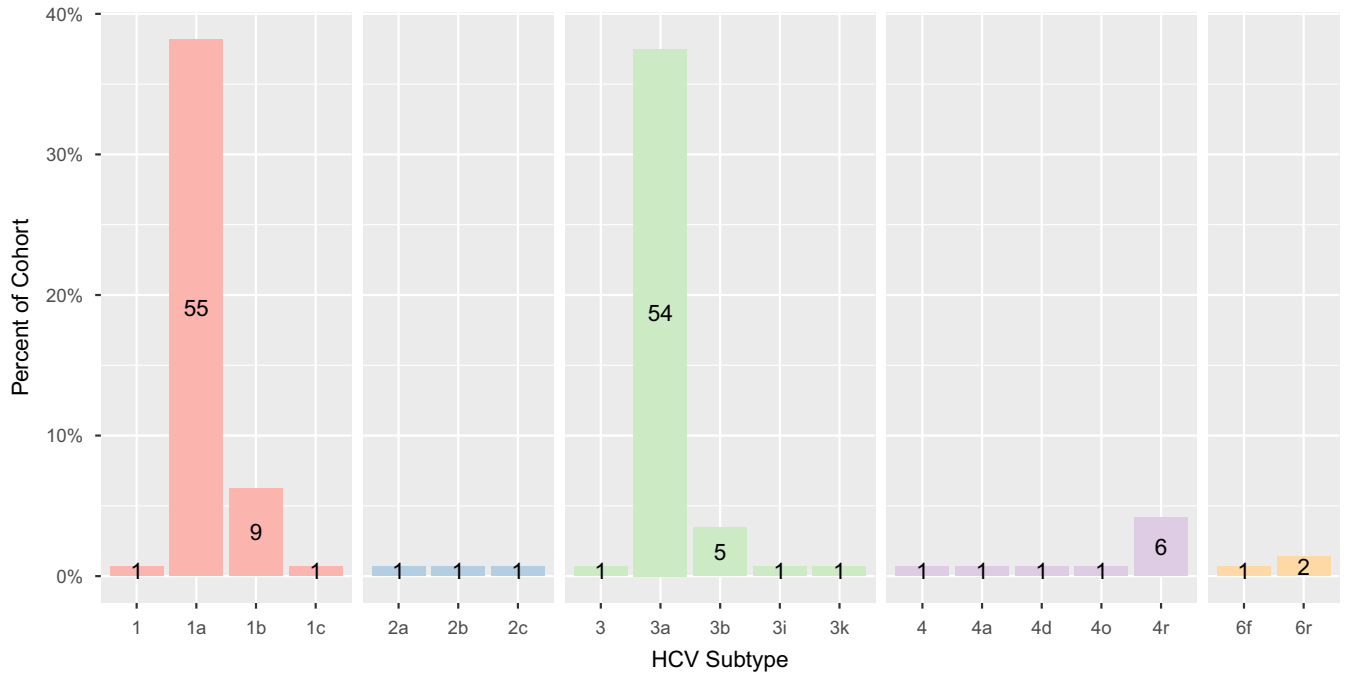

FIGURE 1 HCV Subtypes of the 144 patients failed by first-line DAA therapy and retreated with SOF/VEL/VOX. The percentage prevalence of each subtype is shown broken down by HCV genotype. Sequences which could not be assigned to subtypes have been labelled with the appropriate genotype

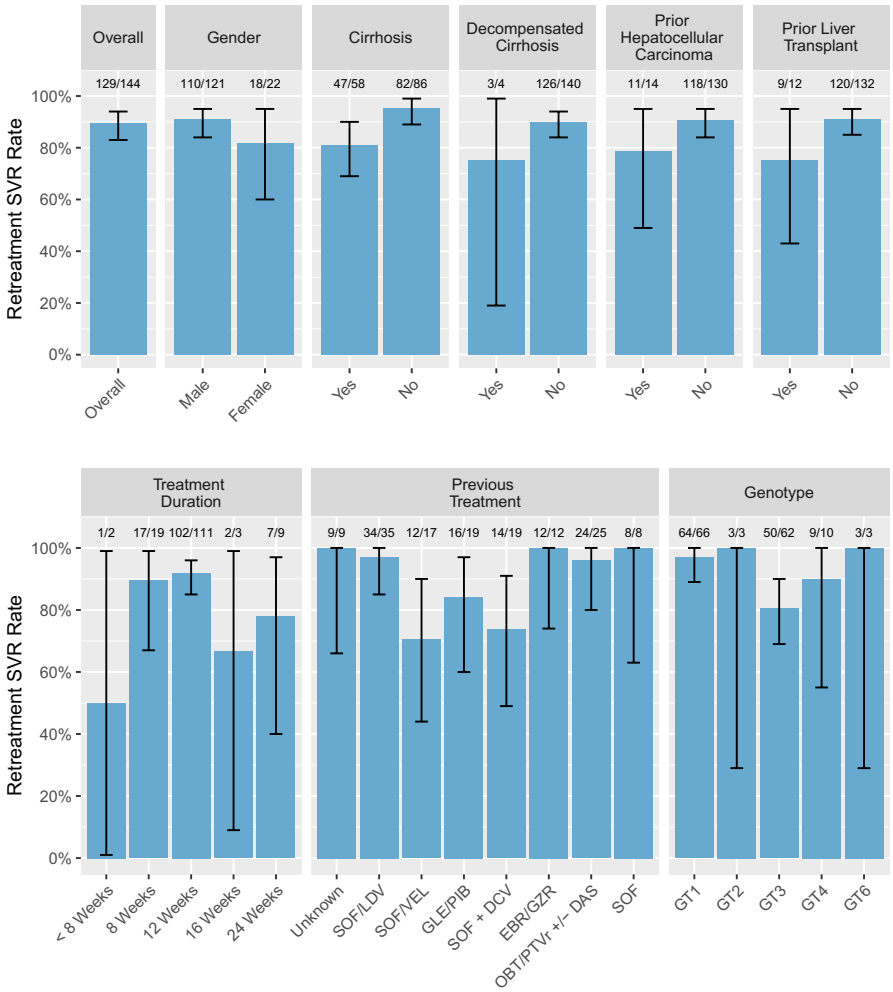

FIGURE 2 Retreatment SVR12 rates for patients retreated with SOF/VEL/VOX according to baseline and treatment characteristics for the whole cohort (n = 144). The SVR rate for each variable is shown with 95% confidence intervals shown. Daclatasvir (DCV), Sofosbuvir (SOF), Glecaprevir (GLE), Pibrentasvir (PIB), Grazoprevir (GZR), Elbasvir (EBR), Ledipasvir (LDV), Paritaprevir (PTV), Ombitasvir (OBV) Ritonavir (r), Dasabuvir (DAS), Velpatasvir (VEL)

combination of proteins was not significantly associated with the outcome (Table 2). When each RAS (Full list in Table 3) was considered independently using logistic regression, A30K and Y93H RAS in NS5A were associated with retreatment failure in the whole cohort (A30K p = .02, Y93H p = .01) (Table 3). The A30K RAS is unique to GT3a (it is wild-type in GT3b) and the Y93H substitution was much more common in GT3 patients compared to other genotypes (Supplementary Figure 2). When the analysis is limited to GT3 patients, the SVR rates for patients with these RAS were still reduced (for A30K SVR, 71% and Y93H SVR, 78%) but this was no longer statistically significant (A30K p = .2, Y93H p = .3). In addition, when the genotype is added as a cofactor to the logistic regression Y93H is no longer associated with the outcome. Whilst individually the A30K and Y93H RAS are common, the combination of A30K + Y93H is found rarely and is not associated with treatment outcome in this cohort (Supplementary Figure 3). No other RAS was significantly associated with outcome within the whole cohort or within a specific genotype of patients.

4 | DISCUSSION

This cohort represents both the largest reported cohort of patients retreated with SOF/VEL/VOX in the UK, and one of the largest cohorts of GT3-infected patients retreated with SOF/VEL/VOX. Our results show that retreatment of patients with SOF/VEL/VOX who have been failed by first-line therapy is very effective for GT1. However, patients with GT3 infection, cirrhosis or prior treatment with SOF/VEL or SOF +DCV have significantly lower SVR rates with SOF/VEL/VOX retreatment.

Our data shows that GT3-infected patients achieved lower SVR rates to SOF/VEL/VOX retreatment; the lowest SVR12 rates (42%) were observed in patients with GT3 infection, cirrhosis and prior SOF/VEL exposure. This is consistent with the data from Llaneras et al,[13] which also showed a SVR rate of 81% for GT3-infected patients and 69% for GT3-infected patients with cirrhosis. However, Papaluca et al[19] have shown an SVR rate of 90% in GT3 infected patients with cirrhosis. Belperio et al[11] have shown that GT1-infected patients with prior SOF/VEL exposure had a reduced SVR rate of 79% (15/19), yet a GT3-infected group with prior SOF/VEL exposure had a SVR rate of 85% (11/13) which is greater than the 75%(12/16) that was observed in our study but, these numbers remain small.

The overall prevalence of RAS was very high, but the presence of RAS in the NS3, NS5A or NS5B protein was not associated with SVR; this is in line with the analysis of RAS data from the POLARIS-1 and 4 studies by Sarrzin et al.[20] When RAS were analysed separately the presence of the NS5A inhibitor RAS Y93H was significantly associated with treatment failure across the

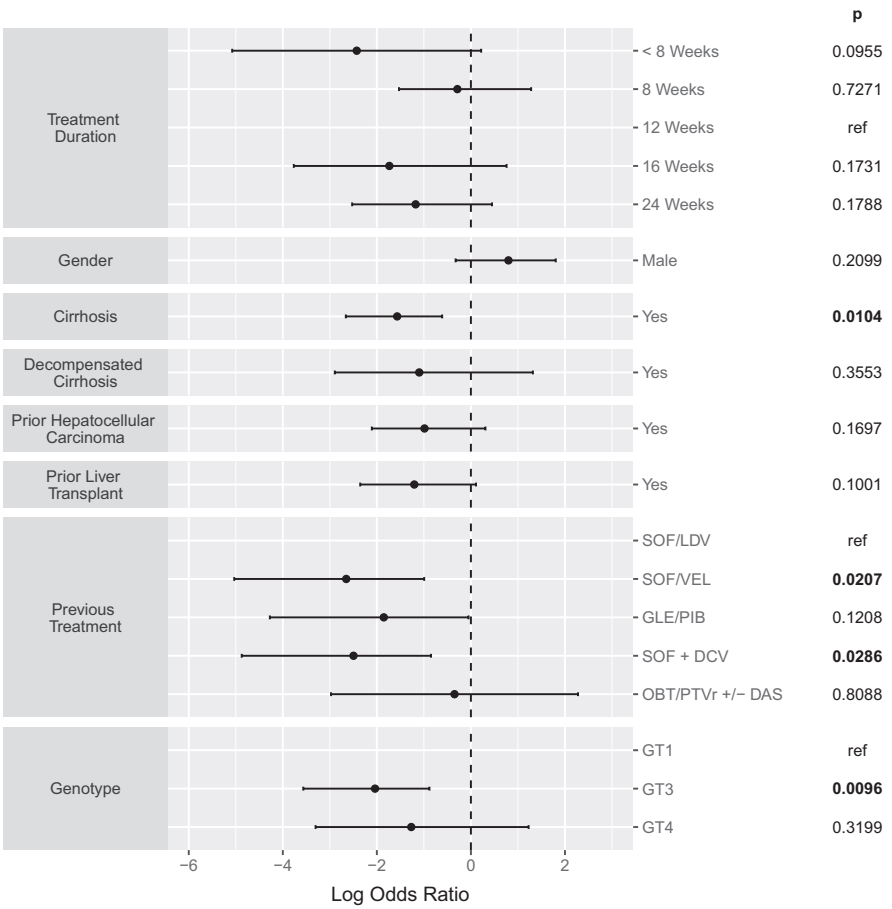

FIGURE 3 Univariate analysis of clinical factors associated with SVR for patients retreated with SOF/VEL/VOX according to baseline and treatment characteristics for the whole cohort (n = 144). The log odds ratio with 95% confidence intervals shown calculated using logistic regression. Values for which the SVR rate was 100% have not been included. Reference values used in regression when number of values is greater than two (ref), Daclatasvir (DCV), Sofosbuvir (SOF), Glecaprevir (GLE), Pibrentasvir (PIB), Grazoprevir (GZR), Elbasvir (EBR), Ledipasvir (LDV), Paritaprevir (PTV), Ombitasvir (OBV) Ritonavir (r), Dasabuvir (DAS), Velpatasvir (VEL)

TABLE 2 Prevalence of pre-retreatment RAS and SVR rates for patients retreated with SOF/VEL/VOX

Presence of RAS	Prevalence % (n)	SVR Rate % (n)	p	log Odds ratio	Standard error
No RAS	30% (43/144)	93% (40/43)	NA	NA	NA
NS3	16% (23/144)	100% (23/23)	.9	15.9	2062
NS5A	51% (74/144)	86% (64/74)	.3	−0.7	0.8
NS5B	34% (49/144)	84% (41/49)	.5	−0.5	0.96
NS3 + NS5A	8% (12/144)	100% (12/12)	.9	15.9	1882
NS3 + NS5B	0% (0/144)	NA	NA	NA	NA
NS5A + NS5B	22% (31/144)	80% (25/31)	.1	−1.1	0.75
NS3 + NS5A + NS5B	1% (1/144)	100% (1/1)	.9	15.9	6522

Logistic regression was used to test the association between presence of RAS in the NS3, NS5A and NS5B proteins with SVR.

whole cohort. However, when the genotype is included in the model used to test association, Y93H is no longer significantly associated with outcome. This data suggests that viral genotype is the more important viral factor for SOF/VEL/VOX retreatment outcome than the presence of RAS. PIB has been shown to be more effective than other NS5A inhibitors against viruses harbouring the Y93H RAS in-vitro.[21] This suggests that GLE/PIB may be a more effective treatment for patients with the Y93H RAS. Thus, RAS testing to guide retreatment therapy could be an effective way to increase retreatment SVR rates. One of the limitations of this study is that the time between previous treatment failure and pre-retreatment resequencing varied greatly in this cohort and in some cases was as long as 32 months. As RAS which have an effect on viral fitness tend to disappear over time, this study may underestimate the RAS present at previous DAA treatment failure.

At present SOF/VEL/VOX is the only recommended retreatment regimen for patients previously failed by a NS5A inhibitor-containing regimen in England. These data suggest that whilst SOF/VEL/VOX may be a preferred regimen for non-GT3 infected patients, an alternative retreatment regimen for GT3-infected patients should also be considered, particularly those with cirrhosis and previous exposure to a DAA regimen containing SOF/VEL or SOF +DCV. Prior exposure to NS5A inhibitors can result in the

TABLE 3 SVR rates for patients retreated with SOF/VEL/VOX with individual pre-retreatment RAS

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 $p<0.05$.

emergence and long-term presence of RAS[22,23] whereas the highly resistant SOF variant S282T in NS5B is rarely found after treatment failure and, when detected, it is more transient.[24,25] This would suggest that prior exposure to NS5A inhibitors in VEL/SOF and DCV +SOF regimens has a greater impact on retreatment. In addition to using SOF/VEL/VOX for 24 rather than 12 weeks or adding ribavirin,[26] one current alternative to SOF/VEL/VOX for GT3 patients is off-label use of GLE/PIB +SOF +/-RBV. This combination was effective in a small retreatment trial[27] and could represent an effective retreatment option for GT3 patients with prior exposure to SOF/VEL. Further retreatment options include adopting a resistance guided approach to treatment, increasing the SOF/VEL/VOX treatment duration or adding ribavirin. Where SOF/VEL/VOX retreatment has failed there are rescue therapy options. A recent study by Dietz J et al[28] also showed that SOF/VEL/VOX +/-RBV (Rescue SVR = 100% 4/4) and GLE/PIB +SOF +/-RBV (Rescue SVR = 79% 11/14) were effective rescue therapies in patients failed by SOF/VEL/VOX with GLE/PIB +/- RBV also being successfully used to retreat two patients.

In summary, our study shows that retreatment outcomes for patients failed by first-line DAA therapy are very successful for non-GT3-infected patients. However, for GT3-infected patients, particularly those with cirrhosis and failed by initial SOF/VEL treatment, SVR rates were significantly lower and alternative retreatment regimens such as GLE/PIB +SOF should be considered.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Clinical and viral sequencing data generated by HCVRUK and STOP-HCV can be requested at https://www.hcvresearchuk.org and https://www.expmedndm.ox.ac.uk/stop-hcv, respectively. The HCV-GLUE software used for resistance calling is available at http://hcv-glue.cvr.gla.ac.uk.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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