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ORIGINAL ARTICLE

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

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Abstract

Virological failure occurs in a small proportion of people treated for hepatitis C virus (HCV) with direct-acting antiviral (DAA) therapies. This study assessed retreatment for virological failure in a large real-world cohort. REACH-C is an Australian observational study ($n = 10,843$) evaluating treatment outcomes of sequential DAA initiations across 33 health services between March 2016 to June 2019. Virological failure retreatment data were collected until October 2020. Of 408 people with virological failure (81% male; median age 53; 38% cirrhosis; 56% genotype 3), 213 (54%) were retreated once; 15 were retreated twice. A range of genotype specific and pangenotypic DAAs were used to retreat virological failure in primary ($n = 56$) and tertiary ($n = 157$) settings. Following sofosbuvir/velpatasvir/voxilaprevir availability

Abbreviations: DAA, direct-acting antiviral; DCV, daclatasvir; ELB, elbasvir; GLE, glecaprevir; GP, general practitioner; GRZ, grazoprevir; GT, genotype; HCV, hepatitis C virus; IDU, injecting drug use; ITT, intention to treat; IFN, interferon; LDV, ledipasvir; OAT, opioid agonist therapy; PIB, pibrentasvir; PP, per-protocol; PrOD, paritaprevir/ritonavir/ombitasvir + dasabuvir; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virological response; VEL, velpatasvir; VOX, voxilaprevir

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in 2019, the proportion retreated in primary care increased from 21% to 40% and median time to retreatment initiation declined from 294 to 152 days. Per protocol (PP) sustained virological response (SVR12) was similar for people retreated in primary and tertiary settings (80% vs 81%; $p = 1.000$). In regression analysis, sofosbuvir/velpatasvir/voxilaprevir (vs. other regimens) significantly decreased likelihood of second virological failure (PP SVR12 88% vs. 77%; adjusted odds ratio [AOR] 0.29; 95%CI 0.11–0.81); cirrhosis increased likelihood (PP SVR12 69% vs. 91%; AOR 4.26; 95%CI 1.64–11.09). Indigenous Australians had lower likelihood of retreatment initiation (AOR 0.36; 95%CI 0.15–0.81). Treatment setting and prescriber type were not associated with retreatment initiation or outcome. Virological failure can be effectively retreated in primary care. Expanded access to simplified retreatment regimens through decentralized models may increase retreatment uptake and reduce HCV-related mortality.

KEYWORDS
direct-acting antivirals, HCV, primary care, retreatment, virological failure

1 | INTRODUCTION

Hepatitis C virus (HCV) infection is associated with increased risk of cirrhosis, hepatic decompensation and hepatocellular carcinoma.[1] The development of tolerable, highly effective direct-acting antiviral (DAA) therapies has transformed clinical management of HCV.[2] Substantial reductions in HCV prevalence, incidence and, importantly, HCV-related mortality have been reported following scale up of DAAs among key populations with transmission risk or advanced liver disease.[3–11] However, a small proportion of those treated do not achieve a sustained virological response (SVR12).[12] Among those with virological failure, risk of liver disease progression and premature mortality persist.[13–16]

In Australia, DAAs can be prescribed by any medical practitioner, including for retreatment of virological failure.[17,18] Within 4 years of unrestricted access, prescribing by general practitioners surpassed that of specialists, from 18% of prescriptions in March 2016 to over 50% by the end of 2019.[19] The changing prescribing patterns reflect an increasing shift from centralized tertiary-based models for provision of HCV care to decentralized primary care-based models.[20–22] There are several real-world studies assessing treatment uptake and outcomes in primary care[23,24] although currently there is limited data assessing retreatment for virological failure.

The real-world effectiveness of antiviral therapy in chronic hepatitis C (REACH-C) is an observational cohort that represents 14% ($n = 10{,}843/76{,}830$) of the Australian population treated with DAAs from March 2016 to June 2019.[25] The aim of this analysis is to evaluate virological failure occurrence, retreatment uptake and retreatment outcomes at a diverse range of primary and tertiary services in Australia.

2 | METHODS

2.1 | Study design and participants

REACH-C is an observational cohort study that included consecutive individuals initiating DAA therapy for HCV infection across 33 diverse health services in Australia between March 2016 to June 2019. Detailed methodology has been described previously.[26] In brief, data were collected at baseline treatment initiation and SVR12 assessment through a combination of retrospective and prospective means, primarily through review of medical records or clinic databases. If an individual was retreated, data were collected at retreatment initiation and retreatment SVR12 assessment. Data collected at treatment (or retreatment) initiation included demographic characteristics (age, gender, Indigenous identification, clinic attended, prescriber type, location of health service provision), cirrhosis, co-infection with human immunodeficiency virus (HIV), previous HCV treatment experience, recent injecting drug use (IDU; defined as in the 6 months prior to commencing DAA therapy), current opioid agonist therapy (OAT), HCV genotype (GT), previous HCV treatment (interferon-based or DAA) and prescribed DAA regimen, duration and date commenced. For individuals with quantifiable HCV RNA at SVR12, data on HCV genotype or sequencing (if performed by sites), treatment discontinuation, and other factors that may have contributed to treatment failure were collected. Treatment outcome, retreatment initiation, reason for retreatment and retreatment outcome data were collected until October 2020. Retreatment data was collected for individuals retreated at non-study sites and who remained engaged with the REACH-C study site providing initial treatment.

Government subsidized DAAs were made available through the Australian Pharmaceutical Benefits Scheme (PBS) from March 2016 under an unrestricted access scheme, with no limitations on the number of times an individual could be retreated.[18,27] Genotype specific DAAs were listed on the PBS from 2016, pangenotypic regimens from 2017 and the salvage regimen sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) from 2019 (Table S1). The choice of DAA regimen and duration was made by the treating clinician. A small number of individuals in REACH-C gained access to retreatment regimens prior to PBS listing dates through early access schemes and in some cases, prescribers constructed non-PBS listed salvage regimens. A small number of individuals entering REACH-C had been previously treated with DAAs through clinical trials or at non-study sites and received salvage regimens as initial treatment in the study.

Prescriber types were classified as HCV specialists (gastroenterologist, hepatologist, infectious disease physician), other specialists (general physician, drug and alcohol physician, sexual health physician, nurse practitioners, mental health practitioners) and general practitioners (GPs). Treatment settings were classified as tertiary services (specialist liver clinics) and primary services (general practice, community health clinics, sexual health services, drug and alcohol services, outreach services, telehealth services, Indigenous health services, mental health services, prisons). Location of health service provision (major city, regional or remote area) was classified according to Australian Bureau of Statistics Geography Standard.[28] Details of health services in REACH-C are available in Table S2.

2.2 | Case definitions

SVR12 was defined as HCV RNA below the lower limit of quantification ≥12 weeks post-treatment. Reinfection was defined as quantifiable HCV RNA after achieving SVR12 *or* quantifiable HCV RNA at SVR12 with an HCV strain distinct from the pre-treatment strain (identified by genotype/subtype switch or sequencing if available). Virological failure was defined as quantifiable HCV RNA at SVR12 assessment with the same genotype/subtype as pre-treatment (unless identified as reinfection by sequencing). Individuals discontinuing treatment early (defined as stopping treatment with >30% doses of treatment remaining) with quantifiable HCV RNA at SVR12 assessment were included as virological failures. HCV RNA results were not reported during or at end of treatment; therefore, sub-classification of virological failure as non-response, viral breakthrough or relapse was not possible. Sequencing of virological failure to exclude reinfection and identify resistance associated substitutions (RAS) was at the discretion of study sites. An individual was considered lost to follow-up if they did not have a documented HCV RNA test ≥12 weeks post-treatment.

2.3 | Statistical analysis

Categorical parameters were summarized as number and proportion. Continuous variables were summarized by median and interquartile range (IQR). Fishers exact test were used to determine associations between categorical variables. *T*-test were used to determine associations between continuous variables.

Analysis of treatment outcomes used two approaches:

(i) Per protocol (PP): included individuals who commenced DAA treatment and underwent assessment for virological response at least 12 weeks post-treatment
(ii) Intention-to-treat (ITT): included all individuals who commenced DAA treatment, including those who were lost to follow-up, died, or had an unknown SVR12 (assessed as not achieving SVR12).

The factors associated with virological failure for initial and retreatment regimen (second virological failure) were assessed using logistic regression. Covariates for inclusion in the regression analyses were selected a priori from demographic, clinical and treatment characteristics available in REACH-C. Adjusted odds ratios (AOR) were calculated using logistic regression controlling for variables with $p \leq 0.2$ in univariate analyses. Statistically significant factors were assessed at the $p \leq 0.05$ (two sided).

2.4 | Ethics statement

Ethical approval for the REACH-C study was obtained from; St Vincent's Hospital Sydney Human Research Ethics Committee (HREC/16/SVH/223), Aboriginal Health and Medical Research Council (1280/17), Northern Territory Department of Health and Menzies School of Health Research Human Research Ethics Committee (2018–3118), Central Australian Human Research Ethics Committee (CA-18-3172), Western Australian Aboriginal Health Ethics Committee, Kimberley Aboriginal Health Planning Forum (2018–008) and, Tasmanian Health and Medical Research Ethics Committee (H0017728).

3 | RESULTS

Of the 10,843 individuals initiating DAAs, 8829 achieved SVR12, 408 had virological failure, 22 had reinfection detected at SVR12, and 1584 had an unknown SVR12 outcome (Figure 1). In the overall study population (male 69%; median age 50 [IQR 41–57]), 22% had cirrhosis and 52% had GT1 infection (Table 1). The proportion of individuals initiating DAAs in primary care increased from 37% in 2016 to 65% in 2019. The proportion of virological failure following initial treatment among those with a known SVR12 outcome (PP population) was 4.4%, including 2.8% ($n = 140/4791$) for GT1, 6.1%

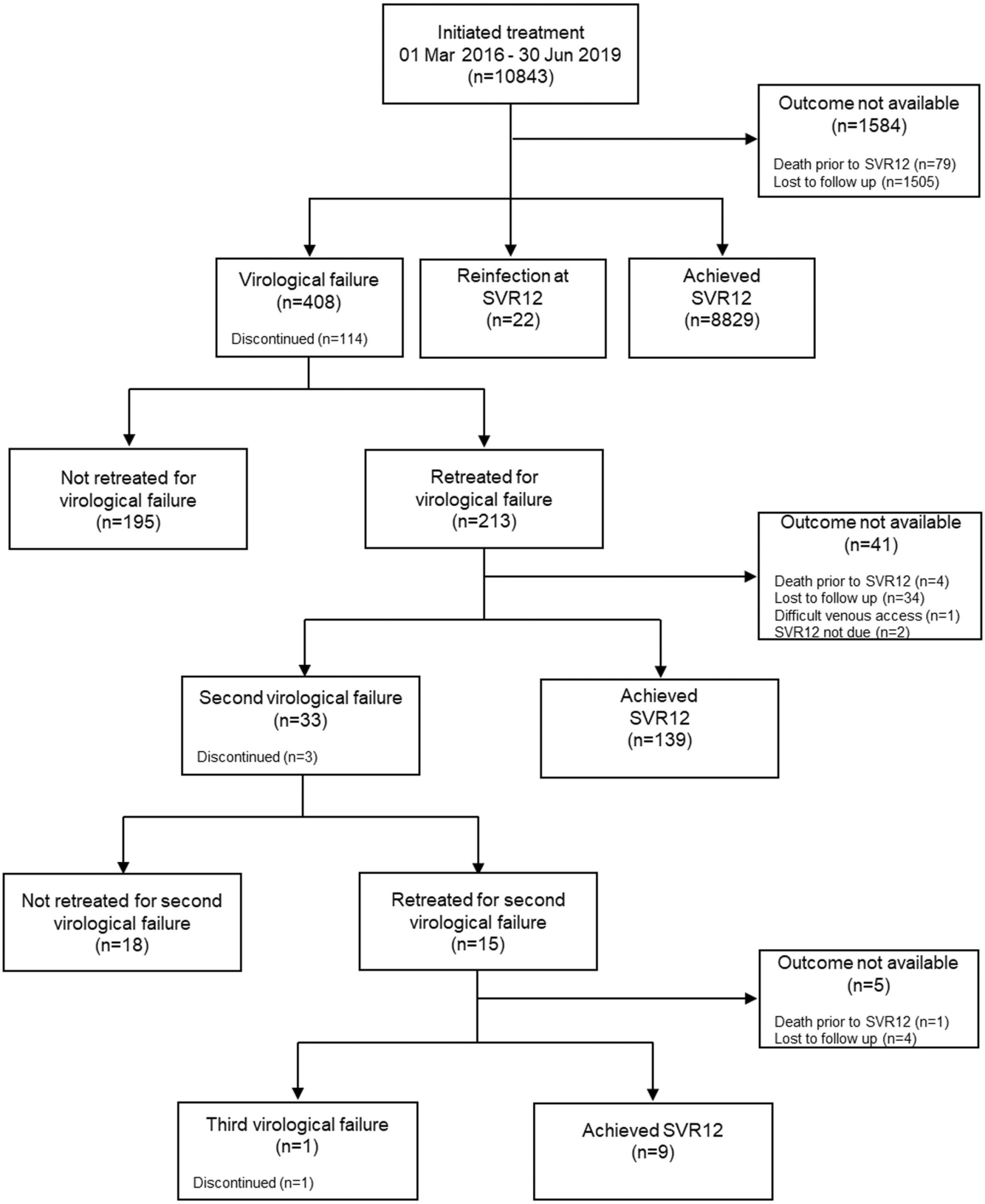

FIGURE 1 Overview of individuals receiving treatment in REACH-C. SVR12, sustained virological response

TABLE 1 Characteristics of individuals in REACH-C at commencement of initial treatment

Characteristic	Achieved SVR12 (*n* = 8829)	Virological Failure (*n* = 408)	Reinfection at SVR12 (*n* = 22)	Unknown SVR12 (*n* = 1584)	Total (*n* = 10,843)
Gender, *n* (%)					
Female	2786 (32)	78 (19)	5 (23)	472 (30)	3341 (31)
Male	6029 (68)	330 (81)	17 (77)	1108 (70)	7484 (69)
Other/unknown	14 (0)	0 (0)	0 (0)	4 (0)	18 (0)
Age, median (IQR)					
Age in years	51 (42–58)	53 (44–59)	36 (26–49)	45 (37–53)	50 (41–57)
Indigenous identifying, *n* (%)					
No	6649 (75)	320 (78)	12 (55)	1114 (70)	8095 (75)
Yes	673 (8)	36 (9)	5 (23)	201 (13)	915 (8)
Unknown	1507 (17)	52 (13)	5 (23)	269 (17)	1833 (17)
Recent injecting drug use, *n* (%)					
No	5921 (67)	299 (73)	3 (12)	784 (49)	7007 (65)
Yes	1265 (14)	71 (17)	17 (77)	422 (27)	1775 (16)
Unknown	1643 (19)	38 (9)	2 (10)	378 (24)	2061 (19)
Current opioid agonist therapy, *n* (%)					
No	6493 (74)	333 (82)	17 (77)	1046 (66)	7889 (73)
Yes	1521 (17)	57 (14)	4 (18)	355 (22)	1937 (18)
Unknown	815 (9)	18 (4)	1 (5)	183 (12)	1017 (9)
HIV coinfection, *n* (%)					
No	8054 (91)	383 (94)	20 (91)	1446 (91)	9903 (91)
Yes	359 (4)	11 (3)	1 (5)	26 (2)	397 (4)
Unknown	416 (5)	14 (3)	1 (5)	112 (7)	543 (5)
Cirrhosis, *n* (%)					
No	6909 (78)	252 (62)	17 (77)	1321 (83)	8499 (78)
Yes	1920 (22)	156 (38)	5 (23)	263 (17)	2344 (22)
Previous HCV treatment, *n* (%)					
No	7619 (86)	326 (80)	18 (82)	1475 (91)	9438 (87)
Yes-DAA	114 (1)	13 (3)	2 (9)	27 (2)	156 (1)
Yes-IFN based	1096 (12)	69 (17)	2 (9)	82 (5)	1249 (12)
Time period treatment commenced, *n* (%)					
2016–2017	7142 (81)	319 (78)	12 (55)	973 (61)	8446 (78)
2018–2019	1687 (19)	89 (22)	10 (45)	611 (39)	2397 (22)
Pre-treatment genotype, *n* (%)					
GT1	4791 (54)	140 (34)	14 (64)	722 (46)	5667 (52)
GT2	383 (4)	25 (6)	0 (0)	55 (3)	463 (4)
GT3	3369 (38)	227 (56)	8 (36)	748 (47)	4352 (40)
GT4-6	176 (2)	12 (3)	0 (0)	29 (2)	217 (2)
GT mixed/unknown	110 (1)	4 (1)	0 (0)	30 (2)	144 (1)
DAA regimen, *n* (%)					
SOF/LDV	3655 (41)	101 (25)	8 (36)	466 (29)	4230 (39)
SOF + DCV	2497 (28)	161 (40)	4 (18)	405 (26)	3067 (28)
PrOD	101 (1)	4 (1)	0 (0)	6 (0)	111 (1)

(Continues)

TABLE 1 (Continued)

Characteristic	Achieved SVR12 (*n* = 8829)	Virological Failure (*n* = 408)	Reinfection at SVR12 (*n* = 22)	Unknown SVR12 (*n* = 1584)	Total (*n* = 10,843)
GRZ/ELB ± SOF[a]	383 (4)	16 (4)	1 (5)	63 (4)	463 (4)
GLE/PIB ± SOF[b]	301 (3)	20 (5)	3 (14)	112 (7)	436 (4)
SOF/VEL ± VOX[c]	1695 (19)	84 (21)	6 (27)	516 (32)	2301 (39)
SOF + RBV ± IFN[d]	195 (2)	21 (5)	0 (0)	15 (1)	231 (2)
Other	2 (0)	1 (0)	0 (0)	1 (0)	4 (0)
Ribavirin added to DAA regimen, *n* (%)					
No	8386 (95)	359 (88)	21 (95)	1541 (97)	10,307 (95)
Yes	443 (5)	49 (12)	1 (5)	43 (3)	536 (5)
Prescribed treatment duration, *n* (%)					
8 weeks	1148 (13)	35 (9)	6 (27)	250 (16)	1439 (13)
12 weeks	6640 (75)	227 (68)	15 (68)	1234 (78)	8166 (75)
16–24 weeks	1041 (12)	96 (24)	1 (5)	100 (6)	1238 (11)
Treatment setting, *n* (%)					
Tertiary	4904 (56)	247 (61)	8 (36)	601 (38)	5760 (53)
Primary	3925 (44)	161 (39)	14 (64)	983 (62)	5083 (47)
Prescriber type, *n* (%)					
HCV specialist	5817 (66)	291 (71)	14 (64)	801 (51)	6923 (64)
Other specialist	1049 (12)	33 (8)	5 (23)	276 (17)	1363 (13)
GP	1963 (22)	84 (21)	3 (14)	507 (32)	2557 (24)
Location of health service provision, *n* (%)					
Major city	5728 (65)	233 (57)	14 (64)	969 (61)	6994 (64)
Regional or remote area	3101 (35)	175 (43)	8 (36)	615 (39)	3889 (36)

Abbreviations: DAA, direct-acting antiviral; DCV, daclatasvir; ELB, elbasvir; GLE, glecaprevir; GP, general practitioner; GRZ, grazoprevir; GT, genotype; HCV, hepatitis C virus; IFN, interferon; LDV, ledipasvir; PIB, pibrentasvir; PrOD, paritaprevir/ritonavir/ombitasvir + dasabuvir; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virological response; VEL, velpatasvir; VOX, voxilaprevir.

[a] GRZ/ELB + SOF (*n* = 11/463).

[b] GLE/PIB + SOF (*n* = 2/436).

[c] SOF/VEL/VOX (*n* = 26/2301).

[d] SOF + RBV + IFN (*n* = 7/231).

(*n* = 25/383) for GT2, 6.3% (*n* = 227/3369) for GT3, 6.4% (*n* = 12/176) for GT 4–6 and 3.5% (*n* = 4/110) for mixed or unknown GT.

3.1 | Virological failure characteristics, management and outcomes

Of the 408 individuals with virological failure (81% male; median age 53 [IQR 44–59]; Table 1), 38% had cirrhosis and 56% had GT3 infection. The proportion of virological failures identified in primary care settings increased from 34% in 2016–2017 to 64% in 2018–2019. Early discontinuation was reported in 114 (28%) individuals with virological failure and was more common in those with recent IDU than those without (45% vs 23%; $p < .001$) and those aged under 35 years (46% vs 26%; $p = .026$). The reported reasons for discontinuation were forgetting or running out of medication (22%), side effects (22%), mental health issues (9%), alcohol or drug use (5%), prison discharge or incarceration (5%), social issues (3%), hepatocellular carcinoma diagnosis (2%), other health priority (2%) and not specified (30%). All treatment discontinuations were among individuals receiving interferon-free regimens, but only a small number of individuals received interferon-containing regimens as their initial therapy within REACH-C (*n* = 7/10,843). Among individuals who discontinued due to side effects (*n* = 25), non-serious adverse events were reported among 52% (headache, nausea, vomiting, diarrhoea, dizziness, lethargy and rash), neuropsychiatric adverse events among 16% (insomnia, anxiety, agitation and suicidal ideation), serious adverse events among 12% (renal dysfunction and hepatic decompensation) were not specified in 20%.

TABLE 2 Factors associated with retreatment initiation among those with virological failure

Characteristic	Total virological failure ($n = 408$)	Untreated virological failure ($n = 195$)	Retreated virological failure ($n = 213$)	Odds ratio (95% CI)	*p*-value	Adjusted odds ratio (95%CI)	*p*-value
Gender, *n* (%)							
Female	78 (19)	37 (19)	41 (19)	1.00	–		
Male	330 (81)	158 (81)	172 (81)	0.98 (0.60–1.61)	.944		
Age, median (range)							
Age in years	53 (19–86)	51 (19–86)	55 (20–77)	1.03 (1.01–1.04)	.006	1.02 (0.99–1.04)	.169
Indigenous identifying, *n* (%)							
No	320 (78)	148 (76)	172 (81)	1.00	–	1.00	–
Yes	36 (9)	27 (14)	9 (4)	0.29 (0.13–0.63)	.002	0.36 (0.15–0.81)	.016
Unknown	52 (13)	20 (10)	32 (15)	1.38 (0.76–2.51)	.297	1.79 (0.88–3.64)	.108
Recent injecting drug use, *n* (%)							
No	337 (83)	159 (82)	176 (84)	1.00	–	1.00	–
Yes	71 (17)	36 (18)	35 (16)	0.70 (0.42–1.17)	.175	0.80 (0.44–1.43)	.444
Unknown	38 (9)	34 (17)	4 (2)	0.08 (0.03–0.24)	<.001	0.07 (0.02–0.21)	<.001
Current opioid agonist therapy, *n* (%)							
No	333 (82)	151 (77)	182 (85)	1.00	–	–	
Yes	57 (14)	31 (16)	26 (12)	0.70 (0.39–1.22)	.208		
Unknown	18 (4)	13 (7)	5 (2)	0.32 (0.03–0.24)	.034		
HIV coinfection, *n* (%)							
No	383 (94)	181 (93)	202 (95)	1.00	–		
Yes	11 (3)	4 (2)	7 (3)	1.57 (0.45–5.44)	.479		
Unknown	14 (3)	10 (5)	4 (2)	0.36 (0.03–0.24)	.087		
Cirrhosis, *n* (%)							
No	252 (62)	116 (59)	136 (64)	1.00	–		
Yes	156 (38)	79 (41)	77 (36)	0.83 (0.56–1.24)	.365		
Previous HCV treatment, *n* (%)							
No	326 (80)	152 (78)	174 (82)	1.00	–		
Yes, IFN based or DAA	82 (20)	43 (22)	39 (18)	0.79 (0.49–1.29)	.347		
Time period virological failure identified, *n* (%)							
2016–2017	271 (66)	125 (64)	146 (69)	1.00	–		
2018–2019	137 (34)	70 (36)	67 (31)	0.82 (0.54–1.24)	.343		
Genotype, *n* (%)							
GT1	140 (34)	67 (34)	73 (34)	1.00	–	1.00	–
GT2	25 (6)	8 (4)	17 (8)	1.95 (0.79–4.81)	.147	2.23 (0.79–6.26)	.129
GT3	227 (56)	114 (58)	113 (53)	0.91 (0.60–1.39)	.660	0.94 (0.60–1.47)	.770
GT4, GT6 or other	12 (4)	6 (3)	10 (5)	1.53 (0.53–4.44)	.434	1.69 (0.52–5.46)	.379
Treatment setting, *n* (%)							
Specialist clinic	161 (39)	78 (40)	83 (39)	1.00	–		
Primary clinic	247 (61)	117 (60)	130 (61)	0.96 (0.64–1.42)	.831		

(Continues)

TABLE 2 (Continued)

Characteristic	Total virological failure ($n = 408$)	Untreated virological failure ($n = 195$)	Retreated virological failure ($n = 213$)	Odds ratio (95% CI)	p-value	Adjusted odds ratio (95%CI)	p-value
Prescriber type, *n* (%)							
HCV specialist	291 (71)	140 (72)	151 (71)	1.00	–		
Other specialist	33 (8)	15 (8)	18 (8)	1.11 (0.54–2.29)	.772		
GP	84 (21)	40 (21)	44 (21)	1.02 (0.63–1.66)	.937		
Location of health service provision, *n* (%)							
Major city	233 (57)	104 (53)	129 (61)	1.00	–	1.00	–
Regional or remote area	175 (43)	91 (47)	84 (39)	0.74 (0.50–1.10)	.141	0.72 (0.46–1.13)	.157
Discontinued initial treatment, *n* (%)							
No	292 (72)	138 (71)	154 (72)	1.00			
Yes	116 (28)	57 (29)	59 (28)	0.93 (0.60–1.43)	.732		

Abbreviations: DAA, direct-acting antiviral; GP, general practitioner; GT, genotype; HCV, hepatitis C virus; IFN, interferon.

In logistic regression analysis, factors associated with increased likelihood of virological failure included male gender (AOR 1.87; 95%CI 1.44–2.42; $p < .001$), recent IDU (AOR 1.44; 95%CI 1.06–1.97; $p = .021$), cirrhosis (AOR 1.72; 95%CI 1.32–2.26; $p < .001$), GT3 (vs. G1; AOR 2.05; 95%CI 1.38–3.04; $p < .002$), treatment with sofosbuvir + ribavirin ± interferon (vs. sofosbuvir/ledipasvir [SOF/LDV]; AOR 3.42; 95%CI 1.48–7.98; $p = .004$), previous treatment with DAAs (AOR 2.21; 95%CI 1.20–4.06; $p = .011$) and treatment provision in a regional or remote location (vs. major cities; AOR 1.29; 95%CI 1.04–1.61; $p = .021$; Table S3). Treatment setting and prescriber type were not associated with virological failure.

Retreatment was initiated for 213 (52%) individuals with virological failure, in primary care (26%) and tertiary care (74%) settings. In logistic regression analysis, identifying as Indigenous (AOR 0.36 95%CI 0.15–0.81; $p = .016$) and having unknown IDU (AOR 0.07 95%CI 0.02–0.21; $p < .001$) were associated with decreased the likelihood of retreatment (Table 2). Initial treatment setting, prescriber type and initial treatment discontinuation were not associated with retreatment initiation.

Among those with virological failure identified in primary care ($n = 83$), 46% were referred to tertiary care. Among those with virological failure identified in tertiary care ($n = 130$), 8% were retreated in primary care. Referral to tertiary services decreased from 54% for virological failure identified in primary care in 2016–2017 to 33% for those identified 2018–2019. The proportion of virological failures retreated in primary care increased from 17% in 2016–2018 to 40% in 2019–2020 ($p < .001$). Compared to those retreated in tertiary care settings, a higher proportion retreated in primary care settings were younger, Indigenous, had recent IDU, or were receiving OAT (Table 3).

The median time from identification of virological failure to retreatment was 350 days (IQR 191–589; range 17–1136); including 407 days (IQR 252–652), 518 days (IQR 203–723), 294 days (IQR 188–477) and 152 days (IQR 82–232) for virological failures identified in 2016, 2017, 2018 and 2019, respectively. Sequencing for RAS was reported in 20%. The regimens used to retreat virological failure were SOF/VEL/VOX (39%), sofosbuvir/velpatasvir (SOF/VEL; 23%), glecaprevir/pibrentasvir±sofosbuvir (GLE/PIB ± SOF; 14%), grazoprevir/elbasvir±sofosbuvir (GRZ/ELB ± SOF; 14%), sofosbuvir + daclatasvir (5%), SOF/LDV (4%) and paritaprevir/ritonavir/ombitasvir + dasabuvir (1%). Those without treatment discontinuation ($n = 154$) were most commonly retreated with SOF/VEL/VOX 12-week duration (48%), whereas those with discontinuation ($n = 59$) were most commonly retreated with SOF/VEL 12-week (34%) and GLE/PIB 8-week durations (20%). Initial and retreatment regimens for GT1 and GT3 virological failures are displayed in Figure S1.

Of those retreated for virological failure ($n = 213$), 172 had a known retreatment outcome, 39 had an unknown outcome and two had not reached SVR12 at study close (Figure 1). PP SVR12 for retreatment of virological failure was 81%, and similar for those retreated in primary care or tertiary care settings (80% vs 81%; $p = 1.000$), and those with or without initial treatment discontinuation (82% vs 80%; $p = 1.000$; Figure 2). There was no significant difference in PP SVR12 for individuals with or without initial treatment discontinuation who were retreated with SOF/VEL/VOX (100% vs 86%; $p = 1.000$), SOF/VEL (72% vs 79%; $p = .720$), GLE/PIB ± SOF (75% vs 82%; $p = 1.000$) or GRZ/ELB ± SOF (100% vs 70%; $p = .290$).

ITT SVR12 was 66% and similar for those retreated in primary care or tertiary care settings (60% vs 68%; $p = .322$). Reasons for having an unknown retreatment outcome ($n = 39$), included lost to follow-up (87%), death (10%) and difficult venous access (3%). A higher proportion of those with an unknown retreatment outcome had recent IDU (29% vs 13% $p = .033$) or were aged under 35 years (17% vs 5%; $p = .018$).

TABLE 3 Characteristics of individuals retreated for virological failure by treatment setting at commencement of retreatment

Characteristic	Total retreated (*n* = 213)	Retreated in tertiary care (*n* = 157)	Retreated in primary care (*n* = 56)	*p*-value
Gender, *n* (%)				
Female	41 (19)	27 (17)	14 (25)	
Male	172 (81)	130 (83)	42 (75)	.237
Age at retreatment, median (range)				
Age in years	56 (22–78)	58 (30–74)	46 (22–78)	<.001
Indigenous Identifying, *n* (%)				
No	172 (81)	131 (83)	41 (73)	
Yes	9 (4)	3 (2)	6 (11)	.010
Unknown	32 (15)	23 (15)	9 (16)	
Recent injecting drug use, *n* (%)				
No	174 (82)	143 (91)	31 (55)	
Yes	35 (16)	11 (7)	24 (42)	<.001
Unknown	4 (2)	3 (2)	1 (2)	
Current opioid agonist therapy, *n* (%)				
No	183 (86)	148 (94)	35 (63)	
Yes	26 (12)	8 (5)	18 (32)	<.001
Unknown	4 (2)	1 (1)	3 (5)	
HIV coinfection, *n* (%)				
No	202 (95)	148 (94)	54 (100)	
Yes	7 (3)	7 (4)	0 (0)	.194
Unknown	4 (2)	2 (1)	2 (4)	
Cirrhosis, *n* (%)				
No	122 (57)	80 (51)	42 (75)	
Yes	91 (43)	77 (49)	14 (25)	.002
Previous treatment experience at baseline, *n* (%)				
No	174 (82)	127 (81)	47 (84)	
Yes, IFN based or DAA	39 (18)	30 (19)	9 (16)	.691
Time period virological failure identified, *n* (%)				
2016–2017	146 (69)	115 (73)	31 (55)	
2018–2019	67 (31)	42 (27)	25 (45)	.019
Time period retreatment commenced, *n* (%)				
2016–2018	125 (59)	104 (66)	21 (37)	
2019–2020	88 (41)	53 (34)	35 (63)	<.001
Genotype, *n* (%)				
GT1	73 (34)	59 (38)	14 (25)	
GT2	17 (8)	13 (8)	4 (7)	
GT3	113 (53)	75 (48)	38 (68)	
GT4, GT6	10 (5)	10 (6)	0 (0)	.031
DAA retreatment regimen, *n* (%)				
SOF/VEL	49 (23)	36 (23)	13 (23)	
SOF/VEL/VOX	82 (39)	61 (39)	21 (38)	
GLE/PIB ± SOF	30 (14)	17 (11)	13 (23)	.147

(Continues)

TABLE 3 (Continued)

Characteristic	Total retreated ($n = 213$)	Retreated in tertiary care ($n = 157$)	Retreated in primary care ($n = 56$)	p-value
GRZ/ELB ± SOF	29 (14)	25 (16)	4 (7)	
Other (SOF + DCV, SOF + LDV, PrOD)	23 (11)	18 (11)	5 (9)	
Ribavirin added to DAA retreatment regimen, *n* (%)				
No	179 (84)	128 (82)	51 (91)	
Yes	34 (16)	29 (18)	5 (9)	.067
Location of health service provision, *n* (%)				
Major city	129 (61)	91 (58)	38 (68)	
Regional or remote area	84 (39)	66 (42)	18 (32)	.207
Discontinued initial treatment, *n* (%)				
No	154 (72)	117 (75)	37 (66)	
Yes	59 (28)	40 (25)	19 (34)	.229

Abbreviations: DAA, direct-acting antiviral; DCV, daclatasvir; ELB, elbasvir; GLE, glecaprevir; GP, general practitioner; GRZ, grazoprevir; GT, genotype; HCV, hepatitis C virus; IFN, interferon; LDV, ledipasvir; PIB, pibrentasvir; PrOD, paritaprevir/ritonavir/ombitasvir + dasabuvir; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

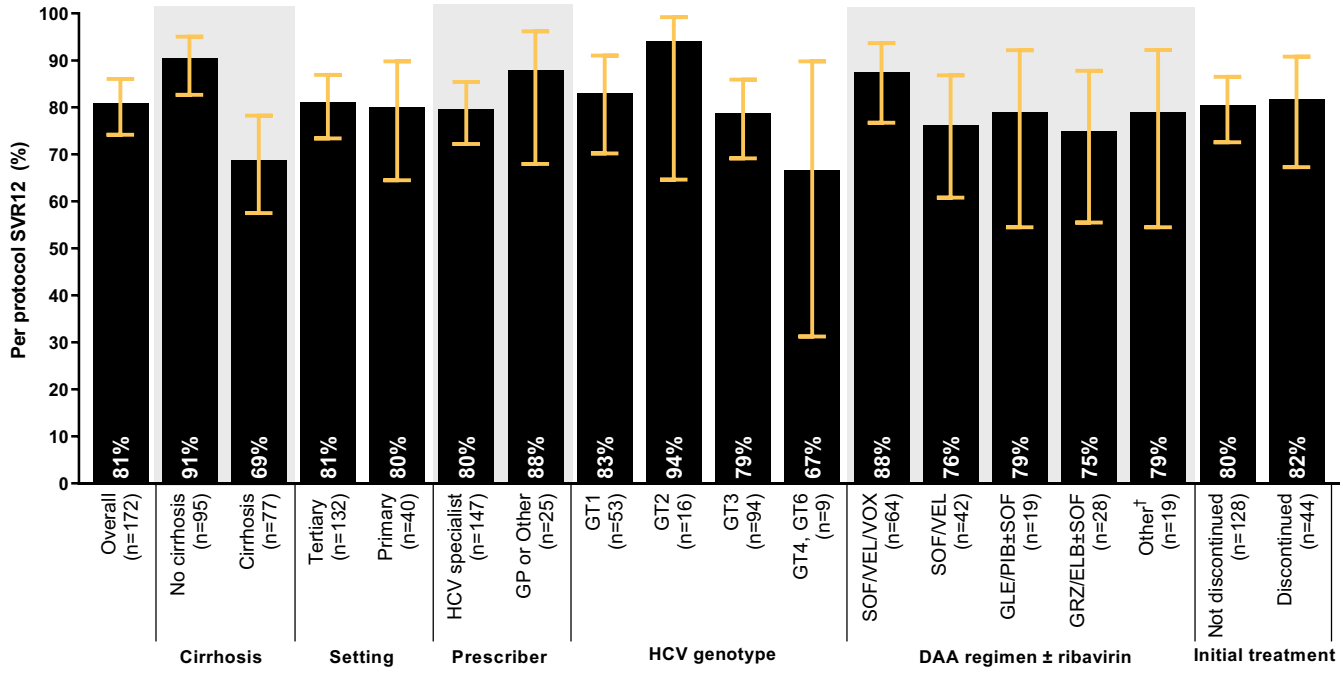

FIGURE 2 Per protocol SVR12 outcomes for retreatment of virological failure. †Other: sofosbuvir/daclatasvir, sofosbuvir/ledipasvir, paritaprevir/ritonavir/ombitasvir + dasabuvir. GLE, glecaprevir; GP, general practitioner; GT, genotype; HCV, hepatitis C virus; PIB, pibrentasvir; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virological response; VEL, velpatasvir; VOX, voxilaprevir

3.2 | Second virological failure characteristics, management and outcomes

Of those retreated for virological failure, 33 had second virological failure (male 89%; median age 57 years [IQR 54–63]; cirrhosis 73%; GT3 61%). Three individuals with second virological failure discontinued treatment due to mental health issues ($n = 1$), alcohol/drug use ($n = 1$) and side effect ($n = 1$). In logistic regression analysis, cirrhosis was associated with increased likelihood of second virological failure (AOR 4.26; 95%CI 1.64–11.09; $p = .003$), while SOF/VEL/VOX retreatment (vs. other regimens) with decreased likelihood (AOR 0.29; 95%CI 0.11–0.81; $p = .018$; Table 4). Retreatment setting and prescriber type were not associated with second virological failure.

Retreatment was initiated for fifteen (45%) individuals with second virological failure in tertiary (73%) and primary (27%) settings. The median time to second retreatment was 244 days (IQR 147–337;

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)	*p*-value	Adjusted AOR (95% CI)	*p*-value
Gender, *n* (%)							
Female (ref.)	29 (21)	4 (12)	33 (19)	1.00	–		
Male	110 (79)	29 (88)	139 (81)	1.91 (0.62–5.87)	.258		
Age at retreatment, median (IQR)							
Age in years	57 (47–61)	57 (54–63)	57 (48–61)	1.04 (1.00–1.09)	.051	1.03 (0.98–1.08)	.234
Indigenous identifying, *n* (%)							
No (ref.)	110 (79)	26 (79)	136 (79)	1.00	–		
Yes	7 (5)	1 (3)	8 (5)	0.60 (0.07–5.13)	.644		
Unknown	22 (16)	6 (18)	28 (16)	1.15 (0.43–3.13)	.779		
Recent injecting drug use, *n* (%)							
No (ref.)	115 (83)	30 (91)	145 (84)	1.00	–		
Yes	20 (14)	3 (9)	23 (13)	0.58 (0.16–2.06)	.396		
Unknown	4 (3)	0 (0)	4 (2)	–			
Current opioid agonist therapy, *n* (%)							
No (ref.)	119 (86)	30 (91)	154 (90)	1.00	–		
Yes	15 (11)	3 (9)	18 (10)	0.79 (0.22–2.92)	.728		
Unknown	5 (4)	0 (0)	5 (3)	–			
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
Genotype, *n* (%)							
GT1 (ref.)	44 (32)	9 (27)	53 (31)	1.00	–	1.00	–
GT2	15 (11)	1 (3)	16 (9)	0.33 (0.04–2.79)	.306	0.28 (0.03–2.59)	.260
GT3	74 (53)	20 (61)	94 (55)	1.32 (0.55–3.16)	.531	1.63 (0.63–4.26)	.315
GT4, GT6	6 (4)	3 (9)	9 (5)	2.44 (0.51–11.64)	.199	2.87 (0.47–17.31)	.251
DAA retreatment regimen ± ribavirin, *n* (%)							
SOF/VEL/VOX	56 (40)	8 (24)	64 (37)	0.43 (0.18–1.03)	.058	0.29 (0.11–0.81)	.018
Other regimens[a] (ref.)	83 (60)	25 (76)	108 (63)	1.00	–	1.00	–
Prescribed retreatment duration, *n* (%)							
8–12 weeks (ref.)	124 (89)	25 (76)	149 (87)	1.00	–	1.00	–
16–24 weeks	15 (11)	8 (24)	23 (13)	2.65 (1.01–6.91)	.047	1.16 (0.37–3.61)	.43
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		

(Continues)

TABLE 4 (Continued)

Characteristic	Achieved retreatment SVR12 (*n* = 139)	Second virological failure (*n* = 33)	Total (*n* = 172)	Unadjusted OR (95% CI)	*p*-value	Adjusted AOR (95% CI)	*p*-value
Location of health service provision, *n* (%)							
Major city (ref.)	84 (60)	19 (58)	103 (60)	1.00	–		
Regional or remote area	55 (39)	14 (42)	69 (40)	1.13 (0.52–2.43)	.764		
Discontinued initial treatment, *n* (%)							
No (ref.)	103 (74)	25 (76)	128 (74)	1.00	–		
Yes	36 (26)	8 (24)	44 (26)	0.92 (0.38–2.21)	.845		

Abbreviations: DAA, direct-acting antiviral; GP, general practitioner; GT, genotype; HCV, hepatitis C virus; IFN, interferon; SOF, sofosbuvir; SVR12, sustained virological response; VEL, velpatasvir; VOX, voxilaprevir.

[a] Other: sofosbuvir/velpatasvir (39%); grazoprevir/elbasvir + sofosbuvir (16%); glecaprevir/pibrentasvir (15%); grazoprevir/elbasvir (10%); sofosbuvir/daclatasvir (9%); sofosbuvir/ledipasvir (6%); glecaprevir/pibrentasvir + sofosbuvir (3%); paritaprevir/ritonavir/ombitasvir + dasabuvir (3%).

range 28–465). Sequencing for RAS was reported in 27%. Regimens used were SOF/VEL/VOX (73%), GLE/PIB (20%) and SOF/VEL (7%). Of those not retreated (*n* = 17), seven had major comorbidities (hepatocellular carcinoma [*n* = 3], non-Hodgkin lymphoma [*n* = 2], renal disease [*n* = 2]), three had ongoing heavy alcohol consumption, and three had difficulties with adherence.

Of those retreated for second virological failure (*n* = 15), ten had a known retreatment outcome and five had an unknown outcome. The PP SVR12 for retreatment of second virological failure was 90%. The PP SVR12 was 89% (*n* = 8/9) for SOF/VEL/VOX and 100% (*n* = 1/1) for GLE/PIB. The one individual failing second retreatment discontinued with >95% doses remaining and subsequently entered palliative care for hepatocellular carcinoma. ITT SVR12 for retreatment of second virological failure was 60%. Among those with an unknown retreatment outcome (*n* = 5), four were lost to follow-up and one died prior to SVR12.

4 | DISCUSSION

The REACH-C study has enabled real-world assessment of retreatment for virological failure within the context of unrestricted prescribing of DAAs. Retreatment was delivered through a diverse range of primary and tertiary health services with a per-protocol cure rate of around 80%. No impact of treatment setting or prescriber type on retreatment uptake or retreatment outcome was observed. These findings demonstrate the effectiveness of retreatment for virological failure delivered in primary care settings and support decentralization of HCV care at all stages of disease management.

Broad access to pangenotypic and salvage regimens during the later stages of the REACH-C study corresponded to increased prescribing of retreatment for virological failure, including within primary care. The proportion of virological failures retreated in primary care doubled from 17% in 2016–2018 to 40% in 2019–2020. Indicative of high potency, those retreated with SOF/VEL/VOX were less likely to have secondary virological failure than those retreated with other regimens. Prior to government subsidization of SOF/VEL/VOX in April 2019, a range of DAA regimens were used or constructed for retreatment.

As expected, the proportion of virological failures identified in primary care increased over time, as the proportion of initial treatments in primary care rose from 37% in 2016 to 65% in 2019. Reductions in median time to retreatment were observed following government subsidization of SOF/VEL/VOX, halving from 294 days for virological failures identified in 2018 to 152 days for those identified in 2019. As indication of increasing confidence to manage virological failure in primary care, the proportion of individuals referred to tertiary services for retreatment decreased from 54% for virological failures identified in 2016–2017 to 33% for those identified in 2018–2019. Despite this, approximately half of virological failures identified in REACH-C were not known to have been retreated by study end.

Patient, prescriber and setting level factors influence HCV treatment uptake,[29–31] a situation likely to be replicated for retreatment. Those not retreated likely comprise a diverse group that have disengaged from care, refused retreatment, were not considered suitable for retreatment by the prescriber or were retreated elsewhere. There was a lower likelihood of retreatment among those identifying as Indigenous, with a higher proportion receiving retreatment in primary care. Referral to tertiary services may represent a barrier to HCV care among the Indigenous population and further engagement of the primary care sector, including Indigenous health services, may improve retention in HCV care.[32–35] A lower likelihood of retreatment among those with unknown recent IDU, likely reflects higher engagement with health services among those retreated and more complete data being available.

Although not broadly available until early 2019, SOF/VEL/VOX was most commonly prescribed for virological failure (39%) and most effective (PP SVR12 88%). Similarly high effectiveness of SOF/VEL/VOX was reported in real-world cohorts of virological failures

from the United Kingdom (PP SVR12 90%, $n = 144$) with comparable cirrhosis and GT3 distribution.[36] Although some real-world studies have reported PP SVR12 rates similar to clinical trials (>95%),[37–40] our findings are encouraging given the lack of exclusion criteria in REACH-C, the diverse range of prescriber types and treatment settings and the inclusion of treatment discontinuations in PP SVR12 assessment. Lower cure rates were observed for those retreated with other regimens (PP SVR12 76–79%) in REACH-C. Sequencing guided retreatment for virological failure with extended duration first-line regimens can provide cure rates comparable to SOF/VEL/VOX[41]; however, this approach is resource intensive, requiring specialist expertise and infrastructure not readily available in many settings. Sequencing was performed in a minority of virological failures within REACH-C, even in the setting of second treatment failure. By contrast, simplified pangenotypic salvage regimens can be prescribed without complex clinical assessment and as demonstrated in this analysis, by any prescriber, in any clinical setting.

Those entering REACH-C with previous DAA experience had increased likelihood of virological failure, potentially due to the presence of RAS or advanced liver disease.[36–39] The prevalence of cirrhosis increased from 22% in the overall REACH-C cohort, to 38% among those with virological failure, to 76% among those with second virological failure. Those with cirrhosis were more likely to have virological failure, with this association further strengthened in the context of second virological failure and consistent with real world studies from other settings.[36,42] Considering the high prevalence of cirrhosis among those with second virological failure, retreatment cure rates were particularly encouraging (PP SVR12 90%), with the only individual failing second retreatment discontinuing with >95% doses remaining.

Although recent IDU was not associated with retreatment initiation or retreatment outcome, those with recent IDU had increased likelihood of virological failure, likely relating to higher rates of treatment discontinuation. Additionally, higher lost to follow-up following treatment (24%) and retreatment (29%) was observed. Community based services capable of addressing the complex health needs of people who inject drugs may be uniquely positioned to both prevent and retreat non-adherent virological failures. On-treatment support delivered through a low-threshold, multidisciplinary service yielded high adherence among a marginalized population with high prevalence injecting risk behaviours, homelessness and mental health diagnoses.[43]

Whilst acknowledging that referral to tertiary services will be necessary to manage complex cases of virological failure, our findings clearly support building retreatment capacity within primary care. In recent meta-analyses, provision of HCV care through decentralized models was associated with increased uptake of initial treatment and consistently high cure rates.[23,24] Aside from the potential to improve retreatment uptake among key populations, retreating in primary care would likely result in greater cost-effectiveness. In a study randomizing patients to primary or tertiary models for HCV care, total economic costs of treatment initiation in primary care were less than half those of tertiary care.[44] International HCV treatment guideline recommendations for retreatment of virological failure through tertiary care services and with viral sequencing[45] should be reconsidered given our study findings.

A strength of REACH-C was consecutive sampling at a diverse range of sites and lack of any exclusion criteria, providing a representative sample of virological failures, retreatment uptake and retreatment outcomes. However, this study has several limitations. Firstly, HCV RNA results were not collected during treatment or at end of treatment; therefore, differentiation of virological failure as non-response, viral breakthrough or relapse was not possible. Secondly, sequencing of virological failure was at discretion of study sites and although data were requested on whether sequencing was performed, results of this were not systematically reported. As such, we were unable to determine the prevalence of RAS among those with virological failure or assess the impact on retreatment outcome. There was potential for misclassification of reinfection at SVR12 with the same pre-treatment genotype as virological failure, however, given the low rate of reinfection by SVR12 in this cohort the impact was expected to be minimal. Thirdly, with exception of treatment discontinuation among virological failures, adherence was not systematically captured, nor was consumption of alcohol during treatment. Fourthly, primary care providers in REACH-C were higher caseload prescribers, whose knowledge and experience managing HCV likely differed from lower caseload prescribers. As such, retreatment uptake through these services may differ from lower caseload services. Finally, if an individual was retreated outside the REACH-C network and no longer engaged with the service providing initial treatment this was not reported.

In conclusion, virological failure can be effectively retreated in primary care with comparable outcomes to those reported in tertiary settings. Retreatment will be essential to reduce HCV-related disease and mortality among those with virological failure. Access to affordable salvage regimens, including through decentralized models of care, will be key to optimizing virological failure retreatment uptake and outcomes on a global scale.

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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 on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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