# Real world efficacy of antiviral therapy in chronic hepatitis C in Australia

**Issue #1** July 2017[1]

## Uptake and outcomes of new treatment for chronic hepatitis C during 2016 in the REACH-C network

The REACH-C project comprises a national network of diverse clinical services. Within the network, 1618 individuals initiated direct acting antiviral (DAA) treatment for chronic hepatitis C virus (HCV) infection between March and December 2016. Of these individuals, 70% were men, 56% were ≥50 years old and 19% had cirrhosis. The majority of individuals (84%) had not received prior HCV therapy. The most commonly prescribed regimen was sofosbuvir/ledipasvir (56%), followed by sofosbuvir/daclatasvir (41%). A portion of individuals were treated outside of guidelines, including 12% prescribed sofosbuvir/daclatasvir for 24 weeks who were eligible for a 12-week course due to genotype 3 infection and no cirrhosis. Of individuals expected to reach 12 weeks post-treatment (SVR12) by 31 March 2017, treatment outcomes were unknown in 19%. In 1167 individuals with known treatment outcomes, 96.5% achieved SVR12. SVR12 rates were high across all baseline characteristics with a slight reduction in SVR12 in those with cirrhosis vs no cirrhosis (93% vs 97%) and in treatment-experienced individuals vs treatment-naïve (92% vs 98%). SVR12 rates were similar in those with and without HIV (98% vs 96%), on OST (98% vs 96%) and with a history of injecting in the last 6 months (99% vs 96%). People who inject drugs were more likely to have a missing SVR12 outcome (33%) than individuals who do not inject drugs (14%).

1. The Kirby Institute. Real world efficacy of antiviral therapy in chronic hepatitis C in Australia (Issue 1). The Kirby Institute, UNSW Sydney, Sydney, NSW, Australia, July 2017 (available online at: https://kirby.unsw.edu.au). For more information, contact Associate Professor Gail Matthews (gmatthews@kirby.unsw.edu.au) or Jasmine Skurowski (jskurowski@kirby.unsw.edu.au).

Since March 2016, new treatments for chronic hepatitis C virus (HCV) have been listed on the Pharmaceutical Benefits Scheme (PBS). These direct acting antiviral (DAA) therapies included sofosbuvir/ledipasvir (Harvoni®), sofosbuvir/daclatasvir (Sovaldi®/Daklinza®), sofosbuvir/ribavirin (Sovaldi®/Ibavyr®), and sofosbuvir/pegylated interferon-alfa-2a/ribavirin (Sovaldi®/Pegysus®/ribavirin) in March 2016, ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira PAK®) in May2016 and elbasvir/grazoprevir (Zepatier®) in January 2017.

The REACH-C project comprises an observational cohort from a national network of ten diverse clinical services, including tertiary clinics, general practice and drug and alcohol centres. Details of participating clinics are given in Table 1.

Data reported by the REACH-C network was used to describe the characteristics of individuals initiating treatment between March and December 2016. For individuals who commenced treatment during this period and expected to reach 12 weeks post-treatment (SVR12) by 31 March 2017, treatment outcomes were also evaluated.

## Hepatitis C DAA treatment uptake

Across Australia, an estimated 32,400 individuals initiated treatment for chronic hepatitis C from March to December 2016[2]. Of these individuals, 57% were over 50 years old and 66% were men.

Within the REACH-C network, 1618 individuals initiated chronic HCV therapy between March and December 2016. Fifty six percent were aged 50 years or older and 70% were male (Table 2). HCV genotype was reported as 1 and 3 in 57% and 37% of individuals, respectively. These characteristics are similar to the overall Australian population that initiated DAA treatment in 2016.

In the REACH-C cohort, 8% were coinfected with HIV, 19% were engaged in opioid substitution therapy (OST) and 15% had injected drugs in the past 6 months. The majority of individuals (84%) had not received any prior HCV therapy.

The most commonly prescribed regimen was sofosbuvir/ledipasvir (56%), followed by sofosbuvir/daclatasvir (41%). Of the individuals who were treated with sofosbuvir/ledipasvir, 26% received 8 weeks of treatment and 9% received 24 weeks.

Based on treatment guidelines[3], it was expected that the majority of individuals prescribed sofosbuvir/daclatasvir for 24 weeks would be genotype 3-infected individuals with cirrhosis. However, 12% of those who received sofosbuvir/daclatasvir for 24 weeks were genotype 3 without cirrhosis.

Table 1. Details of REACH-C clinics

| Clinic | Patients | Location | Type of service/s |
|---|---|---|---|
| Cairns and Hinterland HHS | 608 | Cairns, QLD | Tertiary, sexual health, outreach specialist, drug and alcohol, prison |
| Royal Adelaide Hospital | 113 | Adelaide, SA | Tertiary |
| St Vincent's Hospital | 426 | Sydney, NSW | Tertiary, drug and alcohol |
| Scope Gastroenterology | 171 | Melbourne, VIC | Private specialist practice |
| Prince St Medical Centre | 82 | Orange, NSW | General practice |
| Toormina Medical Centre | 34 | Coffs Harbour, NSW | General practice |
| The Byrne Surgery | 28 | Sydney, NSW | General practice |
| Kirketon Road Centre | 111 | Sydney, NSW | Primary care |
| Langton Centre | 34 | Sydney, NSW | Drug and alcohol |
| Matthew Talbot Hostel | 10 | Sydney, NSW | Primary care |

2. The Kirby Institute. Monitoring hepatitis C treatment uptake in Australia (Issue 7). The Kirby Institute, UNSW Sydney, Sydney, NSW, Australia, July 2017
3. Pharmaceutical Benefits Scheme. General statement for drugs for the treatment of hepatitis C. Canberra: PBS, 1 June 2017. Available at http://www.pbs.gov.au/info/healthpro/explanatory-notes/general-statement-hep-c [Accessed 22 June 2017]

Table 2. Baseline characteristics for all patients who commenced treatment during March to December 2016 (n=1618) by regimen

| Characteristic | All patients (n=1618) | SOF/LDV 8 weeks (n=232) | SOF/LDV 12 weeks (n=595) | SOF/LDV 24 weeks (n=83) | SOF+DCV 12 weeks (n=479) | SOF+DCV 24 weeks (n=184) | Other (n=45) |
|---|---|---|---|---|---|---|---|
| **Age, n (%)** | | | | | | | |
| >=50 years | 899 (55.6) | 102 (44.0) | 388 (65.2) | 65 (78.3) | 189 (39.5) | 118 (64.1) | 37 (82.2) |
| <50 years | 703 (43.4) | 129 (55.6) | 198 (33.3) | 18 (21.7) | 286 (59.7) | 65 (35.3) | 7 (15.6) |
| Unknown | 16 (1.0) | 1 (0.4) | 9 (1.5) | 0 (0) | 4 (0.8) | 1 (0.5) | 1 (2.2) |
| **Gender, n (%)** | | | | | | | |
| Male | 1129 (69.8) | 135 (58.2) | 432 (72.6) | 59 (71.1) | 330 (68.9) | 141 (76.6) | 32 (71.1) |
| Female | 483 (29.9) | 97 (41.8) | 160 (26.9) | 24 (28.9) | 146 (30.5) | 43 (23.4) | 13 (28.9) |
| Transgender | 5 (0.3) | 0 (0) | 2 (0.3) | 0 (0) | 3 (0.6) | 0 (0) | 0 (0) |
| Unknown | 1 (0.1) | 0 (0) | 1 (0.2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **HIV status n (%)** | | | | | | | |
| Positive | 123 (7.6) | 2 (0.9) | 54 (9.1) | 7 (8.4) | 47 (9.8) | 13 (7.1) | 0 (0) |
| Negative | 1478 (91.3) | 228 (98.3) | 530 (89.1) | 75 (90.4) | 430 (89.8) | 171 (92.9) | 44 (97.8) |
| Unknown | 17 (1.0) | 2 (0.9) | 11 (1.8) | 1 (1.2) | 2 (0.4) | 0 (0) | 1 (2.2) |
| **Stage of liver disease, n (%)** | | | | | | | |
| No or mild fibrosis (F0-F1) | 677 (41.8) | 148 (63.8) | 241 (40.5) | 5 (6.0) | 260 (54.3) | 7 (3.8) | 16 (35.6) |
| Moderate fibrosis (F2) | 200 (12.4) | 25 (10.8) | 93 (15.6) | 5 (6.0) | 61 (12.7) | 10 (5.4) | 6 (13.3) |
| Advanced fibrosis (F3} | 131 (8.1) | 8 (3.4) | 49 (8.2) | 6 (7.2) | 42 (8.8) | 18 (9.8) | 8 (17.8) |
| Cirrhosis (F4) | 240 (14.8) | 1 (0.5) | 66 (11.1) | 48 (57.8) | 10 (2.1) | 107 (58.2) | 8 (17.8) |
| Unknown | 370 (22.9) | 50 (21.6) | 146 (24.5) | 19 (22.9) | 106 (22.1) | 42 (22.8) | 7 (15.6) |
| **HCV genotype, n (%)** | | | | | | | |
| 1 | | | | | | | |
| 1a | 734 (45.4) | 190 (81.9) | 457 (76.8) | 63 (75.9) | 18 (3.8) | 4 (2.2) | 2 (4.4) |
| 1b | 136 (8.4) | 36 (15.5) | 83 (13.9) | 7 (8.4) | 2 (0.4) | 0 (0) | 8 (17.8) |
| 1, not specified | 47 (2.9) | 4 (1.7) | 34 (5.7) | 6 (7.2) | 0 (0) | 3 (1.6) | 0 (0) |
| 2 | 68 (4.2) | 0 (0) | 0 (0) | 0 (0) | 33 (6.9) | 2 (1) | 33 (73.3) |
| 3 | 601 (37.1) | 2 (0.9) | 4 (0.7) | 4 (4.8) | 420 (87.7) | 170 (92.4) | 1 (2.2) |
| 4 | 11 (0.7) | 0 (0) | 6 (1.0) | 2 (2.4) | 2 (0.4) | 0 (0) | 1 (2.2) |
| 5 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| 6 | 6 (0.4) | 0 (0) | 6 (1.0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Other | 2 (0.2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (1.0) | 0 (0) |
| Unknown | 13 (0.8) | 0 (0) | 5 (0.8) | 1 (1.2) | 4 (0.8) | 3 (1.6) | 0 (0) |
| **HCV RNA, n (%)** | | | | | | | |
| <6 million IU/mL | 748 (46.2) | 161 (69.4) | 216 (36.3) | 30 (36.1) | 225 (47.0) | 84 (45.7) | 32 (71.1) |
| >6 million IU/mL | 215 (13.3) | 6 (2.6) | 108 (18.2) | 21 (25.3) | 47 (9.8) | 27 (14.7) | 6 (13.3) |
| Unknown | 655 (40.5) | 65 (28.0) | 271 (45.6) | 32 (38.5) | 207 (43.3) | 73 (39.6) | 7 (15.5) |
| **Previous HCV therapy, n (%)** | | | | | | | |
| No | 1361 (84.1) | 230 (99.1) | 503 (84.5) | 32 (38.6) | 423 (88.3) | 135 (73.4) | 38 (84.4) |
| Yes, interferon-containing | 177 (10.9) | 2 (0.9) | 63 (10.6) | 33 (39.8) | 42 (8.8) | 34 (18.5) | 3 (6.7) |
| Yes, interferon- free | 10 (0.6) | 0 (0) | 1 (0.2) | 5 (6.0) | 0 (0) | 3 (1.6) | 1 (2.2) |
| Yes, no specified | 62 (3.8) | 0 (0) | 23 (3.9) | 13 (15.7) | 12 (2.5) | 12 (6.5) | 2 (4.4) |
| Unknown | 8 (0.5) | 0 (0) | 5 (0.8) | 0 (0) | 2 (0.4) | 0 (0) | 1 (2.2) |
| **IDU past 6 months, n (%)** | | | | | | | |
| Yes | 246 (15.2) | 46 (19.8) | 82 (13.8) | 5 (6.0) | 84 (17.5) | 25 (13.6) | 4 (8.9) |
| No | 1050 (64.9) | 148 (63.8) | 400 (67.2) | 67 (80.7) | 277 (57.8) | 120 (65.2) | 38 (84.4) |
| Unknown | 322 (19.9) | 38 (16.3) | 113 (19.0) | 11 (13.3) | 118 (24.6) | 39 (21.2) | 3 (6.7) |
| **Current OST, n (%)** | | | | | | | |
| Yes | 312 (19.3) | 45 (19.4) | 106 (17.8) | 7 (8.4) | 110 (23.0) | 39 (21.2) | 5 (11.1) |
| No | 1091 (67.4) | 161 (69.4) | 410 (68.9) | 68 (81.9) | 293 (61.1) | 119 (64.7) | 40 (88.9) |
| Unknown | 215 (13.3) | 26 (11.3) | 79 (13.3) | 8 (9.6) | 76 (15.9) | 26 (14.1) | 0 (0) |

SOF: Sofosbuvir; LDV: Ledipasvir; DCV: Daclatasvir; IDU: injecting drug use; OST: opioid substitution therapy

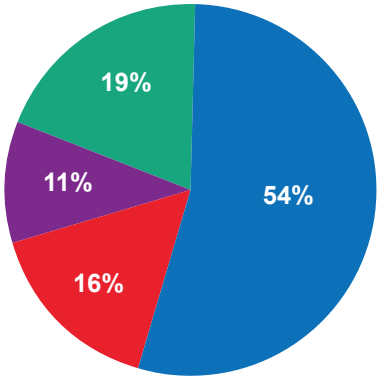



Figure 1. Distribution of liver disease in all patients who commenced treatment in 2016 (n=1618)

F0-1: No or mild fibrosis

F2: Moderate fibrosis

F3: Advanced fibrosis

F4: Cirrhosis

*Unknown: n=370*

## Hepatitis C DAA treatment regimens for genotype 1

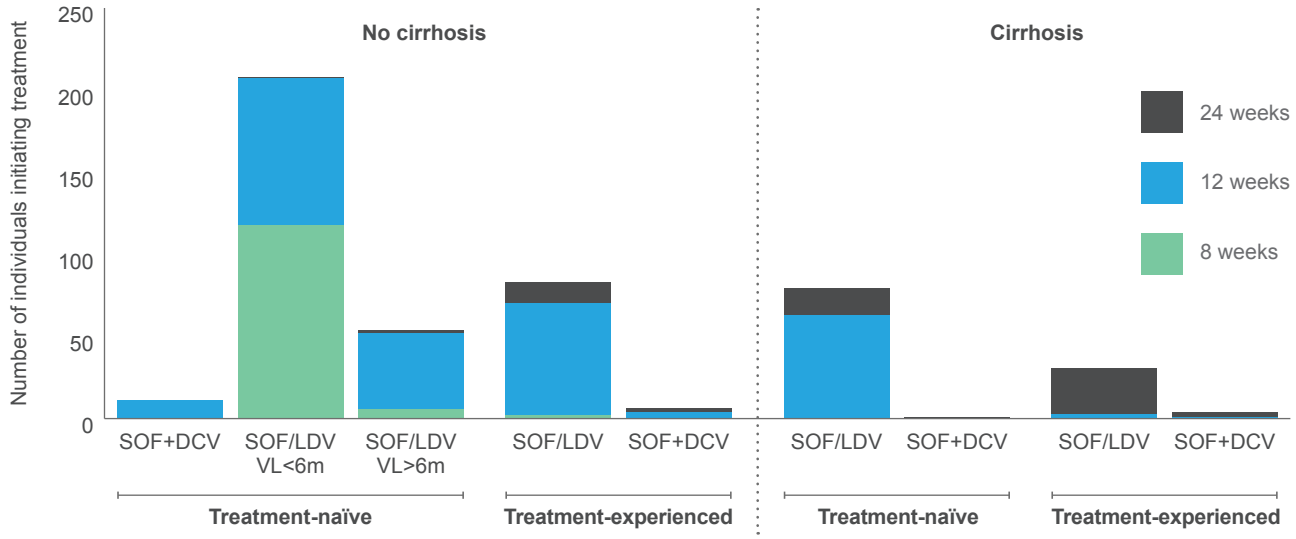
Of the 917 individuals with genotype 1, 52% (n=477) had details of all clinical characteristics, including HCV RNA level, relevant to treatment prescription.

Sofosbuvir/ledipasvir prescribed for treatment-naïve individuals without cirrhosis and with pre-treatment HCV RNA <6 million IU/mL, may be delivered as an 8-week treatment course[4]. Of the 208 individuals eligible for 8 weeks of treatment, 57% received an 8-week course, 43% a 12-week course and <1% a 24-week course (Figure 2).

All treatment-naïve individuals without cirrhosis who were prescribed sofosbuvir/daclatasvir received it for 12 weeks, in accordance with treatment guidelines[4].

Thirty five treatment-experienced individuals with cirrhosis commenced treatment with sofosbuvir/ledipasvir (89%) or sofosbuvir/daclatasvir (11%). The majority received a 24-week treatment course (89%), the recommended duration for both regimens in this subgroup[4].

Figure 2. Prescribed treatment durations for all Genotype 1 patients with details of relevant clinical characteristics who initiated treatment from March to December 2016 (n=477)



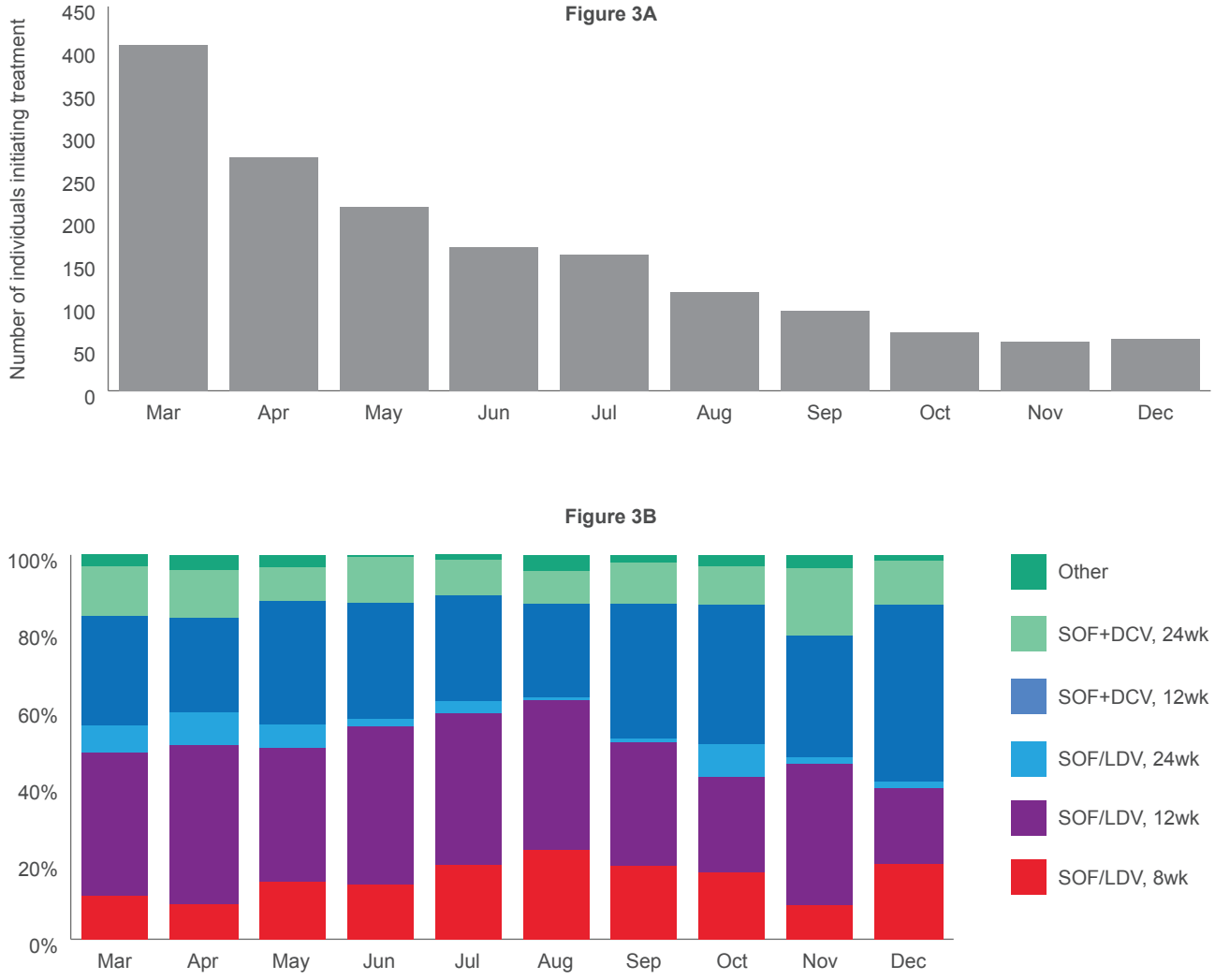

SOF: Sofosbuvir; LDV: Ledipasvir; DCV: Daclatasvir; VL<6m: HCV RNA viral load <6million IU/mL; VL>6m: HCV RNA viral load >6million IU/mL

4. Pharmaceutical Benefits Scheme. General statement for drugs for the treatment of hepatitis C. Canberra: PBS, 1 June 2017. Available at http://www.pbs.gov.au/info/healthpro/explanatory-notes/general-statement-hep-c [Accessed 22 June 2017]

## Hepatitis C DAA treatment uptake throughout 2016

Individuals initiating DAA treatment was highest in March (25%), followed by April (17%) and May (13%; Figure 3). The initial decreasing trend, which reached a relative plateau around October, is consistent with Australia-wide PBS data[5]. This results from a "warehouse" effect, where large numbers of patients awaiting access to DAAs were treated in the initial months of PBS listing.

Figure 3. Number of individuals initiating treatment (A) and distribution of regimen and duration (B) in each month during March to December 2016 (n=1618)




SOF: Sofosbuvir; LDV: Ledipasvir; DCV: Daclatasvir

5. The Kirby Institute. Monitoring hepatitis C treatment uptake in Australia (Issue 7). The Kirby Institute, UNSW Sydney, Sydney, NSW, Australia, July 2017

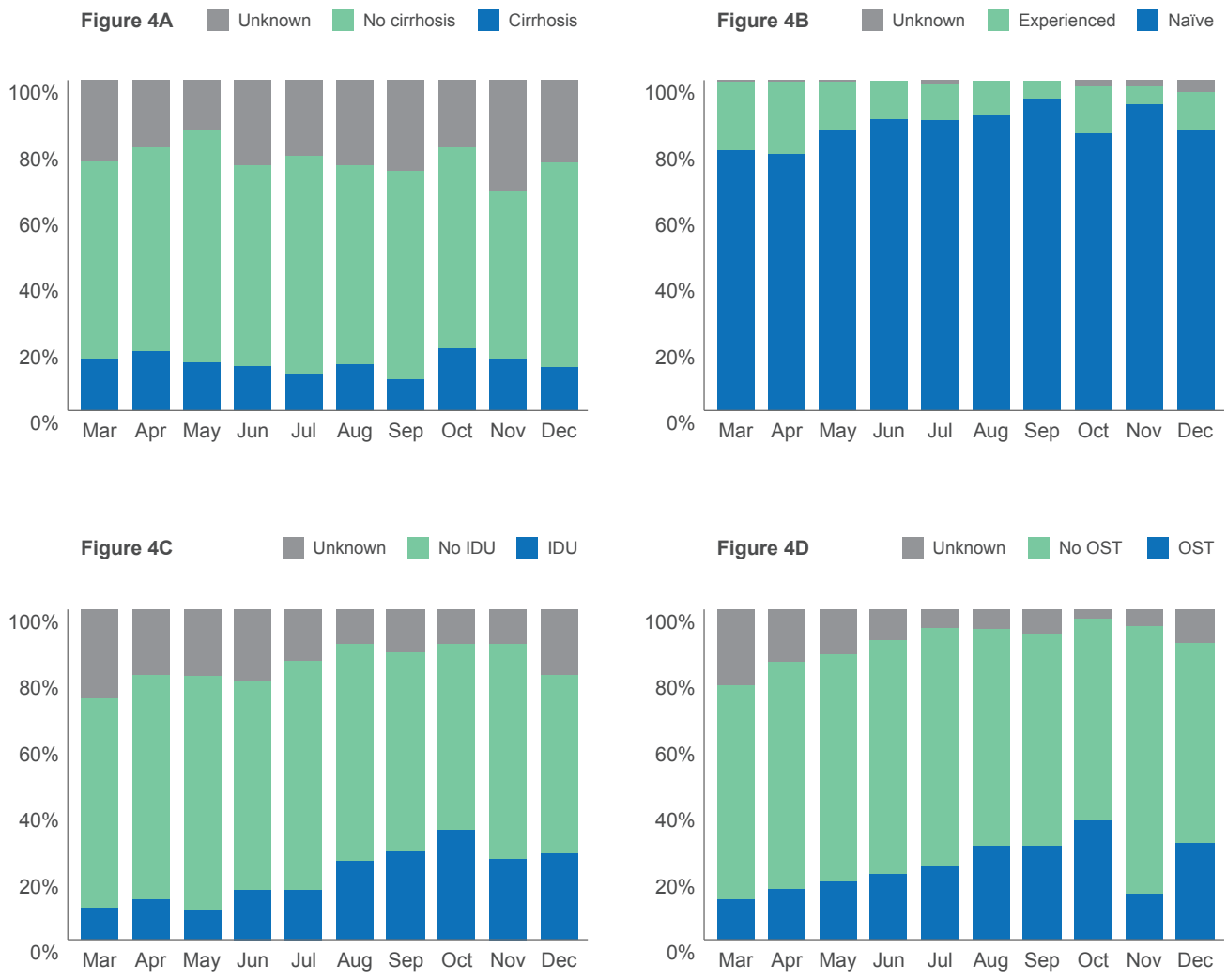
## Hepatitis C DAA treatment uptake throughout 2016 by clinical characteristics

The proportion of individuals commencing treatment with cirrhosis fluctuated between 10 and 19% each month, and the proportion of those who were treatment-experienced averaged 15% across the year (Figure 4).

Nineteen percent of individuals initiating DAA treatment were receiving OST and 15% had injected in the previous 6 months.

There were no obvious trends in treatment uptake over time based on clinical characteristics.

Figure 4. Distribution of individuals initiating treatment in each month during March to December 2016, by cirrhosis status (A), HCV treatment history (B), injecting drug use in the past 6 months (C) and current OST (D).



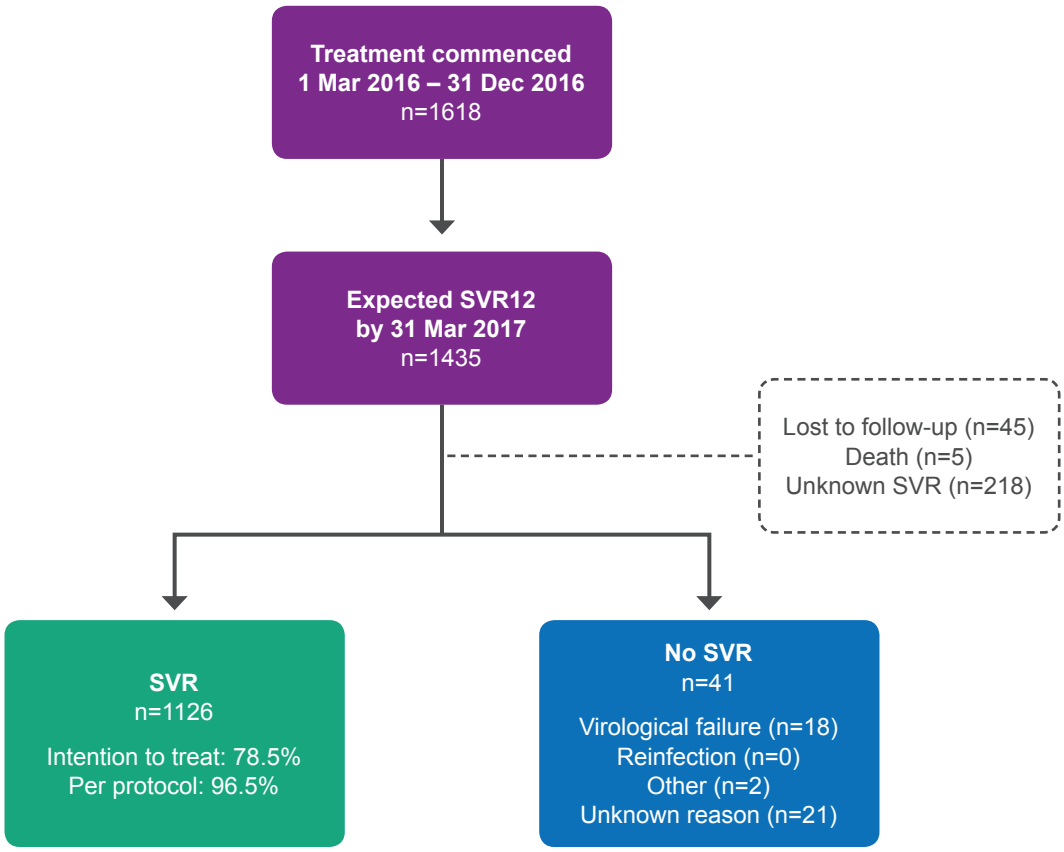
## Overall hepatitis C DAA treatment outcomes

Of the 1618 individuals who commenced treatment between March and December 2016, 1435 individuals were expected to reach 12 weeks post-treatment (SVR12) by 31 March 2017 (Figure 5).

Overall, 1126 of 1435 individuals (78.5%) achieved SVR12 in the ITT population. In the PP analysis, 1126 of 1167 individuals (96.5%) achieved SVR12.

To date only 18 cases of virological failure have been reported (1.2%) and no cases of reinfection.

Figure 5. Patient disposition. ITT population n=1435, PP population n=1167.




SVR12: sustained virological response 12 weeks after treatment; ITT: intention to treat; PP: per protocol

## Hepatitis C DAA treatment outcomes (per protocol analysis)

In individuals who received sofosbuvir/ledipasvir, the SVR12 rate was 98% for a 12-week course and 94% for a 24-week course. In those who received 8 weeks of sofosbuvir/ledipasvir, there were five individuals who did not achieve SVR12, resulting in an SVR12 rate of 97%.

Among individuals with genotype 1a and 1b, SVR12 rates in the PP population were 98% and 97%, respectively. The SVR12 rate was 95% for genotype 3.

Genotype 4-infected individuals had the lowest rate of SVR12 (78%), but this included only 9 individuals. In this group, two individuals (of five) treated with 12 weeks of sofosbuvir/ledipasvir did not achieve SVR12.

SVR12 rates were high across all baseline characteristics with a slight reduction in SVR12 in those with cirrhosis vs no cirrhosis (93% vs 97%) and in treatment-experienced individuals vs naïve (92% vs 98%). SVR12 rates were similar in those with and without HIV (98% vs 96%), on OST (98% vs 96%) and with a history of injecting in the last 6 months (99% vs 96%).

Figure 6. SVR12 rates by genotype (A) and clinical characteristics (B) in the PP population


IDU: injecting drug use; OST: opioid substitution therapy

## Hepatitis C DAA treatment outcome (intention to treat analysis)

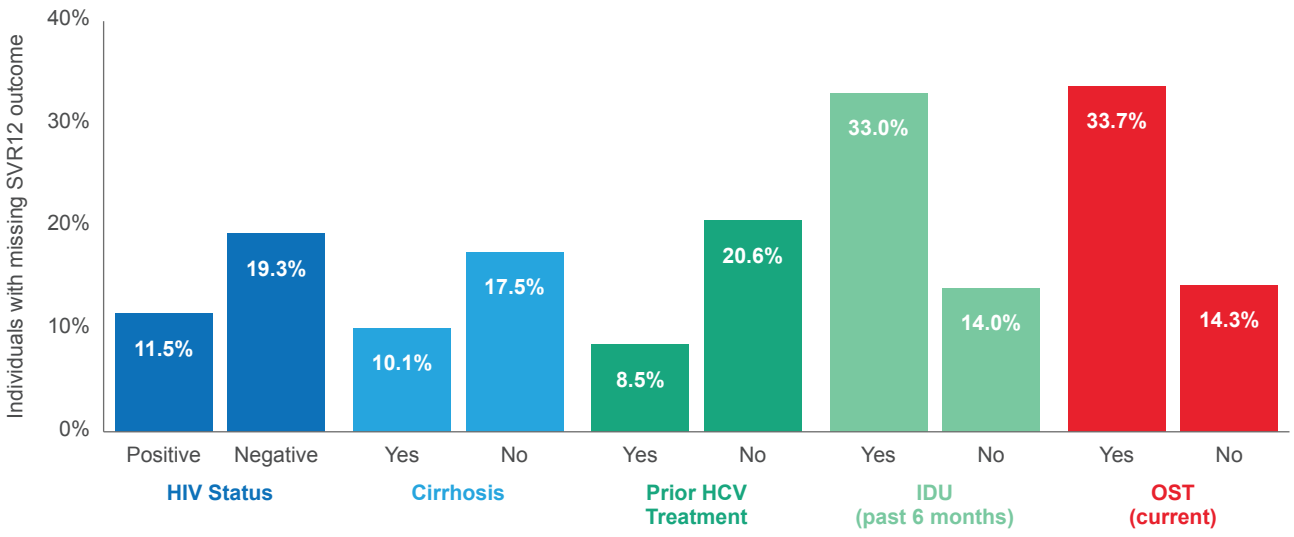
The overall SVR12 rate by ITT analysis was considerably lower than by per protocol analysis, driven by a proportion of individuals in whom SVR12 follow-up data could not be obtained.

Of the 1435 individuals with expected SVR12 by March 2017, 19% did not have treatment outcomes available (Figure 5). Given the ongoing nature of REACH-C data collection, it is anticipated that treatment outcomes will be obtainable for many individuals currently missing this information.

People who injected drugs in the 6 months prior to treatment initiation were more likely to have a missing SVR12 outcome (33%) than individuals who did not (14%; Figure 7). Similarly, individuals receiving OST were more likely to have an unknown treatment outcome (34%) than those who were not engaged in OST (14%).

No major differences were seen in missing data by cirrhosis status or genotype, although a trend to less missing data was observed in those who were HIV positive and in those with treatment experience, most likely reflecting higher engagement in care.

Figure 7. Distribution of individuals with missing SVR12 outcome by baseline characteristics




IDU: injecting drug use; OST: opioid substitution therapy

## Methodology

REACH-C is a national prospective multi-centre observational cohort. The choice of regimen and duration of treatment was at the discretion of the treating clinician as individuals were treated in routine practice.

Consecutive individuals commencing treatment for HCV with DAAs were identified at each clinic. Baseline characteristics such as gender, HCV genotype, cirrhosis status and HCV treatment history were collected through review of medical records. Information about planned treatment regimen, duration and date of prescription was also recorded. All individuals who initiated treatment between March and December 2016 were included in analysis of baseline characteristics.

Efficacy of treatment was determined by the proportion of individuals who achieved a sustained virological response, defined as undetectable HCV RNA 12 weeks post-treatment (SVR12).

Treatment outcomes were examined in individuals who were expected to reach SVR12 by 31 March 2017. Clinics reported whether individuals achieved SVR12, and were asked to provide a reason if SVR12 was not achieved (virological failure, reinfection, lost to follow-up, death, other).

Analysis of treatment outcomes was performed using two approaches;

i) Intention to treat (ITT): all individuals with expected SVR12 by 31 March 2017, including those who were lost to follow-up, died, or with an unknown SVR12 (counted as treatment failures).

ii) Per protocol (PP): individuals with a known SVR12 virological outcome by 31 March 2017.

It should be noted that data collection from clinics is ongoing and the information presented herein may not include every individual in the network who initiated treatment during 2016. Additionally, a portion of reported missing data may be retrievable from clinics in the future.