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Real-world outcomes of unrestricted direct-acting antiviral treatment for hepatitis C in Australia: The South Australian statewide experience

Short running title:

South Australian DAA outcomes for HCV

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Abstract and Keywords

In March 2016, the Australian government offered unrestricted access to direct-acting antiviral (DAA) therapy for chronic hepatitis C (HCV) to the entire population. This included prescription by any medical practitioner in consultation with specialists until sufficient experience was attained. We sought to determine the outcomes and experience over the first twelve-months for the entire state of South Australia. We performed a prospective, observational study following outcomes of all treatments associated with the state's four main tertiary centres. 1909 subjects initiating DAA therapy were included, representing an estimated 90% of all treatments in the state. Overall, SVR12 was 80.4% in all subjects intended for treatment and 95.7% in those completing treatment and follow-up. 14.2% were lost to follow-up (LTFU) and did not complete SVR12 testing. LTFU was independently associated with community treatment via remote consultation (OR 1.50, 95% CI 1.04-2.18, $p=0.03$), prison-based treatment (OR 2.02, 95% CI 1.08-3.79, $p=0.03$) and younger age (OR 0.98, 95% CI 0.97-0.99, $p=0.05$). Of the 1534 subjects completing treatment and follow-up, decreased likelihood of SVR12 was associated with genotype 2 (OR 0.23, 95% CI 0.07-0.74,

p=0.01) and genotype 3 (OR 0.23 95% CI 0.12-0.43, p<0.01). A significant decrease in treatment initiation was observed over the twelve-month period in conjunction with a shift from hospital to community-based treatment. Our findings support the high responses observed in clinical trials, however a significant gap exists in SVR12 in our real-world cohort due to LTFU. A declining treatment initiation rate and shift to community-based treatment highlights the need to explore additional strategies to identify, treat and follow-up remaining patients in order to achieve elimination targets.

Keywords:

DAA; Viral Hepatitis; Outcome; Effectiveness; Sustained Virological Response;

Introduction

The advent of direct-acting antiviral (DAA) therapy has represented a revolution in the management of chronic hepatitis C virus (HCV). The ambitious goal of global elimination as a major public health threat by 2030 is now seen as achievable.(1) Exhibiting high efficacy, a favorable adverse-effect profile and short treatment duration, the all oral DAA therapies offer almost all patients afflicted with HCV a cure.(2) However, without widespread and coordinated uptake of these revolutionary therapies, HCV-related mortality and disease burden is projected to triple over the coming decade in the United States and Australia.(3,4) Sustained virological response (SVR12) rates for DAA therapy in controlled trials are consistently good, at or above 90% with demonstrated improvement in outcomes including all-cause mortality and hepatocellular carcinoma.(5,6) Similarly, real-world outcomes have consistently demonstrated high efficacy, albeit mostly within the confines of highly selective patient populations, genotypes or treatment regimes.(5,7,8) Many countries continue to offer treatment only to those with advanced fibrosis, and often exclude those with ongoing substance abuse or incarceration from accessing therapy despite the long-term cost effectiveness.(9,10) Current real-world outcomes have reflected the limitations imposed by systematic rationing and restriction of DAA therapy, with reports often limited to highly selective patient groups.

The Australian 'real-world' experience differs from the majority of other countries to date. Australia represents one of the first countries to offer unrestricted subsidised access to DAA therapy for an entire population irrespective of other factors. In March 2016, access to three all oral DAA regimens was provided, with subsequent addition of two further regimens

within the year, now covering all genotypes. Prescription was permitted by any medical practitioner to any patient with confirmed HCV and a life expectancy greater than 12-months, in consultation with specialists until sufficient experience is obtained.(11,12) To gain necessary prescribing experience, community based non-specialists were recommended to use a remote consultation form whereby HCV assessment information could be reviewed and approved by a specialist prior to community treatment initiation. Understanding the effectiveness and outcomes in the setting of rapid treatment uptake, whereby all treatments, genotypes, clinicians and patients are eligible represents a vastly different landscape to the current real-world experience and may serve as a guide for future programs elsewhere. An estimated 34,000, or 16% of the total 227,000 HCV-infected Australians were treated in 2016 alone.(13,14) South Australia is one of six state jurisdictions and two territories which constitute the Commonwealth of Australia, with a population of 1.7 million, accounting for 7.14% of the Australian population.(15) An estimated 11,682 people were living with chronic HCV infection in South Australia at the beginning of 2016.(16)

Our aim was to document the clinical characteristics, demographics, outcomes and initial 12-month experience across an entire state jurisdiction of Australia following the introduction of subsidised DAA therapy across all settings, prescribers, genotypes, fibrosis stages and treatments.

Materials and Methods

An observational, prospective study of all HCV-infected subjects initiated on DAA therapy in South Australia in association with its four tertiary referral centres (Royal Adelaide Hospital, Flinders Medical Centre, The Queen Elizabeth Hospital and Lyell McEwin Hospital) between 1st March 2016 and 28th February 2017 was conducted. Outcomes were collected prospectively. Additional data collected retrospectively at some sites included biochemistry, transient elastography score (Fibroscan®) and co-morbidity data. Collection of outcomes concluded in November 2017. This study was approved by the Central Adelaide Local Health Network Human Research and Ethics Committee (approval HREC/17/RAH/146).

Treatment Outcome

SVR12 was defined as at least one negative HCV RNA test at 12-weeks post treatment completion. Subjects that did not complete an SVR12 blood test by 24-weeks post

completion of treatment and/or within the study period were considered lost to follow-up (LTFU). Those that were within 24-weeks of treatment completion at the conclusion of the study period and who had not undergone HCV RNA testing were excluded. Virological failure (both relapse and breakthrough) was included, defined by a positive HCV RNA at or beyond the end of treatment with DAA therapy.

Baseline Characteristics

Demographic and baseline clinical characteristics were prospectively collected. Patient residence (rural or urban) was determined using the Accessibility/Remoteness Index of Australia (ARIA) score, calculated from postcode.⁽¹⁷⁾ Where a postcode spanned two ARIA classification zones, the more urban classification was accepted. Hepatitis B Virus (HBV) co-infection was defined as a positive HBV surface antigen (HBsAg) or current use of HBV antiviral therapy. Cirrhosis was defined as either transient elastography (Fibroscan®) score of higher than 12.5kPa or clinician determination as cirrhotic in the medical records. Where there was discordant transient elastography score and clinician assessment, clinician assessment was accepted. Aspartate aminotransferase-to-platelet ratio index (APRI) and FIB-4 scores were calculated from the most recent biochemistry performed prior to DAA treatment initiation. An APRI > 1.0 and FIB-4 > 3.25 was used in further analysis based on current Australian consensus guidelines.⁽¹¹⁾

Statistical Analysis

The primary endpoint was SVR12 with the denominator including all patients that were prescribed DAA therapy in the observational period (primary analysis). A secondary analysis included only those completing treatment and attending all follow-up. Univariate analysis used the Pearson Chi-squared or Fisher Exact test for categorical variables. Continuous variables (age, platelet count, albumin level, APRI, FIB-4 and transient elastography score) were assessed for normality using a Shapiro-Wilk test then analysed using a Kruskal-Wallis test. Continuous variables are expressed as median/interquartile range where distribution is not distributed normally. Categorical variables are expressed as count number and proportion of complete data in the variable presented. A multivariate binomial logistic regression model was used to estimate the predictors of SVR12 on the secondary analysis. A post-hoc multivariate analysis examining predictors of loss to follow-up was performed. Variables

with a significance $p < 0.10$ on univariate analysis were included in the multivariate model. Analysis was performed using Stata 13.0 (Stata Corporation, College Station TX, USA).

Results

Overall Outcomes

One thousand, nine hundred and twenty-one patients were initiated on DAA therapy between 1st March 2016 and 28th February 2017 at, or in consultation with, four tertiary hospitals in South Australia, representing an estimated 90% of all treatment initiated in the state.(14) Figure 1 details the overall outcomes in the cohort. Twelve were excluded from analysis as no SVR12 test was available but were still within the defined follow-up period. Of the remaining 1909 included in the final analysis, 34 did not complete treatment due to: 6 (0.3%) never commencing treatment, 6 (0.3%) discontinuing due to adverse effects, 9 (0.5%) were non-compliant and discontinued during the treatment period and 13 (0.9%) died during the treatment or follow-up period. Two hundred and seventy-two (14.2%) were LTFU, with no SVR12 testing performed by 24 weeks post treatment or within the study period. Overall 1534 (80.4%) of subjects that were intended for DAA treatment achieved confirmed SVR12.

Baseline Characteristics

Baseline characteristics of the cohort are presented in Table 1. Overall, 66.9% were male, median age was 54 years (interquartile range 46-59) and 18.6% had previously undergone interferon-based treatment. The majority of treatment was initiated in the hospital setting (80.3%) and in subjects that resided in an urban location (74.5%). Eighty-eight (4.6%) resided in a remote or very remote region. Treatment outside of the tertiary hospitals included 4.8% in the prison system and 19.7% by non-specialists in the community via remote consultation. Injecting drug use history was available in 1081 subjects, 77.6% of which previously injected drugs and 5.7% were currently using (within the prior 6-months). Overall, the majority were infected with genotype 1 (1a 43.6%, 1b 9.2%, 1 non-subtype 4.3%) and genotype 3 (38.2%). Lesser numbers were treated genotype 2 (3.5%), genotype 4 (1.0%) and genotype 6 (0.3%). No subjects infected with genotype 5 were treated.

Overall, 25.5% of treatments were in cirrhotic subjects, 93.8% of whom were treated in a hospital rather than community setting. Child-Pugh status was not specified in 17.8% of those

with cirrhosis. Transient elastography was performed in 68.3% of subjects prior to DAA therapy. Those treated in the community via remote consultation were less likely to have transient elastography performed prior to therapy (57.1% v 70.1%, $p < 0.01$). Overall 21.2% had a transient elastography (Fibroscan®) score above 12.5kPa and an additional 17.3% demonstrated a score between 8kPa and 12.5kPa indicating significant fibrosis.

Treatment Regimen

Genotype 1 subjects without cirrhosis were most commonly treated with sofosbuvir/ledipasvir (92.5%) for either 8 (24.7%) or 12 weeks (64.2%). Smaller proportions were treated with either paritaprevir/ritonavir/ombitasvir/dasabuvir (2.5%), elbasvir/grazoprevir (3.5%) or sofosbuvir/daclatasvir (2.1%). Nearly all genotype 1 cirrhotics were treated with sofosbuvir/ledipasvir (91.9%). Sofosbuvir/ribavirin was the only regimen approved for genotype 2 during the study period and accounted for 94.1% of treatments in this group. Similarly, sofosbuvir/daclatasvir was the only genotype 3 DAA regimen available and accounted for 98.6% of treatments for this genotype. Genotype 3 cirrhotics were treated predominately with a 24-week sofosbuvir/daclatasvir regimen (83.2%), with a smaller proportion treated with the addition of ribavirin for a total of 12-weeks (4.3%) or 24-weeks (7.0%). Sixty-two patients (3.2%) were treated with a regimen outside the Australian recommended guidelines, most commonly a 12-week course of sofosbuvir/daclatasvir without ribavirin in genotype 3 cirrhosis or a 24-week course of sofosbuvir/daclatasvir in non-cirrhotic genotype 3.

Secondary analysis

Further analysis was performed on those completing treatment and all follow-up (1603/1909, 84.0%). Unadjusted SVR12 rates by genotype, cirrhosis, treatment experience, comorbidity and treatment regimen are presented in Table 2. Overall, 1534 patients (95.7%) achieved SVR12 and 69 (4.3%) failed DAA therapy. Genotype 2 (4/52, 7.7%) and genotype 3 (45/588, 7.7%) accounted for the highest rates virological failure. All genotype 2 subjects failing DAA treatment were cirrhotic, with the highest rate of failure overall seen in those who were treatment experienced (2/4, 50%). Treatment experienced genotype 3 cirrhotics exhibited the lowest SVR12 rates amongst this genotype (59/71, 83.1%). The majority of those failing DAA therapy (62.3%) did not have an end of treatment HCV RNA performed.

There was no significant difference in SVR12 rates between regimens for both non-cirrhotic and cirrhotic genotype 1 subjects.

Univariate analysis of predictors of SVR12 by subgroup are presented in Figure 2. Lower SVR12 was significantly associated with cirrhosis overall (92.6% v 96.8%, $p<0.01$), prior treatment experience (92.2% v 96.0%, $p=0.01$) and genotype 2 or 3 compared to genotype 1. Higher SVR12 was exhibited in those treated via remote consultation (97.7% v 95.1%, $p=0.06$). Those treated via community remote consultation were significantly less likely to be cirrhotic (10.6% v 31.7%, $p<0.01$). Genotype 2 (OR 0.23, $p=0.01$) and genotype 3 (OR 0.23, $p<0.01$) remained significantly associated with a lower rate of SVR12 when adjusted for age, diabetes, cirrhosis and prior treatment experience on multivariate logistic regression.

Adverse effects and deaths

Six subjects (0.3%) discontinued treatment due to adverse effects and 13 (0.7%) died during the treatment or follow-up period. Of those discontinuing, 2/6 (33%) were due to ribavirin associated adverse-effects. Amongst those discontinuing in non-ribavirin containing regimens, 3/4 (75%) received sofosbuvir/ledipasvir and 1/4 (25%) received sofosbuvir/daclatasvir. This subject restarted the same regimen and was able to complete the prescribed course. Nausea, fatigue and dizziness were reported as reasons for discontinuation in non-ribavirin related cases. All discontinuations due to adverse effects occurred in subjects without cirrhosis or prior treatment experience and whom were older than 50-years old (range 51 – 82).

Of the thirteen deaths, nine (69.2%) occurred in subjects with cirrhosis, seven (77.8%) of whom were Child-Pugh B or C. The most common cause of death as listed in medical records during final admission was sepsis, with a smaller proportion due to drug overdose, heart failure or refractory encephalopathy. Non-cirrhotic deaths were predominately due to drug overdose unrelated to DAA therapy.

Loss to follow-up

Two hundred and seventy-two (14.2%) of all patients prescribed DAA therapy were LTFU. Median follow-up time post end of treatment in the LTFU group was eleven months (range 6 – 18). Higher rates of LTFU were seen in younger subjects (median 50 v 54 years, $p=0.02$),

those treated via remote consultation in the community compared to hospital-based treatment (LTFU 24.3% v 12.2%, $p<0.01$) and those treated in the prison system compared to non-prison-based treatment (24.4% v 13.9%, $p<0.01$). Of 17 prisoners lost to follow-up in our cohort, 9/17 (52.3%) were released from prison prior to their planned SVR12 date.

Significantly lower rates of LTFU were seen in those with cirrhosis (9.1% v 16.0%, $p<0.01$) and prior treatment experience (9.5% v 15.3%, $p<0.01$). None of 27 subjects with HIV, nor 13 subjects with HBV co-infection, were LTFU in our cohort. No significant association was found between PWID, Aboriginal and Torres Strait Islander background, rurality or gender and LTFU. Table 3 outlines a *post-hoc* univariate and multivariate analysis of patient and treatment characteristics predicting LTFU. A significant association was found on logistic regression analysis between younger age (OR 0.98, $p=0.05$), remote consultation (OR 1.5, $p=0.03$), prison-based treatment (OR 2.02, $p=0.03$) and LTFU rates.

Treatment Initiation Rates and Location

Figure 3 presents the overall treatment initiation rates with stratification into hospital and community settings over the twelve-month period. There was a significant decrease in treatment initiation in the latter six-months (657 v 1252 treated). Treatment proportionally shifted from hospital to community settings via remote consultation in the latter six-months (12.1% v 34.0% remote consultations, $p<0.01$). The absolute number of community-based treatments increased from 144 to 212 in the latter six-months. Current injecting drug users were more likely to be treated in the community via remote consultation than those who had never injected drugs (33.3% v 12.9%, $p<0.01$).

In comparison to the first six-months of treatment availability, subjects in the latter six-months were younger (51 v 54 years, $p<0.01$), less likely to be cirrhotic (18.9% v 29.3%, $p<0.01$), resided in more rural areas (28.8% v 23.6%, $p=0.01$) and were more likely to be currently using injecting drugs (9.9% v 3.5%, $p<0.01$).

Discussion

Our study reports the real-world experience over the first 12-months of introducing unrestricted subsidised DAA therapy to an entire state-wide population, including prescription by any medical practitioner. We included all patients that were intended for

treatment, in order to capture rates of loss to follow-up and the effect this may impart. The relative completeness of our dataset allowed for multivariate analysis on over 85% of included subjects without the need for multiple imputation methods. Our inclusion of 1909 treatments represents an estimated 90-95% of all DAA therapy initiated in South Australia over the period and treatment of an estimated 16% of all prevalent HCV in the state.(14) The remaining minority of uncaptured treatments outside of our cohort were likely from private specialists and physicians working outside of the four tertiary Gastroenterological and Infectious Disease units.

Restrictions and rationing of DAA therapy continues in most countries. The HEP-Core study examining twenty-seven countries in Europe (as well as Egypt) revealed only three countries without restriction on DAA medication access. Restriction primarily was instituted according to fibrosis stage and/or ongoing substance abuse. Seven countries allowed prescription in non-hospital settings and no single country allowed unrestricted access such as in Australia.(9) Iceland and Georgia were other countries amongst the first to offer unrestricted access to DAA therapy for all patients. In June 2016, Georgia offered nation-wide access to sofosbuvir/ledipasvir and sofosbuvir/ribavirin via designated treatment sites, reporting an overall SVR12 of 84% for 5,400 out of 28,000 treated where results were available.(18) Similarly, Iceland has made available sofosbuvir based regimens for the estimated 800-1000 patients nationwide. Real-world outcomes have not been reported to date from a setting of unrestricted access to multiple treatment regimens that may be prescribed by any medical practitioner for any HCV-infected patient. Our study represents the first and largest outcome data from such a setting and allows context for other countries that seek to liberalise access to these effective medications.

The significant LTFU in our cohort is of particular concern and appears higher than documented in prior real-world studies. Loss to follow-up is rarely reported per se and carries significant importance both in the risk of unrecognised virological failure and in developing strategies to improve this aspect of care. Our findings indicate that loss to follow-up is significantly higher in younger patients as well as in community and prison treatment settings. Kanwal *et al.* (2014) discuss the chasm that exists between efficacy and effectiveness in HCV treatment in the DAA era.(19) Whilst DAA therapy is proven highly efficacious in both trial and real-world settings, the overall effectiveness of an elimination program will in part depend on adequate delivery and follow-up. This is pertinent in the

context of our findings. It is probable that a significant proportion of LTFU in our study will have achieved SVR12 and not necessarily ceased or failed treatment. Importantly, the potential of 'missing' virological failure in those LTFU does have onward implications for persistent transmission and eventual eradication of HCV. Amongst the current real-world literature, missing SVR data ranges between 2-9% in larger observational studies. (7,8,20) Elsharkawy et al.(2001) report the highest level of loss to follow-up at 29% in a large observational study of 20,324 genotype 4 patients completing DAA therapy in Egypt.(21) Lower rates of loss to follow-up to than seen in our cohort have been observed in traditionally difficult highly marginalised community treated patients in Australia with the support of individualised treatment adherence plans.(22) This suggests that the availability of viral hepatitis clinical nurse specialists in the hospital setting and/or more intensive community support in DAA treatment may be a defining factor maintaining adherence to follow-up schedules and SVR12 testing.

The rapid decrease in treatment initiation in the latter half of our study period highlights the 'warehouse' effect and early presentation of those who are likely highly motivated to seek treatment.(23) Similar experiences including a rapid decline in treatment initiation has been reported when introducing unrestricted access to DAA therapy in other countries such as Georgia.(18) Although community DAA initiation from General Practitioners proportionally increased over the 12-month period in our cohort, the absolute increase was small. Treating an estimated 8% of the current Australian PWID annually or 40 per 1,000 PWID is projected to reduce HCV transmission by 90% within 12 years in order to achieve WHO elimination targets.(24,25) In our cohort over twelve months, 62 confirmed current injecting drug users of an estimated 6700 users in South Australia were treated.(26) Even allowing for the likely underestimation of current injecting drug use in our cohort given missing data, it is far short of the number required to significantly reduce transmission and achieve elimination targets. Australia has demonstrated a high level of HCV antibody testing amongst PWID, mostly through General Practitioners, however only 49% have undergone confirmatory HCV RNA testing. (27,28) In our cohort, a significantly higher proportion of current PWID were treated in the community, highlighting a need to support both screening, education and linkage to care for community based General Practitioners in order to move towards elimination targets. The use of HCV testing interventions such as alerts and patient solicitation methods has demonstrated improvement in screening and diagnosis rates in some centres.(29,30) Our

finding of excellent outcomes in PWID with no increase in LTFU compared to the general population supports current guidelines that ongoing drug should not preclude treatment.(31)

SVR12 rates were higher in genotypes 1 (98.0%), 4 (94.4%) and 6 (100%) than genotype 2 (92.3%) and 3 (92.4%). Our overall results for those completing all treatment and follow-up indicate excellent efficacy in most subgroups, comparable with Phase IIb/III and real-world studies.(5) No significant difference in outcome was found between individual treatment regimens for genotype 1, including an 8-week course of sofosbuvir/ledipasvir. Current Australian guidelines are similar to internationally accepted indications for an 8-week course of sofosbuvir/ledipasvir for genotype 1 subjects with a viral load <6 million IU/ml, at clinician discretion. Our finding of 98.3% SVR12 in this group exceeds published Phase IIb and real-world studies of 88-94%.(32-35) The more frequent use of fibroelastography in detecting advanced fibrosis in our cohort rather than FIB-4 definitions of cirrhosis may be one potential reason for this.(35) Our small proportion of Genotype 2 cirrhotics exhibited the lowest SVR12 rates in our study (9/13, 69.2%), which appears lower than phase III and initial real-world experience elsewhere.(36) Sofosbuvir/ribavirin for 12-weeks was the only all oral DAA regimen approved for use in Australia over this time period for genotype 2. More recent real-world data similarly have demonstrated lower SVR12 rates in treatment-experienced and cirrhotics genotype 2 subjects receiving sofosbuvir/ribavirin.(37) In August 2017, sofosbuvir/velpatasvir became available for this genotype; this is expected to significantly improve SVR12 in this group.(38,39) Our finding of an association between prior treatment experience, cirrhosis and genotype 2/3 is consistent with other studies and guidelines.(5,40,41)

Our study has a number of limitations, mostly inherent in the observational, real-world design and data collection. This included the incomplete data records, particularly documentation of injecting drug history and Child-Pugh status in cirrhotics. However, the vast majority of other data points were over 98% complete. Local practice discrepancies and the risk of data collection and entry errors is possible in this observational design. Our definition of loss to follow-up at six-months post treatment was felt to be an acceptable time period to capture SVR12 data, although risks incorrectly defining those that may intend to follow-up at a later period. Similarly, we continued follow-up on all patients to the end of the study period, which may in part account for the higher LTFU when comparing rates between the first and last six-months of the year. The latter six-months however may more truly represent the

ongoing population requiring treatment given the initial few months of treatment often included long-term, compliant, warehoused cohorts. Despite these limitations, the majority of our LTFU group were followed up for almost twelve months post completion of therapy without undergoing a test for SVR12. The higher LTFU than reported in the vast majority of other real-world studies may compromise the overall effectiveness of a population based DAA rollout and may signal one of many barriers in the pathway to HCV eradication once initial access to treatment worldwide is attained. LTFU in the Australian setting has been associated with homelessness, which we were unable to record in our study.(22) The study design similarly did not allow for measures of medication adherence or obesity, which may be further confounding factors on SVR12. Our reliance on clinician assessment of cirrhosis as the gold standard carries obvious limitations, however it reflects real-world management and the complexities of fibrosis assessment. Specific data pertaining to the validity of each individual transient elastography result was not recorded in our study. We were unable to stratify virological failures into breakthrough or relapse or assess time of relapse due to the vast majority of subjects not undergoing end of treatment HCV RNA, in combination with widely varying time periods at which SVR12 testing was performed.

Our findings highlight the need to continue real-world observational data in this area and focus on further strategies to prevent loss to follow-up, support community hepatitis C treatment and maintain treatment initiation rates following exhaustion of warehoused cohorts. Efficacy of DAA therapy in the real-world remains outstanding in the setting of unrestricted access by all patients and prescription by all practitioners. However, the effectiveness of a large population-based treatment is dependent on a coordinated, adequately resourced program to ensure follow-up and confirmation of cure.

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Tables

Table 1: Baseline characteristics (All subjects intended for treatment).

	Overall (n=1909)	
Demographics		
Age (years)	54.0	(46-59)
Sex, male	1277	66.9%
Prisoner	87	4.6%
ATSI	37	1.9%
PWID, current	62	3.2%
PWID, ex	839	43.9%
PWID, never	180	9.4%
PWID, unknown	828	43.4%
Patient Residence Location		
Major City	1423	74.5%
Inner Regional	176	9.2%
Outer Regional	213	11.2%
Remote	74	3.9%
Very Remote	14	0.7%
Rural (Overall)	477	25.0%
Treatment Location		
Hospital	1456	80.3%
Remote Consultation (Community)	357	19.7%
Clinical Characteristics		
Diabetes	197	10.3%
HBV	13	0.7%
HIV	27	1.4%
Post <u>Liver</u> Transplant	34	1.8%
Treatment Experienced	304	18.6%
<u>HCV Genotype</u>		
Genotype 1	1088	57.0%
Genotype 2	66	3.5%
Genotype 3	729	38.2%
Genotype 4	19	1.0%
Genotype 6	6	0.3%
<u>Laboratory Results</u>		
Platelet ($\times 10^3/\text{mm}^3$)	220	(165-272)

Albumin level (g/dL)	39	(36-41)
AST (IU/L)	48	(33-77)
ALT (IU/L)	59	(37-102)
Post treatment ALT >45IU/L	150	10.1%
Fibrosis Assessment		
Cirrhosis, Overall	486	25.5%
Cirrhosis, Child-Pugh A	331	17.3%
Cirrhosis, Child-Pugh B	58	3.0%
Cirrhosis, Child-Pugh C	13	0.7%
APRI < 1.0	1362	73.1%
APRI > 1.0	501	26.9%
FIB4 < 1.45	912	48.9%
FIB4 1.45 – 3.24	618	33.2%
FIB4 > 3.24	334	17.9%
Fibroscan® 8.0 – 12.4kPa	215	17.4%
Fibroscan® > 12.5kPa	262	21.2%

Continuous variables reported as median (interquartile range). Categorical variables reported as proportion of complete data.

Abbreviations: ATSI, Aboriginal and Torres Strait Islander; PWID, Persons Who Inject Drugs; APRI, AST to Platelet Ratio Index; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; HIV, Human Immunodeficiency Virus; HBV, Hepatitis B virus;

Table 2: Unadjusted SVR12 rates by genotype and cirrhosis status, subjects completing all treatment and follow-up (secondary analysis).[†]

	Genotype 1				Genotype 2				Genotype 3				Genotype 4			
	Cirrhosis		No Cirrhosis		Cirrhosis		No Cirrhosis		Cirrhosis		No Cirrhosis		Cirrhosis		No Cirrhosis	
	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n
Overall	96.9	216/223	98.3	697/709	69.2	9/13	100	38/38	89.2	165/185	93.8	376/401	87.5	7/8	100	10/10
Gender																
Male	95.8	160/167	98.2	438/446	70.0	7/10	100	24/24	90.0	126/140	92.4	244/264	100	4/4	100	6/6
Female	100	56/56	98.5	258/262	66.7	2/3	100	14/14	86.7	39/45	96.3	131/136	75.0	3/4	100	4/4
Comorbidity																
HBV	-	-	100	6/6	-	-	100	1/1	100	1/1	100	2/2	-	-	-	-
HIV	100	5/5	100	14/14	-	-	100	1/1	100	2/2	100	4/4	-	-	-	-
Diabetes	95.7	44/46	96.4	54/56	80	4/5	100	4/4	89.7	35/39	85	17/20	100	2/2	100	2/2
Post-Transplant	100	4/4	100	21/21	-	-	100	1/1	100	1/1	100	7/7	-	-	-	-
Prior Rx																
Naïve	97.4	110/113	98.2	533/543	77.8	7/9	100	25/25	91.2	83/91	93.4	282/302	85.7	6/7	100	6/6
Experienced	97.5	78/80	97.3	71/73	50.0	2/4	100	5/5	83.1	59/71	91.7	33/36	100	1/1	-	-
Regimen																
SOF/LDV 8	100	3/3	98.3	175/178	-	-	-	-	-	-	100	1/1	-	-	-	-
SOF/LDV 12	96.8	122/126	98.1	455/464	100	1/1	-	-	-	-	100	5/5	-	-	-	-
SOF/LDV 24	97.5	78/80	100	14/14	-	-	-	-	100	1/1	-	-	-	-	-	-
SOF/LDV/RBV 12	100	2/2	100	12/12	-	-	-	-	-	-	-	-	-	-	-	-
SOF/DCV 12	100	1/1	100	11/11	-	-	100	1/1	75.0	6/8	93.5	358/383	-	-	-	-
SOF/DCV 24	100	1/1	100	1/1	-	-	-	-	92.2	142/154	100	10/10	100	1/1	-	-
SOF/DCV/RBV 12	100	4/4	-	-	-	-	-	-	75.0	6/8	100	2/2	-	-	-	-

SOF/DCV/RBV 24	-	-	-	-	-	-	-	-	69.2	9/13			-	-	-	-
SOF/RBV 12	-	-	-	-	63.6	7/11	100	37/37	-	-	-	-	-	-	-	-
EBR/GZR 12	80.0	4/5	100	13/13	-	-	-	-	-	-	-	-	80.0	4/5	100	10/10
PrOD 12	100	1/1	100	14/14	-	-	-	-	-	-	-	-	-	-	-	-

† There were no genotype 5 and four genotype 6 subjects (not included). Only treatments prescribed > 10 subjects in total included.

Abbreviations: SOF, Sofosbuvir; LDV, Ledipasvir; RBV, Ribavirin; DCV, Daclatasvir; EBR, Elbasvir; GZR, Grazoprevir; PrOD, Paratapravir Ritonavir Ombitasvir Dasabuvir

Table 3: Predictors of loss to follow-up, logistic regression analysis (*post-hoc* analysis).

	Univariate	Multivariate analysis	
	p-value	Odds Ratio (95% CI)	p-value
Age	<0.01	0.98 (0.97 – 0.99)	0.05
Gender (Male)	0.81		
PWID	0.11		
Remote Consultation	<0.01	1.50 (1.04 – 2.18)	0.03
Prison	<0.01	2.02 (1.08 – 3.79)	0.03
Rural patient residence	0.94		
ATSI	0.20		
Cirrhosis	<0.01	0.74 (0.48 – 1.13)	0.17
Prior treatment experience	<0.01	0.79 (0.50 – 1.25)	0.31
HIV [†]	0.03		
HBV	0.14		
Diabetes	0.09	0.77 (0.45 – 1.33)	0.35

[†] Not included in multivariate analysis due to collinearity

Figure Legends

Figure 1: Outcomes of DAA therapy for HCV in South Australia, March 1st 2016 – February 28th 2017.

Figure 2: Predictors of SVR12, univariate analysis of subjects completing all treatment and follow-up (secondary analysis).

Figure 3: Number and location of treatments initiated in South Australia, March 1st 2016 – February 28th 2017.

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