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Hepatitis C virus testing, liver disease assessment and treatment uptake among people who inject drugs pre- and post-universal access to direct-acting antiviral treatment in Australia: The LiveRLife study

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Abstract

Gaps in hepatitis C virus (HCV) testing, diagnosis, liver disease assessment and treatment uptake among people who inject drugs (PWID) persist. We aimed to describe the cascade of HCV care among PWID in Australia, prior to and following unrestricted access to direct-acting antiviral (DAA) treatment. Participants enrolled in

Abbreviations: ANSPS, Australian Needle and Syringe Program Survey; BMI, body mass index; CI, confidence intervals; DAA, direct-acting antiviral; HCV, hepatitis C virus; OR, odd ratios; OST, opioid substitution treatment; PWID, people who inject drugs; WHO, World Health Organization.

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an observational cohort study between 2014 and 2018 provided fingerstick whole-blood samples for dried blood spot, Xpert HCV Viral Load and venepuncture samples. Participants underwent transient elastography and clinical assessment by a nurse or general practitioner. Among 839 participants (mean age 43 years), 66% were male (n = 550), 64% (n = 537) injected drugs in the previous month, and 67% (n = 560) reported currently receiving opioid substitution therapy. Overall, 45% (n = 380) had detectable HCV RNA, of whom 23% (n = 86) received HCV treatment within 12 months of enrolment. HCV treatment uptake increased from 2% in the pre-DAA era to 38% in the DAA era. Significant liver fibrosis (F2-F4) was more common in participants with HCV infection (38%) than those without (19%). Age 50 years or older (aOR, 2.88; 95% CI, 1.18-7.04) and attending a clinical follow-up with nurse (aOR, 3.19; 95% CI, 1.61-6.32) or physician (aOR, 11.83; 95% CI, 4.89-28.59) were associated with HCV treatment uptake. Recent injection drug use and unstable housing were not associated with HCV treatment uptake. HCV treatment uptake among PWID has increased markedly in the DAA era. Evaluation of innovative and simplified models of care is required to further enhance treatment uptake.

KEYWORDS

cascade of care, direct-acting antiviral, hepatitis C virus, linkage to care, treatment uptake

1 | INTRODUCTION

People who inject drugs (PWID) are a priority population to test and treat for hepatitis C virus (HCV) in efforts to meet the World Health Organization (WHO) elimination targets of 80% reduction in new HCV infections and 65% reduction in HCV-related mortality by 2030.[1] Although the introduction of highly effective and tolerable, short-duration oral direct-acting antiviral (DAA) therapy gave impetus to HCV elimination targets, gaps in HCV diagnosis and related liver disease assessment,[2-4] and HCV treatment uptake among PWID persist.[1,5,6] Further, data on the burden of HCV-related liver disease among PWID in community-based settings are sparse.[7-9] Scale-up of simplified and integrated HCV and liver disease screening strategies for PWID in community settings is needed.

Viral hepatitis is a leading cause of global mortality, responsible for an estimated 1.34 million deaths per year; surpassing mortality due to HIV/AIDS.[1] Around 30% of these deaths are attributed to long-term HCV-related sequelae (cirrhosis and hepatocellular carcinoma).[1] In many countries, the burden of HCV-related liver morbidity and mortality among PWID is predicted to escalate due to ageing cohorts, high HCV prevalence and low HCV treatment uptake.[10] This burden is further compounded by co-factors among PWID associated with accelerated disease progression including, male sex, co-infection with hepatitis B virus or HIV, obesity and type-2 diabetes, and heavy alcohol consumption.[10,11]

In order to meet the WHO elimination targets, significant improvements along the cascade of HCV care for PWID are required. Individual, provider and structural barriers to HCV treatment uptake experienced by PWID in the interferon era have been well elucidated.[12-15] Despite major advances in HCV treatment in the DAA era, particularly enhanced drug tolerability and shortened treatment duration, and evidence of increased treatment uptake in some settings, cascade of care barriers remain for PWID populations.

This study aimed to (a) describe the cascade of HCV care among PWID in Australia participating in the LiveRLife study by documenting HCV RNA prevalence, liver disease burden, linkage to care and treatment uptake and outcomes; (b) examine factors independently associated with significant liver fibrosis; and (c) examine HCV treatment uptake in the pre-DAA and DAA eras, and identify factors independently associated with DAA treatment uptake.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

LiveRLife is an observational cohort study assessing a community-based model of care integrating a liver health promotion campaign and noninvasive liver fibrosis assessment with linkage to care and HCV treatment among people with a history of injection drug use. The development of the health promotion resource materials has been described in detail elsewhere.[16]

Participants were enrolled between 12 August 2014 and 22 February 2018 from 16 sites in Australia covering three states including 12 drug and alcohol clinics (n = 8 NSW; n = 3 QLD; n = 1 SA), one needle and syringe program (QLD), one medically supervised

injecting centre (NSW), one community health clinic (NSW) and one Aboriginal Medical Service (NSW).

Between May and October 2014, inclusion criteria were age ≥ 18 years, written informed consent and a history of injection drug use. Exclusion criteria included currently or previously received HCV treatment, and underwent transient elastography assessment and/or liver biopsy assessment in the previous two years and current pregnancy. The protocol was revised to remove the exclusion criteria (except for current pregnancy) and add fingerstick capillary whole-blood point-of-care HCV RNA testing (using the Xpert HCV Viral Load Fingerstick assay) to the study procedures for participants recruited after 14 Jan 2016.

All participants provided written informed consent, and the study protocol and amendments were approved by the Human Research Ethics Committee at St. Vincent's Hospital, Sydney.

2.2 | Procedures

Prior to the LiveRLife campaign days, recruitment posters were displayed at the study sites and clinic staff encouraged eligible participants to attend future campaign days. On LiveRLife campaign days, peer support workers and site staff provided information about the study to the participants while they were accessing services. Eligible participants were then consecutively enrolled during the LiveRLife campaign days. Each clinic site held four campaign days (either one campaign day per week for four weeks or four consecutive campaign days).

At enrolment, participants received an educational resource package (including a LiveRLife campaign coffee mug, and liver health promotion and education booklet) and an AU$20 shopping voucher for their time. Enrolment assessments included fingerstick capillary whole-blood sample collection for point-of-care HCV RNA testing using Xpert® HCV Viral Load Fingerstick assay, dried blood spot collection, self-reported behavioural survey on tablet computers, transient elastography (FibroScan®; Echosens) and clinical nurse assessment (including standard of care assessment). Participants also provided blood samples collected by venepuncture for standard of care clinical testing (including HCV RNA testing) as they were not provided their Xpert® HCV test results, given that the Xpert® HCV Viral Load Assay is not approved in Australia. Xpert® HCV results were provided to clinic staff to inform subsequent clinical follow-up, and venepuncture samples for standard of care HCV RNA testing were used to confirm HCV infection.

Following fingerstick blood collection, participants completed a self-administered survey on tablet computers collecting demographic information, drug use history, health service utilization and alcohol consumption. Participants were asked if they had injected drugs in the prior six months, and if they had, they were asked if they injected drugs in the prior month. Recent injecting was defined as injecting in the previous month. Participants were categorized as having stable housing or unstable housing based on their responses to the question 'what kind of place do you live in at the moment?' Participants who reported options 'own house/flat; rental house/flat' were classified as having stable housing.[17] Response options of 'staying temporarily with friends; shelter/refuge; street/homeless; parent's place' and any other specified including boarding house, hostel, crisis accommodation and 'couch surfing' were classified as unstable housing.[17] Alcohol consumption was assessed using the AUDIT-C, a 3-item alcohol screen that can help to detect persons who are high-risk alcohol drinkers or who have active alcohol use disorders.[18] The AUDIT-C is scored on a scale of 0-12 with scores of ≥4 in men and ≥3 in women considered as high-risk drinking.[19,20]

After the survey, participants underwent transient elastography by FibroScan® which has a lower and upper detection limit of 2.5 and 75 kPa, respectively, and fibrosis stages were defined by scores 2.5-7.4 (F0/1), 7.5-9.4 (F2), 9.5-12.4 (F3) and ≥12.5 kPa (F4, cirrhosis).[21] A liver stiffness measurement score is considered valid if a minimum of 10 valid readings, with at least a 60% success rate and an interquartile range of ≤30% of the median value, is taken. An extra-large probe was not available.

Liver disease assessment was followed by a clinical HCV assessment by a nurse or medical practitioner. This involved a standard health check and a review of medical history, FibroScan® result (written on a scorecard with liver disease stage infographic[22]) and in some cases blood tests (including HCV RNA testing) for standard clinical care. Where applicable, a referral was made to a specialist for follow-up.

All participants were asked to return 2-12 weeks post-enrolment to receive their HCV test results and for clinical follow-up with a medical practitioner or nurse, and to complete a self-administered survey on demographic characteristics, drug use behaviour since enrolment, post-campaign liver disease knowledge and HCV knowledge. Participants were remunerated with a further AU$20 voucher upon completion of the follow-up interview.

After the Australian Government introduced subsidized unrestricted access to DAA therapy for adults with chronic HCV in March 2016, participants diagnosed with chronic HCV infection were evaluated for HCV DAA treatment and subsequently prescribed HCV treatment as per clinical guidelines. For participants initiating HCV therapy, medical records were audited retrospectively and data collected on a standardized form. Treatment data collection included prescriber type, lifetime and current opioid substitution therapy (OST), drug use behaviour, HIV infection status, HCV genotype, HCV treatment regimen, dosage and duration of treatment, date of HCV treatment initiation and treatment discontinuation.

2.3 | Study outcomes

The study endpoints included HCV infection (detectable HCV RNA), significant liver disease (stage > F2), linkage to care (defined as clinical follow-up attendance) and HCV treatment uptake (treatment initiation). HCV infection was determined by HCV RNA quantification using the Xpert® HCV Viral Load Fingerstick Assay, performed

on fingerstick whole-blood samples.[23,24] Prior to the availability of the Xpert® HCV Viral Load Fingerstick Assay on 14 Jan 2016, HCV RNA testing was completed using a validated in-house qualitative polymerase chain reaction assay, performed on dried blood spots collected by fingerstick whole-blood samples.[25]

2.4 | Statistical analysis

Descriptive statistics, including means, frequencies and percentages, were used to summarize the data. Factors hypothesized a priori to be associated with significant liver disease (F2-F4) were evaluated including older age, male sex, Aboriginal/Torres Strait Islander identity, recent injection drug use (injecting in the previous month), higher body mass index (BMI), high-risk alcohol consumption and detectable HCV RNA at baseline. Factors hypothesized a priori to be associated with HCV DAA treatment uptake were assessed, including older age, male sex, non-Aboriginal/Torres Strait Islander identity, stable housing, no recent injection drug use, current OST, significant liver fibrosis (F2-F4) and never/low-risk alcohol consumption. Unadjusted analyses were performed using univariate logistic regression with odd ratios (OR) and associated 95% confidence intervals (CI). Following unadjusted analyses, multivariable analyses using logistic regression considering all potential variables were performed. To assess factors associated with DAA treatment uptake, logistic regression with random effects was employed to account for heterogeneity across study sites. All *P* values are 2-sided; a level of .05 was considered statistically significant, and statistical analyses were performed using the Stata v14.0.

2.5 | Role of funding source

The funders of the study had no role in study design, data collection, data analysis or data interpretation. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3 | RESULTS

Of the 853 participants enrolled at 16 sites (median 50 participants per site, IQR = 38-58.5) between May 2014 and February 2018, 14 participants were excluded because they failed to complete enrolment assessments. Number of participants enrolled, HCV infection prevalence and treatment uptake per site are summarized in Table S1.

Overall, the mean age of participants was 43 years (SD 9.7), 66% (n = 550) were male, and 31% (n = 262) reported unstable housing at baseline (Table 1). Most participants (64%; n = 537) reported injecting drugs in the month prior to enrolment, and 67% (n = 560) reported receiving opioid substitution treatment (OST). Of participants reporting injection drug use in the previous month (n = 537), 34% (n = 208) reported injecting daily or more frequently, and the last drug injected was predominantly an opioid (58%; n = 316) or methamphetamine (39%; n = 210). Thirty-three per cent (n = 281) screened positive for high-risk alcohol consumption using the AUDIT-C tool.

At enrolment, 45% (n = 380) had detectable HCV RNA consistent with active HCV infection (Figure 1). Most participants diagnosed with HCV infection reported having 'hepatitis C' (82%; n = 312), while 15% (n = 58) reported not having or not knowing if they had 'hepatitis C', and 3% had missing data.

All participants received a liver disease assessment by transient elastography, with median liver stiffness score 5.9 kPa (IQR 4.7-7.7). The majority (68%) had no or mild fibrosis (F0/F1), 12% had moderate fibrosis (F2), 6% had severe fibrosis (F3), 8% had cirrhosis (F4), 4% had an invalid score (XL probe was unavailable for large waist circumference), and 1% were missing (Table 1). As expected, significant liver fibrosis (F2-F4) was more common in participants with HCV infection (38%) compared to those without (19%) (*P* < .001) (Table 2).

In adjusted analysis (Table 2), older age ([36-50 years group: aOR, 1.91; 95% CI, 1.19-3.08], [≥51 years group: aOR, 3.17; 95% CI, 1.87-5.34]), BMI ≥ 30 (aOR, 2.51; 95% CI, 1.66-3.81) and detectable HCV RNA (aOR, 2.79; 95% CI, 1.95-3.99) were associated with significant fibrosis.

Similarly, among participants with detectable HCV RNA, in adjusted analysis, older age ([36-50 years group: aOR, 1.89; 95% CI, 1.00-3.54]; [≥50 year group: aOR, 2.43; 95% CI, 1.19-4.97]) and BMI ≥ 30 (aOR, 1.89; 95% CI, 1.06, 3.39) were associated with significant fibrosis (Table S2). Among participants with undetectable HCV RNA, older age ([36-50 years: aOR, 2.22; 95% CI, 0.94-5.24]; [≥50 years: aOR, 5.65; 95% CI, 2.31-13.82]) and BMI ≥ 30 (aOR, 3.68; 95% CI, 1.91-7.07) were associated with significant fibrosis (Table S3).

Among 839 participants who completed baseline assessments, 45% (n = 378) returned for clinical follow-up as recommended 2-12 weeks post-enrolment. Of these participants, clinical assessment was undertaken by a nurse (66%; n = 249), physician (26%; n = 99) or both nurse and physician (8%; n = 30). Further HCV assessment was recommended for the majority of participants assessed by a nurse (73%; n = 181) or a physician (91%; n = 117) (Table S4).

Overall, over half (56%) of participants with HCV infection attended clinical follow-up, and 34% (131/380) were receiving (n = 26) or initiated (n = 105) HCV treatment (interferon-based n = 3 prior to 2016; DAA n = 128) (Figure 2). In the analysis of treatment uptake among participants with HCV infection enrolled prior to DAA access with a 12-month follow-up time to treatment uptake, four (2%) participants initiated treatment (interferon-based n = 3; DAA n = 1) (Figure 3A). In contrast, among participants enrolled post-DAA access, 38% of participants with HCV infection were receiving or initiated HCV treatment within 12 months of HCV screening (Figure 3B).

Therapy was prescribed by a specialist (infectious diseases, addiction, sexual health and hepatology physicians) (51%; n = 54), general practitioner (36%; n = 37) or nurse practitioner (2%; n = 2), with data unavailable for 12 (12%) participants. HCV genotype, DAA regimen and duration of treatment among participants initiating

TABLE 1 Participant characteristics, stratified by HCV status (n = 839)[a]

Characteristic	Total (n = 839), n (%)[b]	HCV RNA negative (n = 396), n (%)[b]	HCV RNA positive (n = 380), n (%)[b]
Age, mean (SD)	43 (9.7)	43 (10.4)	43 (8.9)
Age groups			
18-35	189 (23%)	96 (24%)	74 (19%)
36-45	313 (37%)	136 (34%)	153 (40%)
46-55	237 (28%)	109 (28%)	114 (30%)
≥56	100 (12%)	55 (14%)	39 (10%)
Sex[c]			
Male	550 (66%)	241 (61%)	265 (70%)
Female	263 (31%)	144 (36%)	106 (27%)
Transgender	8 (1%)	2 (1%)	4 (1%)
Aboriginal/Torres Strait Islander[c]			
Yes	190 (23%)	102 (26%)	72 (19%)
No	622 (74%)	282 (71%)	294 (77%)
Unknown	9 (1%)	3 (1%)	6 (2%)
Completed high school or higher education[c]			
Yes	236 (28%)	108 (27%)	109 (29%)
No	585 (70%)	279 (70%)	263 (69%)
Main source of income[c]			
No income	21 (3%)	15 (4%)	5 (1%)
Full-time/part-time/casual	61 (7%)	28 (7%)	28 (7%)
Government assistance	700 (83%)	330 (83%)	316 (83%)
Other	39 (5%)	14 (4%)	23 (6%)
Housing[c,d]			
Stable	559 (67%)	280 (70%)	245 (64%)
Unstable	262 (31%)	107 (27%)	127 (33%)
Incarceration[c]			
Never	270 (32%)	147 (37%)	105 (28%)
Ever (not in past 12 mo)	391 (47%)	186 (47%)	176 (46%)
In past 12 mo	160 (19%)	54 (14%)	91 (24%)
Age at first injection, median (Range)[e]	18 (9-50)	19 (9-46)	19 (9-45)
Injected drugs in past 6 mo[c]	605 (72%)	268 (68%)	285 (75%)
Frequency of injection in past 6 mo[c]			
None in past 6 mo	216 (26%)	120 (30%)	87 (23%)
<Daily	364 (43%)	160 (40%)	181 (48%)
Daily or more	241 (29%)	108 (27%)	104 (27%)
Injected drugs in past month[c]	537 (64%)	239 (60%)	251 (66%)
Frequency of injection in past month[f]			
None in past month	68 (11%)	29 (11%)	34 (12%)
<Daily	329 (54%)	146 (54%)	163 (57%)
Daily or more	208 (34%)	93 (35%)	88 (31%)
Alcohol consumption (AUDIT-C)[c,g]			
Never drinks	362 (43%)	173 (44%)	166 (44%)
Low-risk male/female	170 (20%)	88 (22%)	72 (19%)
High-risk male/female	281 (33%)	124 (31%)	130 (34%)

(Continues)

TABLE 1 (Continued)

Characteristic	Total (n = 839), n (%)[b]	HCV RNA negative (n = 396), n (%)[b]	HCV RNA positive (n = 380), n (%)[b]
Opioid substitution treatment[h]			
Never	161 (19%)	91 (23%)	49 (13%)
Previous treatment, not current	99 (12%)	49 (12%)	40 (11%)
Current treatment	560 (67%)	246 (62%)	283 (74%)
HCV RNA test result			
Positive	380 (45%)	-	-
Negative	396 (47%)	-	-
Invalid result/missing[i]	63 (8%)	-	-
Currently receiving HCV treatment[j]	44 (5%)	15 (4%)	26 (7%)
Previously received HCV treatment[j]	37 (4%)	23 (6%)	13 (3%)
FibroScan® Liver disease staging			
F0/F1—No/mild fibrosis	568 (68%)	299 (76%)	224 (59%)
F2—Moderate fibrosis	102 (12%)	37 (9%)	59 (16%)
F3—Severe fibrosis	54 (6%)	15 (4%)	32 (8%)
F4—Cirrhosis	66 (8%)	19 (5%)	46 (12%)
Invalid	37 (4%)	20 (5%)	16 (4%)
Result unavailable	12 (1%)	6 (2%)	2 (1%)

[a]HCV RNA test result missing/invalid (n = 63; 8%);

[b]Column percentages;

[c]Participants missing demographic survey in total cohort (n = 18);

[d]Stable housing: living in owned house/flat, rental house/flat or parent's house; Unstable housing: staying temporarily with friends, shelter/refuge, street/homeless;

[e]Participants missing survey in total cohort (n = 35);

[f]Among participants who injected drugs in past 6 mo;

[g]Transgender excluded from the AUDIT-C analysis as studies validated cut-offs in males and females (n = 8);

[h]Participants missing demographic survey in total cohort (n = 19);

[i]Invalid result due to Xpert® Viral Load Assay error (n=45) and missing (n=18);

[j]Prior to February 2016, previous or current HCV treatment was an exclusion criteria.

treatment are summarized in Table S5. Among participants initiating HCV treatment, only 2% (n = 2) reported being previously treated.

After adjusting for potential confounders, age ≥ 50 years (aOR, 2.88; 95% CI, 1.18-7.04) and having attended a clinical follow-up with nurse (aOR, 3.19; 95% CI, 1.61-6.32) or physician (aOR, 11.83; 95% CI, 4.89-28.59) were associated with HCV DAA treatment uptake (Table 3). Recent injection drug use and current OST were not associated with HCV treatment uptake. Similarly, among participants who reported injecting drugs in the six months prior to baseline, in adjusted analysis, having attended a clinical follow-up with nurse (aOR, 2.32; 95% CI, 1.09, 4.91) or physician (aOR, 7.78; 95% CI, 2.95, 20.47) was associated with HCV treatment uptake (Table S6).

4 | DISCUSSION

Among a highly marginalized population, including a majority who are currently injecting drugs, HCV treatment uptake increased markedly following the introduction of unrestricted DAA access. Although encouraging, the 38% DAA era treatment uptake remains suboptimal and highlights the need for the development and evaluation of acceptable and innovative strategies tailored to PWID. The LiveRLife HCV screening and noninvasive liver disease assessment initiative identified a high prevalence of HCV infection and significant liver disease burden among PWID attending health services. Older age, HCV infection and higher BMI were independently associated with fibrosis.

The LiveRLife project was devised as a 'healthy liver' health promotion campaign targeting a population who reported current or previous injection drug use and therefore with an expected high burden of HCV infection. A key objective was to evaluate linkage to ongoing clinical assessment and interventions for liver disease, including HCV treatment. A further objective was to characterize liver disease burden, including among those with and without HCV infection.

The integration of point-of-care fingerstick HCV RNA testing, liver disease staging and clinical review as baseline assessments within the LiveRLife project clearly influenced some elements of the HCV care cascade. Despite this potential 'intervention', a suboptimal proportion of participants (45%) returned for clinical assessment 2-12 weeks following baseline assessment, and HCV treatment in the 12 months following enrolment was strikingly low (2%) during

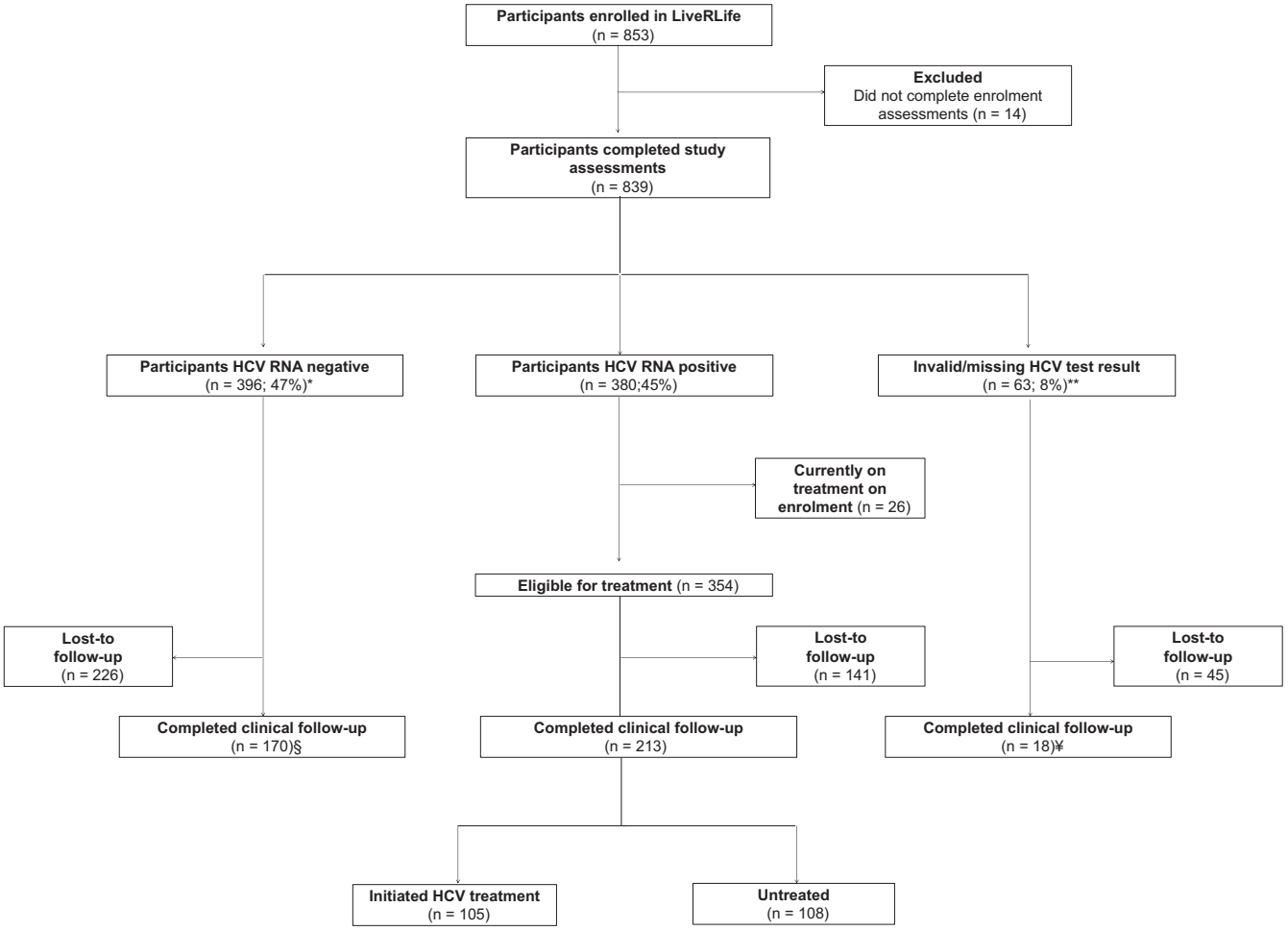

FIGURE 1 Clinical assessment and treatment uptake among the LiveRLife cohort (n = 839). Note: clinical follow-up includes per-protocol follow-up and treatment initiation without per-protocol follow-up; *Includes participants currently on treatment on enrolment (n = 15); §Includes participants acquiring HCV infection after enrolment and receiving treatment n = 7; **Includes participants currently on treatment on enrolment (n = 3); ¥Tested HCV RNA positive after enrolment and treated (n = 1)

the pre-DAA era. The substantial increase in HCV treatment uptake (to 38%) in the DAA era with the same 'healthy liver' health promotion campaign reflects the unrestricted DAA access in Australia from March 2016.[26] Our results are broadly consistent with HCV treatment uptake in the Australian HCV population, including the current PWID population, in the interferon-containing and interferon-free DAA eras. By the end of 2017, an estimated 26% of people with chronic HCV in Australia had received DAA therapy.[5] HCV treatment uptake among current PWID responding to the Australian Needle and Syringe Program Survey (ANSPS) increased markedly, from 1% in 2014 to 39% in 2018.[26] Our observation of the association between older age and treatment uptake is consistent with other studies in Australia that demonstrated higher initial DAA uptake among older ages and those with advanced liver disease.[27] The association between seeing a physician on follow-up and treatment uptake is perhaps unsurprising given that a physician needs to prescribe HCV treatment.

Barriers to HCV care, including individual, provider and structural factors,[28,29] continue in the DAA era.[30] Barriers to accessing care and treatment among PWID such as the belief that HCV acquisition is inevitable, complex life situations and competing priorities, and fear of diagnosis and adverse treatment outcomes remain.[15,30-32] Even in settings where HCV testing uptake is high, poor knowledge among PWID about the effectiveness of DAA treatment has been documented.[30,33] This lack of awareness is compounded by past negative experiences with health providers who hesitate to prescribe HCV treatment to PWID due to fear of wasting resources and concerns about treatment adherence and reinfection.[30,34] Further, many PWID report persistent feelings of being stigmatized by healthcare providers and of being undeserving of treatment (particularly due to high DAA cost), and perceived lack of referral and treatment.[30] Integrated holistic models of care in community-based settings with specific strategies for addressing stigma and discrimination, delivering appropriate education about HCV testing and treatment and providing harm reduction, mental health and social services, are needed.

In regard to characterization of liver disease burden, consistent with previous studies, factors independently associated with significant fibrosis among participants in the current study with HCV infection were older age[35-37] and obesity.[38] PWID are

TABLE 2 Unadjusted and adjusted analyses of factors associated with significant liver fibrosis (F2-F4) among participants enrolled in the LiveRLife study (n = 790)[a]

	Significant liver fibrosis (F2-F4; n = 222), n (%)	Unadjusted Model		Adjusted Model[b]	
		OR (95% CI)	*P*	aOR (95% CI)	*P*
Age					
18-35 y	30 (16%)	1.00		1.00	
36-50 y	116 (29%)	2.07 (1.32, 3.2)	.001	1.91 (1.19, 3.08)	.007
≥51 y	76 (38%)	3.10 (1.91, 5.02)	<.001	3.17 (1.87, 5.34)	<.001
Sex[c]					
Male	156 (29%)	1.00		1.00	
Female	61 (25%)	0.80 (0.57, 1.13)	.208	0.86 (0.59, 1.25)	.421
Aboriginal/Torres Strait Islander[c]					
No	172 (29%)	1.00		1.00	
Yes	45 (26%)	0.85 (0.58, 1.24)	.394	1.00 (0.66, 1.51)	.992
Recent injecting drug use[c]					
Not in previous month	78 (30%)	1.00		1.00	
Injecting in previous month	139 (27%)	0.84 (0.61, 1.17)	.304	0.81 (0.57, 1.15)	.231
Alcohol consumption (AUDIT-C)[c,d]					
Never	107 (31%)	1.00		1.00	
Low-risk male/female	46 (28%)	0.86 (0.57, 1.29)	.459	0.97 (0.62, 1.49)	.874
High-risk male/female	61 (23%)	0.66 (0.46, 0.96)	.029	0.71 (0.48, 1.05)	.087
Body Mass Index (kg/m^2)					
<30	143 (25%)	1.00		1.00	
≥30	58 (41%)	2.13 (1.45, 3.14)	<.001	2.51 (1.66, 3.81)	<.001
Missing	21 (28%)	1.15 (0.67, 1.97)	.608	1.49 (0.83, 2.68)	.184
HCV RNA results					
Negative	71 (19%)	1.00		1.00	
Positive	137 (38%)	2.58 (1.84, 3.60)	<.001	2.79 (1.95, 3.99)	<.001
Missing/Invalid result	14 (24%)	1.31 (0.68, 2.52)	.418	1.64 (0.82, 3.28)	.161

[a]Participants missing/invalid FibroScan score (n = 49);

[b]Participants missing demographic survey and transgender excluded from AUDIT-C analysis (n = 26);

[c]Participants missing demographic survey (n = 18);

[d]Transgender excluded from AUDIT-C analysis as studies validated cut-offs in males and females (n = 8).

generally exposed to HCV early in their injecting careers[39]; therefore, the association with older age reflects a longer duration of time since first injection, and HCV infection, a key factor for liver disease progression.[35,36] Our findings are comparable in terms of the prevalence of significant fibrosis among community-based PWID HCV populations in Australia[40,41] and the United States,[42] but lower than those reported in PWID in India[43] and Portugal.[44] Half of the Indian cohort with chronic HCV had severe fibrosis and a third had cirrhosis.[43] These results were attributed to the comorbidity profile of the Indian sample where metabolic abnormalities (higher insulin resistance), higher BMI, steatosis and alcohol dependence were associated with severe fibrosis and cirrhosis (HBV co-infection also was associated with cirrhosis).[43] Similarly, in the Portuguese sample with chronic HCV, a third had cirrhosis, and HIV co-infection was common (16%) and associated with more advanced liver disease.[44] In contrast, our population of PWID with chronic HCV were predominantly mono-infected.

The association of older age and higher BMI with significant fibrosis in both the HCV-infected and HCV-uninfected populations is an important finding. Ageing PWID populations are driving accelerating liver disease burden through high HCV prevalence,[10,45,46] but may also be at risk of progressive liver disease through chronic conditions such as type 2 diabetes and fatty liver disease. Further characterizations of liver disease burden among community-based PWID, including detailed metabolic assessments, are needed. The lack of an association between risky alcohol intake and significant fibrosis is potentially explained by the limitations of the AUDIT-C brief screening tool which screens for recent hazardous and harmful alcohol consumption and is not diagnostic of alcohol use disorder.

Evaluations of interventions to optimize the cascade of HCV of care among PWID are lacking.[47] The LiveRLife screening strategy may be effective in enhancing HCV testing and liver disease staging; however, the drop-off in the HCV care cascades, between baseline assessment and clinical follow-up, and then to HCV treatment initiation, highlights the need to evaluate strategies that enhance the opportunity for rapid HCV assessment and treatment initiation. Although the project incorporated point-of-care HCV RNA testing, due to a lack of regulatory approval these results were not made available to participants. The development of well-tolerated, pangenotypic DAA regimens and the recent licensing of point-of-care HCV RNA testing technology[23,48] provides the opportunity to enhance linkage to treatment. Studies will shortly commence to evaluate rapid HCV RNA screening and same-day DAA initiation among PWID attending needle and syringe programs and among inmates of a remand prison setting. It is imperative that further evaluations are also performed in low- and middle-income countries, where the majority of the HCV burden lies.[10]

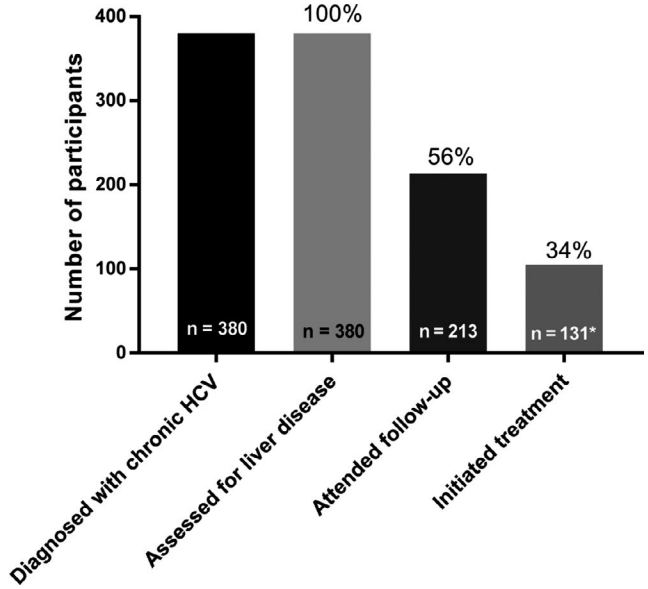

FIGURE 2 Cascade of HCV care among participants with HCV infection in the LiveRLife study. *Includes already on treatment at enrolment (n = 26)

This study has limitations. Participants were recruited from a variety of services targeting PWID including OST and drug user health services and therefore may be already engaged in care and our sample may not be representative of the broader population of PWID, particularly 'harder to reach' subgroups. We compared the demographic and injecting behaviour characteristics in the current PWID population from LiveRLife to ANSPS participants: more than 2,000 PWID enrolled from 53 NSP sites across Australia for cross-sectional behavioural and serosurveys.[26] The two populations were very similar in terms of demographic characteristics (ANSPS population median age, 42 years; 67% male; median age at first drug injection 19 years). The proportion of the LiveRLife participants on current OST (67%) is higher than among ANSPS participants (38% in 2018), given involvement of OST sites in recruitment. Similarly, the proportion of participants injecting daily or more in the ANSPS population (51% in 2018) is higher than reported among current PWID in LiveRLife (34%), a function of the broader eligibility criteria of the LiveRLife study which also included people with former and current injection drug use. A number of participants may have been aware of their HCV diagnosis and linked to care and awaiting DAA treatment prior to baseline. Due to the uncontrolled study design, and the background of the roll-out of unrestricted access to DAA therapy, evaluating the specific impact of the LiveRLife campaign model on DAA treatment uptake was not possible. Self-report data on drug use are also potentially subject to social desirability bias; however, this was minimized by the use of self-administered surveys on computer tablets.[49]

The LiveRLife study has demonstrated a marked increase in HCV treatment uptake in the DAA era and characterized the burden of liver disease among a large population of PWID accessing health services, including those with and without HCV infection. Gaps in the HCV care cascade highlight the need for concerted and ongoing efforts to improve treatment uptake. Comprehensive, innovative and acceptable models of care that also address the structural and social determinants of access to care, and strategies such as outreach to engage hard to reach populations, are required.[15] Further innovation, in relation to both screening strategies and HCV therapeutic interventions, is required to advance HCV elimination efforts among PWID.

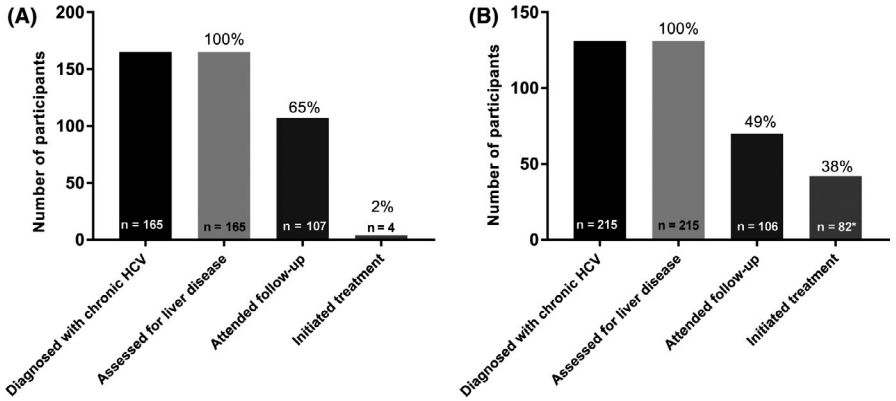

FIGURE 3 Pre- and post-universal DAA access cascade of HCV care among participants with HCV infection with 12 months of follow-up time to treatment uptake. A, Among participants enrolled prior to the availability of subsidized DAA treatment in March 2016 (ie pre-DAA era); B, Among participants enrolled since the availability of subsidized DAA treatment in March 2016 (ie DAA era); *Includes already on treatment at enrolment (n = 26)

TABLE 3 Unadjusted and adjusted analyses of factors associated with DAA treatment uptake among participants with HCV infection (n = 351)

	Treatment uptake (n = 102[a]), n (%)	Unadjusted model		Adjusted model[b,c]	
		OR (95% CI)	*P*	aOR (95% CI)	*P*
Age					
18-35 y	15 (22%)	1.00		1.00	
36-50 y	55 (28%)	1.39 (0.72, 2.67)	.325	2.03 (0.92, 4.49)	.082
≥51 y	32 (36%)	2.02 (0.98, 4.14)	.056	2.88 (1.18, 7.04)	.020
Sex[d]					
Male	77 (31%)	1.00		1.00	
Female	22 (23%)	0.67 (0.39, 1.16)	.150	0.63 (0.33, 1.21)	.168
Aboriginal/Torres Strait Islander[d]					
No	86 (31%)	1.00		1.00	
Yes	13 (21%)	0.59 (0.30, 1.14)	.114	0.74 (0.34, 1.59)	.435
Housing[d]					
Stable	68 (30%)	1.00		1.00	
Unstable	31 (27%)	0.87 (0.53, 1.43)	.580	1.38 (0.74, 2.56)	.312
Completed high school or higher education[d]					
No	67 (28%)	1.00		1.00	
Yes	32 (32%)	1.21 (0.73, 2.01)	.457	1.02 (0.55, 1.91)	.951
Incarceration[d]					
Never	34 (35%)	1.00		1.00	
Yes	65 (26%)	0.65 (0.39, 1.08)	.096	0.72 (0.39, 1.34)	.305
Recent injecting drug use[d]					
Not in previous month	39 (35%)	1.00		1.00	
Injecting in previous month	60 (26%)	0.64 (0.40, 1.05)	.077	0.69 (0.37, 1.29)	.248
Current OST[d]					
No	24 (28%)	1.00		1.00	
Yes	75 (29%)	1.04 (0.60, 1.79)	.883	0.83 (0.40, 1.71)	.614
Alcohol consumption (AUDIT-C)[e]					
Never	45 (29%)	1.00		1.00	
Low-risk male/female	16 (26%)	0.85 (0.44, 1.66)	.633	0.62 (0.28, 1.36)	.235
High-risk male/female	38 (31%)	1.11 (0.66, 1.85)	.703	1.32 (0.70, 2.49)	.386
FibroScan® Liver disease stage					
No/mild fibrosis (F0/F1)	58 (28%)	1.00		1.00	
Significant liver fibrosis (F2-F4)	40 (32%)	1.20 (0.74, 1.95)	.453	1.09 (0.60, 1.96)	.781
Missing/invalid result	4 (24%)	0.80 (0.25, 2.54)	.700	0.86 (0.23, 3.20)	.819
Clinical follow-up attendance					
None	28 (17%)	1.00		1.00	
Nurse follow-up	42 (35%)	2.71 (1.56, 4.71)	<.001	3.19 (1.61, 6.32)	.001
Physician follow-up	27 (59%)	7.16 (3.51, 14.60)	<.001	11.83 (4.89, 28.59)	<.001
Both nurse/physician follow-up	5 (31%)	2.29 (0.74, 7.10)	.152	3.19 (0.89, 11.47)	.076

[a]Denominator = 339;

[b]Participants already on treatment at enrolment excluded (n = 26);

[c]Random effects logistic regression model employed to take into account heterogeneity of treatment uptake across sites;

[d]Denominator = 343 due to missing demographic survey (treatment uptake n = 99);

[e]Denominator = 339 due to missing survey and exclusion of transgender (AUDIT-C studies validated cut-offs in males and females) (treatment uptake n = 99).

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Protocol Steering Committee: Gregory J. Dore (Kirby Institute, UNSW Sydney), Jason Grebely (Kirby Institute, UNSW Sydney), Mary Ellen Harrod (NSW Users and AIDS Association), Lucy Peolim (NSW Users and AIDS Association), Dianne How-Chow (St Vincent's Hospital Sydney), Jo Telenta (Australian Catholic University), Jude Byrne (Australian Injecting and Illicit Drug Users League), Paul Harvey (Hepatitis NSW), Sandra Jones (University of Wollongong), Adrian Dunlop (Newcastle Pharmacotherapy Service), Carla Treloar (Centre for Social Research in Health, UNSW Sydney), Yvonne Samuel (NSW Users and AIDS Association), Fiona Poeder (NSW Users and AIDS Association), Nicky Bath (ACON), Sione Crawford (NSW Users and AIDS Association), Alicia Baxter (St Vincent's Hospital Sydney) and Julian Keats (Newcastle Pharmacotherapy Service).

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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

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