Research Article
Viral Hepatitis

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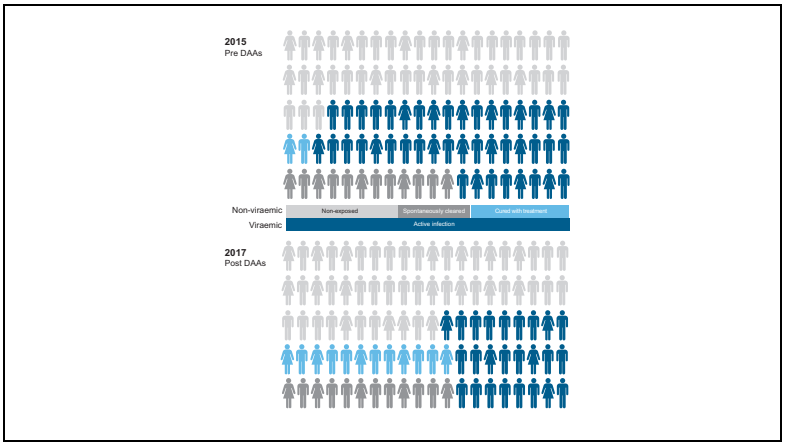
Association between rapid utilisation of direct hepatitis C antivirals and decline in the prevalence of viremia among people who inject drugs in Australia

Graphical abstract



Highlights

- Evidence to support feasibility of elimination of hepatitis C as a public health threat.
- High uptake of hepatitis C treatment reflected in reduction in viraemic prevalence.
- Surveillance and monitoring are required to track progress toward elimination goals.

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Lay summary

The World Health Organization's goal to reduce hepatitis C virus incidence by 80% will be difficult to achieve without widespread scale up and a corresponding reduction in viraemic prevalence among those most at risk of onward transmission. Our results indicate that a population-level reduction in viraemic prevalence is achievable through high levels of treatment and cure among people who inject drugs.

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Association between rapid utilisation of direct hepatitis C antivirals and decline in the prevalence of viremia among people who inject drugs in Australia

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Background & Aims: The World Health Organization (WHO) established targets to eliminate hepatitis C virus (HCV) infection as a public health threat by 2030. Evidence that HCV treatment can lower viraemic prevalence among people who inject drugs (PWID) is limited. Broad accessibility of direct-acting antiviral (DAA) therapy in Australia, since March 2016, provides an opportunity to assess the efficacy of these treatments at a population level in a real-world setting.

Methods: Data from Australia's annual bio-behavioural surveillance examined treatment uptake and estimated viraemic prevalence among PWID attending needle syringe programs nationally between 2015 and 2017. Multivariate logistic regression identified variables independently associated with HCV treatment among those considered eligible (anti-HCV positive excluding HCV RNA negative with no self-reported history of HCV treatment) in 2017.

Results: Annual samples ranged from 1,995–2,380 PWID. Anti-HCV prevalence declined from 57% (2015) to 49% (2017, χ^2 p trend <0.001), with 40–56% of anti-HCV positive respondents providing sufficient sample for HCV RNA testing. Between 2015 and 2017, treatment uptake among those eligible increased from 10% to 41% (χ^2 p trend <0.001) and viraemic prevalence among the overall sample declined from 43% to 25% (χ^2 p trend <0.001). In multivariable analysis, older age (≥50 years adjusted odds ratio [aOR] 1.82; 95% CI 1.09–3.06; $p = 0.023$ and 44–49 years aOR 1.75; 95% CI 1.03–3.00; $p = 0.038$ *vs.* ≤37 years) and history of opioid substitution therapy (aOR 2.06; 95% CI 1.30–3.26; $p = 0.002$) were independently associated with treatment.

Conclusions: This study confirms PWID are willing to initiate treatment when HCV DAA therapy is available and provides population-level evidence of a decline in viraemic prevalence among people most at risk of ongoing HCV transmission. Scaled up surveillance and monitoring are required to evaluate progress toward WHO HCV elimination goals.

Lay summary: The World Health Organization's goal to reduce hepatitis C virus incidence by 80% will be difficult to achieve without widespread scale up and a corresponding reduction in viraemic prevalence among those most at risk of onward transmission. Our results indicate that a population-level reduction in viraemic prevalence is achievable through high levels of treatment and cure among people who inject drugs.

Introduction

The treatment landscape for chronic hepatitis C virus (HCV) infection has transformed over the past five years, with the development of all-oral direct-acting antiviral (DAA) regimens with minimal toxicity and cure rates above 95%.[1] In keeping with the optimism surrounding these new treatments, the World Health Organisation (WHO) recently developed targets with a goal to eliminate viral hepatitis as a public health threat by 2030, including 80% of the eligible chronic HCV population treated, 65% reduction in liver-related mortality and 80% reduction in HCV incidence by 2030.[2]

The WHO goal to eliminate viral hepatitis (HCV and hepatitis B) as a public health threat, is a clear response to the rising burden of liver disease globally, with viral hepatitis ranked as the seventh leading cause of death worldwide in 2013 and ~700,000 deaths attributed to HCV annually.[3] An estimated 71 million people are living with chronic HCV infection,[4] with people who inject drugs (PWID) the predominant affected population in high income countries and a major population in many low and middle-income countries.[5] PWID have been recognised as a priority population for DAA therapy,[6,7] given high HCV prevalence,[8] the rising burden of liver disease,[5] the potential for treatment as prevention benefits[9] and associated enhanced cost-effectiveness.[10] Despite these recommendations, restrictions that exclude people with ongoing substance use limit access to DAA therapy by PWID in many settings.[11,12] Other restrictions, based on the extent of liver disease or a requirement for specialist prescribing also impact uptake by PWID even in settings without substance use restrictions, as the large majority of PWID have early liver disease[13] and often have poor access to specialist services.[14]

Australia implemented unrestricted subsidised access to DAA therapy in March 2016, ensuring that all adults with chronic HCV were eligible for DAA therapy irrespective of liver disease stage and ongoing drug use. Further, all medical practitioners can prescribe DAA therapy, although low caseload non-specialist prescribers are required to consult a specialist prior to

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prescribing. Over the initial 16-month period (March 2016 to June 2017), 43,360 people initiated DAA therapy in Australia, equivalent to 19% of the estimated 227,000 Australians living with chronic HCV in 2015.[15] There is evidence that initial DAA therapy targeted those with more advanced liver disease, with an estimated 70% of people living with HCV-related cirrhosis initiating DAA therapy in 2014–2016, including through pharmaceutical industry compassionate access prior to Government subsidy.[15]

The initial DAA uptake in Australia, including the high coverage of people with HCV-related cirrhosis, has laid a solid foundation for achieving the WHO elimination goals.[2] The 65% mortality reduction goal appears achievable, however, the goal of reducing HCV incidence by 80% will depend on treatment uptake and outcomes (including rate of reinfection) among PWID.[16] Therefore, it is crucial to have a robust surveillance system to monitor DAA treatment uptake, prevalence of HCV RNA infection, HCV incidence and HCV reinfection among PWID. The Australian Needle Syringe Program Survey (ANSPS), incorporating behavioural and simplified serological and virological assessments, has monitored HIV and HCV antibody prevalence among PWID since the mid-1990s. The addition of specific questions on HCV treatment uptake in recent years and HCV RNA testing from 2015 provides a unique opportunity to evaluate the initial impact of unrestricted DAA therapy access in this key population. This study aimed to examine HCV treatment uptake prior to and following unrestricted DAA access among a national sample of PWID to assess the impact of treatment on viraemic prevalence, and determine factors associated with uptake.

Materials and methods

Study design and participants

The ANSPS methodology has been described in detail elsewhere.[17] In brief, the ANSPS is an annually repeated cross-sectional bio-behavioural sentinel surveillance project; conducted over a 1–2-week period in October through a national network of ~50 needle syringe program (NSP) services. All PWID attending participating NSPs during the implementation period are asked by NSP staff if they are willing to participate. Consenting NSP attendees self-complete a brief questionnaire covering demographic characteristics, drug use, HCV testing and treatment behaviours and provide a finger-stick capillary dried blood spot (DBS). Participation is voluntary, anonymous and not financially reimbursed. Response rates were calculated by dividing the number of ANSPS respondents by the number of individual NSP attendees during the survey implementation period and multiplying by 100. Although respondents are eligible to participate only once in each survey round, a small number of respondents participate on more than one occasion.[17] A simple deterministic method was used to create a matching key (using name initials, year/month of birth, gender and indigenous status) and only the first survey record was retained among repeat respondents in each survey round.[17] Ethical approval was obtained from the UNSW Sydney Human Research Ethics Committee (HREC) and relevant jurisdictional and site specific HRECs.

Procedures

In all years, 2015 to 2017, consenting NSP attendees were asked to self-report lifetime and recent (last 12 months) history of HCV testing. Respondents who were aware they had been exposed to HCV were asked "Have you EVER had any treatment for your hepatitis C?", with response options: a) yes, in the last year; b) yes, more than a year ago; and c) no treatment. Respondents who reported a lifetime history of HCV treatment were asked to specify the type of treatment (interferon-based, interferon-free DAAs or specify another type of treatment). Respondents were also asked to report the outcome of treatment (if known). Respondents who reported successful HCV treatment were asked to report lifetime and recent (last 12 months) testing for reinfection and their current HCV viraemic status (if known).

Capillary DBSs were collected on Whatman 903 cotton-fibre protein saver cards using a single use lancet (GE Healthcare, Chicago, United States). Specimens were stored at room temperature and couriered to a central laboratory every other day. A modified third-generation enzyme immunoassay (Monolisa anti-HCV Plus EIA version 3, Bio-Rad, Marnes-la-Coquette, France) detected HCV antibodies (anti-HCV). HCV enzyme immunoassays have demonstrated high specificity (99%) and sensitivity (99%) using DBS specimens.[18] HIV antibodies were detected using Murex 1.2.0 HIV 1/2 ELISA (DiaSorin, Saluggia, Italy), with reactive specimens subjected to Western blot confirmatory testing (Bio-Rad New LAV blot-1, Marnes-la-Coquette, France).

In 2015, HCV RNA was quantified using a modified Abbott RealTime (Illinois, United States) HCV RNA assay. The Abbot RealTime HCV RNA assay involves specimen extraction automation using the Abbott M2000SP coupled with the M2000RT Realtime PCR instrument. A bias (+1.91 Log10) applied post run gave a quantifiable DBS HCV viral load (VL) result with a lower limit of detection of 977 IU/ml (plasma equivalency). In 2016, the Abbot RealTime HCV RNA assay was not compatible with DBS and samples were tested for HCV RNA using the Hologic Panther™. In 2016 and 2017, HCV RNA was quantified using the Aptima HCV Quant Dx assay (Hologic, Inc. San Diego, Calif) which has a limit of quantitation (LOQ) 10 IU/ml and an upper LOQ of 10^8 IU/ml in plasma. An offboard DBS elution protocol was applied prior to sampling. To correct for haematocrit, all post run DBS VL results on the Aptima assay were multiplied by a plasma conversion factor of 36.36. This calculation was based on the following assumptions: 45% haematocrit average per DBS, 50 μl DBS volume and 1000 μl Aptima transport media volume and the lower limit of detection was 525 IU/ml (plasma equivalency).

Outcomes

All ANSPS respondents with sufficient DBS for anti-HCV testing were included in this study. Anti-HCV serology was used to assign respondents to one of two groups: HCV exposed (HCV antibody positive) or HCV non-exposed (HCV antibody negative). Among the HCV-exposed group, HCV RNA determined the proportion with active (quantifiable HCV RNA) or cleared (non-quantifiable HCV RNA) HCV infection at the time of survey implementation. Among those with cleared infection, self-reported HCV treatment history determined respondents with spontaneous*vs.* treatment-induced clearance. Respondents were considered 'ever eligible for treatment' if they had active HCV infection or cleared infection with a self-reported history of HCV treatment (HCV antibody positive excluding those with cleared infection and no history of treatment).

Statistical analysis

Demographic characteristics, drug use and related behaviours and HIV/HCV serological status were compared among annual samples and groups using non-parametric rank-sum test and chi-square test for continuous and categorical variables, respectively. Temporal trends were assessed using $\chi^2 p$ trend. Post stratification weightings were applied to adjust for sample bias with respect to previous and recent initiation of HCV treatment and gender among respondents with sufficient DBS sample for HCV RNA testing. HCV treatment uptake was assessed among respondents determined eligible for treatment. Logistic regression models estimated crude and adjusted odds ratios (aOR) and 95% CIs to assess factors associated with a history of HCV treatment in October 2017. Factors hypothesised to be associated with recent initiation of treatment included gender,[19] Indigenous status,[20,21] sexual identity, language spoken at home by parents, HIV status, age, last drug injected, injection frequency,[22] opioid substitution therapy[23] imprisonment[24] and geographic location.[22] Variables associated with the outcome at p <0.10 in bivariate analysis were considered for inclusion in the multiple logistic regression model using a backwards stepwise approach where factors were sequentially eliminated according to the result of a likelihood ratio test. All analyses were conducted using STATA software version 14.2 (Stata Corporation, College Station, TX, USA).

For further details regarding the materials used, please refer to the CTAT table.

Results

Sample characteristics

After excluding records for respondents who had participated more than once in a survey round (range 9–27), ANSPS samples were 2,295, 2,189 and 2,573 in 2015, 2016 and 2017, respectively (response rate 41% in all years). Respondents with insufficient or equivocal anti-HCV results were excluded, resulting in samples of 2,046 (2015), 1,995 (2016) and 2,380 (2017).

In all survey years, 2015 to 2017, around one-third of respondents were women (range 31–33%), 5–6% reported that parents spoke a language other than English at home, 1.4–2.1% were HIV antibody positive, 0.5–1.0% were HIV and HCV antibody positive (Table S1). Although there were no differences in demographic characteristics, drug use and related behaviours among the 2016 and 2017 samples, the 2015 sample was significantly different to later years. In 2015, a lower proportion of respondents identified as indigenous Australian, last injected stimulants, injected daily or more frequently and reported a history of or recent imprisonment compared to 2016 and 2017 samples. The mean age of respondents and the mean number of years since first injection were also lower in 2015 compared to 2016 and 2017. Conversely, a higher proportion of respondents had last injected opioids, had a lifetime history or were currently on opioid substitution therapy (OST) in 2015 compared to 2016 and 2017. HCV antibody prevalence declined from 57% in 2015 to 49% in 2017 (χ^2 p trend <0.001) (Table 1).

Combined results of anti-HCV and HCV RNA testing and self-reported history of HCV treatment are shown (Table 1). After applying weightings due to adjust for sample bias (Table S2), the proportion of respondents with spontaneous clearance (non-quantifiable HCV RNA and no treatment history) was stable at 21–25% of the HCV antibody positive group between 2015 and 2017 (χ^2 p trend 0.172), comprising 12% of the overall sample (Fig. 1). Among those assessed as eligible for treatment (excluding those with spontaneous clearance), treatment initiation (ever) increased from 10% in 2015 to 41% in 2017 (χ^2 p trend <0.001), while treatment-induced clearance increased from 4% in 2015, to 17% in 2016, to 31% in 2017 (χ^2 p trend <0.001,Fig. 2). Among the overall sample, HCV viraemic prevalence declined from 43% in 2015, to 32% in 2016, to 25% in 2017 (χ^2 p trend <0.001,Fig. 1).

In 2017, 49 (10% adjusted and non-adjusted) respondents had a lifetime history of HCV treatment and quantifiable HCV RNA. This group comprised 21 (4%) who reported interferon-based treatment, 10 (2%) who were currently receiving DAA

Table 1. Hepatitis C antibody and RNA results and self-reported treatment history among ANSPS respondents, 2015 to 2017.

	2015		2016		2017	
Anti-HCV serology						
Sample N	n = 2,295		n = 2,189		n = 2,573	
Insufficient	82		72		110	
Indeterminate	167		122		83	
HCV unexposed (anti-HCV undetected)	880		987		1,217	
HCV exposed (anti-HCV detected)	1,166		1,008		1,163	
HCV RNA results among HCV exposed group	n = 1,166		n = 1,008		n = 1,163	
Insufficient	532		604		515	
Active infection (quantifiable HCV RNA)	481		252		338	
Cleared infection (non-quantifiable HCV RNA)	153		152		310	
HCV RNA and HCV treatment among HCV exposed group	n = 634		n = 404		n = 648	
Active infection (quantifiable HCV RNA):	Unweighted	Weighted[#]	Unweighted	Weighted[#]	Unweighted	Weighted[#]
No treatment history	452	452	227	234	289	287
Recent treatment history	9	6	16	13	28	31
Prior treatment history	20	23	9	9	21	19
Cleared infection (non-quantifiable HCV RNA):						
No treatment history[*]	134	132	92	95	162	161
Recent treatment history	3	3	52	43	111	115
Prior treatment history	16	18	8	10	37	34

ANSPS, Australian Needle Syringe Program Survey; HCV, hepatitis C virus.
[#] Post-stratification weightings adjusted for previous and recent initiation of HCV treatment and gender.
[*] Ineligible for treatment (spontaneously cleared infection).

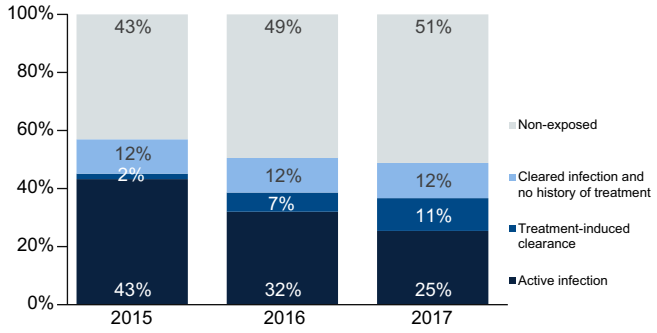

Fig. 1. HCV viraemic status[#] of ANSPS respondents, 2015 to 2017.[#]Post-stratification weightings adjusted for previous and recent initiation of HCV treatment and gender. ANSPS, Australian Needle Syringe Program Survey; HCV, hepatitis C virus.

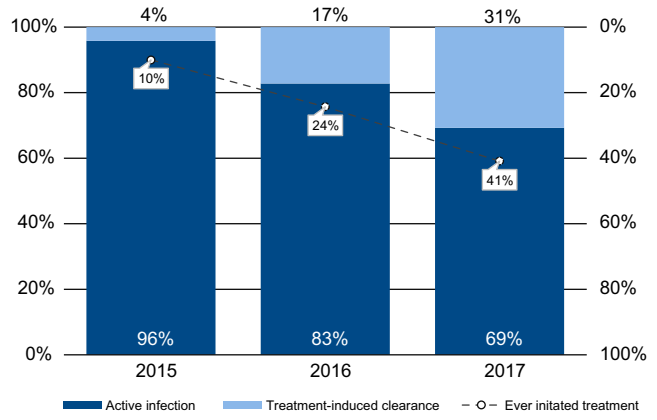

Fig. 2. Hepatitis C viraemic status[#] and hepatitis C treatment uptake among treatment eligible respondents, 2015 to 2017. [#]Post-stratification weightings adjusted for previous and recent initiation of HCV treatment and gender. HCV, hepatitis C virus.

treatment, 10 (2%) who reported successful DAA treatment, 4 (1%) who reported that DAA treatment had not resulted in cleared infection, 2 (0.5%) who withdrew from treatment and 2 (0.5%) who did not provide additional information on DAA treatment outcomes. Thus, we identified 18 respondents with possible relapse or reinfection following DAA treatment. Of these, 3 respondents reported HCV RNA testing to identify re-infection, although only 1 respondent self-reported HCV reinfection.

After restricting the 2017 dataset to 486 respondents assessed as eligible for treatment; older age, non-Indigenous background, injection of opioids and a history of OST were associated with HCV treatment in bivariate analysis (Table 2). In multivariable analysis, older age (50 years or older aOR 1.82; 95% CI 1.09–3.06; $p = 0.023$ and 44–49 years aOR 1.75; 95% CI 1.03–3.00; $p = 0.038$*vs.* 37 years or younger) and a history of OST (aOR 2.06; 95% CI 1.30–3.26; $p = 0{\cdot}002$) were independently associated with HCV treatment. Associations between HCV treatment and potentially vulnerable sub-populations of PWID were not observed; including among those who injected daily or more frequently, those with a history of imprisonment, those residing in regional or remote areas and people from a cultural background where parents speak a language other than English at home. Respondents from an indigenous Australian background were significantly less likely to have initiated HCV treatment than their non-Indigenous counterparts in bivariate analysis (31%*vs.* 43%, $p = 0.030$), however Indigenous status was not associated with the outcome in the adjusted model.

Discussion

The elimination of HCV as a global public health threat will require strategies that provide DAA access to high-risk populations, often those who are highly marginalised in society. This study provides evidence that relatively high rates of HCV treatment can be achieved among PWID when DAA therapy is made available without restrictions. In 2017, an estimated 41% of PWID who were assessed as eligible had initiated treatment and 31% had cleared their infection. This represents an 8-fold increase in treatment-induced clearance among Australian PWID compared to the pre-DAA HCV treatment era, when 4% of treatment eligible PWID had cleared their infection. Remarkably, this rapid increase in treatment uptake and clearance occurred within the first 19 months of implementation of unrestricted access to DAAs, with Australia one of only 12 countries globally considered "on track" to eliminate HCV as a public health treat by 2030.[15,25]

Previous mathematical modelling, based on data from Melbourne, indicated that DAA treatment uptake of 8% per annum among Australian PWID (equivalent to 16% per annum among those with chronic HCV) could potentially achieve HCV elimination among PWID by 2027. Key assumptions in this model were that harm reduction measures (high NSP coverage and access to OST) were maintained, uptake was consistent across risk behaviour groups and HCV reinfection occurred at 5/100 person years.[9] Although it is difficult to distinguish between virological relapse, incomplete therapy and reinfection in this study, treatment uptake was comparable among those in high and lower risk groups, including those who did and did not inject daily, PWID with and without a history of imprisonment, those from culturally and linguistically diverse backgrounds and PWID living in regional/remote locations. To achieve HCV elimination among PWID there needs to be both a progressive reduction in viraemic prevalence, and a subsequent decline in both primary infection and reinfection among susceptible PWID. The significant decline in viraemic prevalence among Australian PWID from 43% in 2015, 32% in 2016 to 25% in 2017, is indicative of initial success in this endeavour and demonstrates the potential of DAA therapy to provide both individual and population-level treatment as prevention benefits.

The clearly demonstrated potential for PWID to be reinfected with HCV following successful DAA therapy is of concern[26] and may contribute to a lack of prioritisation of PWID for treatment in some settings. In 2017, only one respondent self-reported reinfection following DAA treatment, however 18 respondents had evidence of HCV viraemia post-DAA treatment consistent with either virological relapse or reinfection. We believe the best approach to HCV reinfection is enhanced access to harm reduction and rigorous monitoring for reinfection post-treatment, with access to DAA therapy for retreatment. It is inevitable that HCV reinfection cases will occur, particularly in the early years of a rapid DAA scale-up among PWID. However, if DAA uptake continues, modelling suggests that HCV viraemic prevalence will decline to a point where HCV reinfection risk falls dramatically.[27] Earlier detection and successful retreatment of reinfection will

Table 2. Factors associated with hepatitis C treatment uptake among treatment eligible respondents in 2017.

Variable[#]	Total sample (N = 486)	HCV treatment (n = 197)	No HCV treatment (n = 289)	Unadjusted		Adjusted	
				OR (95% CI)	*p* value	aOR (95% CI)	*p* value
Gender							
Male (ref.)	321 (66)	123 (38)	198 (62)	–			
Female	164 (34)	73 (45)	91 (55)	1.29 (0.88–1.89)	0.189		
Sexual identity							
Heterosexual (ref.)	381 (78)	158 (41)	223 (59)	–			
Bisexual/Gay/Lesbian	67 (14)	28 (42)	99 (58	1.01 (0.60–1.72)	0.961		
Age, quartiles (%)							
≤37 years (ref.)	132 (27)	43 (33)	89 (67)	–		–	
38–43 years	122 (25)	45 (37)	77 (63)	1.21 (0.72–2.03)	0.471	1.19 (0.70–2.00)	0.523
44–49 years	111 (23)	51 (46)	60 (54)	1.76 (1.04–2.96)	0.034	1.75 (1.03–3.00)	0.038
≥50 years	120 (25)	58 (48)	62 (52)	1.94 (1.16–3.23)	0.011	1.82 (1.09–3.06)	0.023
Indigenous Australian							
No (ref.)	375 (77)	163 (43)	212 (57)	–			
Yes	99 (20)	31 (31)	68 (69)	0.59 (0.37–0.95)	0.030		
Language other than English spoken at home by parents							
No (ref.)	456 (94)	186 (41)	270 (59)	–			
Yes	27 (6)	11 (41)	16 (59)	1.00 (0.45–2.20)	0.966		
HIV antibody positive							
No (ref.)	482 (99)	194 (40)	288 (60)	–			
Yes	4 (1)	3 (75)	1 (25)	4.45 (0.46–43.13)	0.197		
History of imprisonment							
No (ref.)	172 (35)	71 (41)	101 (59)	–			
Yes	305 (63)	123 (40)	182 (60)	0.98 (0.67–1.42)	0.904		
Last drug injected							
Opioids (ref.)	289 (59)	129 (45)	160 (55)	–			
Stimulants	167 (34)	58 (35)	109 (65)	0.66 (0.45–0.98)	0.039		
Other	30 (6)	10 (33)	20 (67)	0.62 (0.28–1.37)	0.238		
Frequency of injection[*]							
Less than daily (ref.)	224 (46)	99 (44)	125 (56)	–			
Daily or more frequently	259 (53)	98 (38)	161 (62)	0.77 (0.53–1.11)	0.157		
History of opioid substitution therapy							
No (ref.)	117 (24)	32 (27)	85 (73)	–		–	
Yes	369 (76)	165 (45)	204 (55)	2.15 (1.36–3.39)	0.001	2.06 (1.30–3.26)	0.002
Geographic location							
Major cities (ref.)	360 (74)	149 (41)	211 (59)	–			
Regional/remote	126 (26)	48 (38)	78 (62)	0.87 (0.57–1.32)	0.517		

[#] Variables adjusted for missing data.
[*] In the last month.
Logistic regression models estimated crude and adjusted odds ratios, 95% confidence intervals and *p* values.

assist in reduction of HCV viraemic prevalence and overall elimination efforts.

Our study has limitations. First, behavioural data are self-reported and subject to potential recall bias. Second, we captured PWID who were engaged with NSP services and likely to be highly motivated to embark on HCV treatment, having done so in the initial 19 months following broad access to DAAs. We have also likely captured some PWID enrolled in research studies, where there are additional layers of support for engagement and retention in care. Although the demographic characteristics of ANSPS samples are consistent with other surveillance systems among PWID and have been demonstrated to be as representative a sample of the wider population of Australian PWID as practical to obtain,[28] treatment uptake may be overestimated, and the generalisation of findings should be undertaken with caution. This study classified respondents as having active (quantifiable HCV RNA) or cleared (non-quantifiable HCV RNA) infection at the time of survey implementation and was unable to assess sustained virological response. It is therefore critical to continue to monitor HCV treatment uptake, viraemic prevalence and reinfection, including among sub-populations of highly marginalised PWID and those at higher risk of HCV transmission. DBSs are an easily administered and minimally invasive method to obtain specimens for surveillance purposes, with high acceptability among PWID.[29] Studies comparing results from DBS and serum/plasma have demonstrated very high specificity and high sensitivity to detect anti-HCV and very good concordance when detecting HCV RNA.[18,30] While sensitivity using DBS is lower than in serum when detecting HCV RNA among people with low concentrations of HCV RNA,[18] this is rare among people with untreated mono-infection. Importantly, we identified HCV RNA among people who were yet to complete treatment but who may have achieved treatment-induced clearance in the months following the survey. Finally, although demographic characteristics and drug use and related behaviours of respondents in 2016 and 2017 samples were comparable, some differences were observed in the 2015 sample and the 6% decline in HCV antibody prevalence observed between 2015 and 2016 may be due to differences in ANSPS samples, rather than an early treatment as prevention effect.

Australia has implemented a number of specific initiatives that prioritise accessibility of HCV treatment for PWID, including in community settings,[31] correctional facilities[32] and OST clinics.[33] Our finding, that treatment initiation was comparable across sub-populations of highly marginalised PWID (for example people with a history of imprisonment, those injecting daily

or more frequently and those living in regional remote locations), supports these efforts. Our observation that older age was associated with recent treatment initiation among PWID is consistent with initial therapy targeting those with more advanced liver disease and the WHO goal to reduce HCV-related mortality. Nevertheless, more than 1 in 3 PWID had initiated HCV treatment across all age groups. Similarly, our finding that people with a history of OST were more likely to have initiated treatment likely reflects HCV treatment initiatives located with these settings[33] and the willingness of people on OST to engage in their broader health care.[34]

Australia is in an enviable position, with unrestricted subsidised access to DAA therapy among PWID and well established, high coverage harm reduction and prevention programs.[17] Findings from this study, including rapid uptake of DAA therapy and reduced viraemic prevalence of active HCV infection among PWID are encouraging and provide proof of concept that eliminating HCV as a public health threat through HCV treatment as prevention is feasible. In settings where WHO HCV elimination goals are overwhelming due to scale and cost, micro-elimination has been proposed as a way forward.[35] This concept involves setting smaller goals to eliminate HCV among sub-populations, in specific settings or by geographic location. However, in countries where PWID are the predominant group at risk of transmission, a thorough understanding of treatment initiation, including among sub-populations unwilling or unable to access treatment, is necessary to guide progress. Remaining challenges include scaling up DAA therapy among PWID in settings where access is currently limited, maintaining the momentum of scaled-up HCV treatment initiation in settings like Australia and Iceland that are currently on track to achieve WHO HCV elimination targets[25,36] and ensuring equity of access among vulnerable sub-populations of PWID, including those at higher risk of HCV transmission. It will also be necessary to evaluate the impact of reduced viraemic prevalence on HCV primary infection and reinfection among PWID, given this is the population most at risk of ongoing transmission in most countries.

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Conflict of interest

GJD is a consultant/advisor and has received research grants from Merck, Gilead, Bristol-Myers Squibb, and AbbVie outside the submitted work. JG is a consultant/advisor and has received research grants from AbbVie, Cepheid, Gilead, Janssen, and Merck outside the submitted work. All other authors declare no conflict of interest.

Please refer to the accompanyingICMJE disclosure forms for further details.

Authors' contributions

JI and LM designed the study and were provided with funding for the project. JI and LM were involved in data collection. BC and PC conducted all laboratory testing. JI was responsible for analyses, Tables and Figures. All authors critically examined the analyses and findings, contributed to draft versions of the manuscript and approved the final version.

Supplementary data

Supplementary data to this article can be found online athttps://doi.org/10.1016/j.jhep.2018.09.030.

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