Enhancing the care cascade for hepatitis C infection in marginalised populations

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The Kirby Institute

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Background: Morbidity and mortality associated with hepatitis C virus (HCV) infection is rising globally. Direct-acting antiviral (DAA) therapy provides an opportunity to address this burden. HCV elimination goals are dependent on improving the HCV care cascade among marginalised populations, particularly people who inject drugs (PWID). **Aims:** This research aimed to assess the feasibility and outcomes of strategies to enhance HCV testing and diagnosis, liver disease assessment and treatment uptake in PWID and homeless people pre- and post-access to DAA therapy. **Methods:** Chapter 2 presents a systematic review of interventions to enhance HCV testing, linkage to care and treatment uptake among PWID using a search of electronic databases covering interventional studies published before July 2016. Relative risk ratios were generated for included studies. Chapters 3 to 5 draw on an observational cohort study of HCV screening and linkage to care, LiveRLife. Chapter 3 evaluates the acceptability and preferences of a simplified HCV RNA diagnostic algorithm. Acceptability of finger-stick HCV RNA testing and self-reported preferences were assessed (n=565). Chapters 4 and 5 characterise the HCV care cascade among PWID and homeless people. HCV RNA prevalence, liver fibrosis distribution and treatment uptake were evaluated among people attending homelessness services (n=202) and PWID (n=839) enrolled in LiveRLife. **Key Findings:** The systematic review indicated interventions that enhanced the HCV care cascade included onsite-testing, facilitated referral and integration of HCV care within drug treatment and psychiatric services delivered by multi-disciplinary teams. The HCV diagnostic acceptability study found that a majority of participants (65%) preferred finger-stick testing over venepuncture, with preference for results in 60 minutes. In homeless and PWID LiveRLife populations, high HCV RNA prevalence and significant liver fibrosis were observed. HCV treatment uptake increased considerably in the DAA era among homeless people (49%) and PWID (38%); however, concerted efforts are needed for further improvements. **Conclusion:** DAA therapy has rapidly improved the HCV cascade of care among marginalised populations, but major gaps remain. Further innovations, including simplified models of care with rapid HCV diagnosis and linkage to treatment, are required to achieve HCV elimination targets by 2030.

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Details of publication #2:
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Authors: Sahar Bajis, Lisa Maher, Carla Treloar, Behzad Hajarizadeh, Francois MJ Lamoury, Yasmin Mowat, Marcel Schulz, Alison D Marshall, Evan B Cunningham, Victoria Cock, Nadine Ezard, Carla Gorton, Jeremy Hayllar, Julie Smith, Michelle Whelan, Marianne Martinello, Tanya L Applegate, Gregory J Dore, Jason Grebely

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List of publications and conferences

Publications

A list of peer-reviewed publications (i.e. submitted or published) related to the work contained within this thesis is presented below:

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- Bajis, S., Grebely, J., Cooper, L., Smith, J., Owen, G., Chudleigh, A., et al. (2019). Hepatitis C virus testing, liver disease assessment and direct-acting antiviral treatment uptake and outcomes in a service for people who are homeless in Sydney, Australia: The LiveRLife homelessness study. *Journal of Viral Hepatitis. DOI: 10.1111/jvh.1311*. (Chapter 4)
- Bajis, S., Grebely, J., Hajarizadeh, B., Applegate, T., Harrod, M., Byrne, J., et al. (2019). Hepatitis C virus testing, liver disease assessment and direct-acting antiviral treatment uptake and outcomes among people who inject drugs in Australia: The LiveRLife study (submitted to *Journal of Viral Hepatitis* for publication). (Chapter 5)

Conferences presentations

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- Bajis, S., Grebely, J., Cooper, L., Smith, J., Owen, G., Chudleigh, A., et al. Hepatitis C virus testing, liver disease assessment and direct-acting antiviral

treatment uptake and outcomes in a service for people who are homeless in Sydney, Australia: The LiveRLife homelessness study. Oral Presentation: 7th International Symposium on Hepatitis Care in Substance Users, Cascais, Portugal, 19-21 September 2018.

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- Bajis, S., Maher, L., Treloar, C., Hajarizadeh, B., Lamoury, F. M. J., Mowat, Y., et al. Acceptability and preferences of point-of-care finger-stick whole-blood and venepuncture hepatitis C virus testing among people who inject drugs in Australia. Poster: World Hepatitis Summit 2017, Sao Paulo, Brazil, 1-3 November 2017.
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in Australia (poster). Australasian Viral Hepatitis Elimination Conference 2017, August 2017, Cairns, Australia.

Abbreviations

(in alphabetical order)

AHR	adjusted hazard ratio
ALT	alanine aminotransferase
aOR	adjusted odds ratio
AUDIT-C	Alcohol Use Disorders Identification Test – Consumption
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
DAA	direct-acting antiviral
DALY	disability-adjusted life-years
DBS	dried blood spot
FDA	United States Food and Drug Administration
GBD	Global Burden of Disease
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
INT	interferon
ITT	intention-to-treat
kPa	kilopascale
LMIC	low- and middle-income countries
LSM	liver stiffness measurement
MSM	men who have sex with men
NSP	needle and syringe program
NSW	New South Wales
OR	odds ratio
OST	opioid substitution therapy
PAF	population attributable fraction
PBS	pharmaceutical benefits scheme
PWID	people who inject drugs

PWUD	people who use drugs
RBV	ribavirin
RCT	randomised controlled trial
RNA	ribonucleic acid
ROBINS-I	Risk Of Bias In Non-randomized Studies - of Interventions
RR	relative risk ratio
WHO	World Health Organization

Chapter 1: Introduction and literature review

This chapter provides an introductory overview of the literature and rationale for the research presented in this thesis. It begins with a summary of the World Health Organization (WHO) hepatitis C virus (HCV) elimination goals underpinning the body of work presented in this thesis. An overview of the global epidemiology and natural history of chronic HCV infection, with a focus on marginalised populations at high-risk of HCV transmission, in particular people who inject drugs (PWID), is presented. A summary of the evolution of HCV therapy including the development of direct-acting antiviral (DAA) therapy is provided. Finally, a background to the HCV care cascade globally and among PWID, followed by strategies to enhance the HCV care cascade in the general populations and barriers to engaging PWID along the care cascade, is included. The chapter concludes with an overview of the thesis, including its rationale, aim and objectives.

1.1 Hepatitis C virus elimination by 2030

Over the last three decades, the burden of viral hepatitis has increasingly garnered global concern. The vast majority of this burden has been attributed to hepatitis B virus (HBV) and HCV infections,[1, 2] responsible for 96% (~1.34 million) of all hepatitis-related mortality globally.[3] Importantly, HCV-related morbidity and mortality are expected to rise due to ageing populations who became infected during peak HCV epidemics 20-30 years prior.[4-7] In the absence of a vaccine against HCV infection, response to the epidemic has largely focused on prevention strategies such as blood

safety in healthcare settings and harm reduction for people who inject drugs (PWID).[8, 9] Despite the progress made in reducing HCV transmission through these prevention measures,[4, 10-13] the management of people with HCV infection has been limited due to the lack of safe, tolerable and effective treatment options.[14, 15] Recognised as one of the most important breakthroughs in modern medicine, the development of interferon-free, all-oral, short-duration, highly efficacious (>95% cure rates) and tolerable DAA therapy has revolutionised the management of HCV infection and underpinned development of HCV elimination strategies.[16]

The licensure of the first DAA on the market in 2013 marked the beginning of a new era in the clinical and public health management of HCV infection.[17] As such, in 2016, the 69th World Health Assembly endorsed the Global Health Sector Strategy for Viral Hepatitis, which launched an ambitious goal to eliminate HCV infection as a public health threat by 2030.[16]

HCV elimination by 2030 is defined by outcome targets of 80% reduction in new infections (incidence) and 65% reduction in HCV-related deaths compared with the 2015 baseline.[16] According to mathematical modelling, HCV elimination can be achieved through adequate service delivery of five synergistic core prevention and treatment interventions (Table 1).[18, 19] The HCV elimination service targets include the diagnosis of 90% of people living with HCV infection and treatment of 80% of people diagnosed with chronic HCV infection.[16, 20]

PWID are a priority population in the global HCV elimination efforts.[3] With the development of an effective vaccine unlikely in the next decade,[21, 22] the scale-up of harm reduction services and DAA therapy (i.e. treatment as prevention) among populations at high-risk of transmission are fundamental to efforts to reach the incidence reduction target.[23-27] High coverage of combined opioid substitution therapy (OST) and needle and syringe programs (NSP) can lead to a reduction in HCV transmission by up to 80%.[23-30] OST alone can also reduce incidence by 60%.[25, 30, 31] The reversal of the rising burden of HCV is also feasible due to the availability of DAA therapy with high cure rates.[19] In addition, mathematical modelling has suggested DAA therapy scale-up among PWID can lead to considerable reductions in HCV incidence and prevalence,[32, 33] especially in combination with OST and NSP.[34] For example, in a setting of 40% coverage OST and NSP, annually treating 1, 2.3 and 4.2 per 100 PWID would halve HCV prevalence over 10 years in settings with a chronic HCV prevalence of 20%, 40%, or 60%, respectively.[34] To this end, concerted and comprehensive efforts which prioritise broad scale-up of combined harm reduction, screening and treatment services for HCV infection are paramount in order to achieve HCV elimination targets.

Table 1. Service coverage indicators for the core interventions of the Global Health Sector Strategy on HCV: 2015 baseline and targets[3, 20]

Target area	Baseline 2015	2020 targets	2030 targets
Impact target			
***Incidence*:** new cases if chronic HCV infections	23.7/100,000	30% reduction (both HBV and HCV)	80% reduction in new HCV infections
***Mortality*:** HCV-related death	1.4 million deaths reduced to less than 500 000 by 2030 (65% for both HBV and HCV)	10% (both HBV and HCV)	65% reduction
Service coverage targets			
Blood safety	39 countries do not routinely test all blood donations for transfusion-transmissible infections	95% of donations screened in a quality-assured manner	100% of donations screened in a quality-assured manner
	89% of donation screened in a quality-assured manner		
Injection safety: % of injections administered with safe-engineered devices in and out of health facilities	5%	50%	90%
Harm reduction: number of sterile needles and syringes provided per person who injects drugs per year	20	200	300
Diagnosis*:* % of HCV infected diagnosed	20%	30%	90%
Treated: % diagnosed with HCV started on treatment	7%	3 million people treated (cumulative target)	80% of eligible persons with chronic HCV infection treated

1.2 Epidemiology of HCV infection

1.2.1 Global prevalence of HCV infection

HCV was referred to as non-A and non-B hepatitis up until its discovery in 1989.[35] HCV is single-stranded ribonucleic acid (RNA) virus and a member of the genus Hepacivirus in the family Flaviviridae. Seven strains or genotypes (1 to 7) with 67 distinct subtypes have been described.[36] Genotype distribution varies by geographical region, and reflects patterns of HCV epidemics and associated risk factors for transmission.[37, 38]

Prior to 2010, estimates of the prevalence of HCV infection globally were derived from HCV antibody prevalence reports, providing evidence of past or current HCV infection.[39-42] A meta-analysis of data from 21 Global Burden of Disease (GBD) regions,[40] demonstrated that the number and prevalence of people who were HCV antibody positive had escalated from around 122 million to 184 million (2.3% to 2.8%), between 1990 and 2005.[40] This analysis, however, had some important limitations including: 1) articles reporting HCV prevalence among high-risk groups such as PWID, people who are homeless and blood donors were excluded from the analysis; 2) only English-language peer-reviewed articles were included, hence, regional databases and grey literature were not searched; 3) publication bias was inherent given that regional estimates were primarily represented by the most published data from particular countries in the region; for example, the HCV antibody prevalence in South Asia predominantly reflected the HCV antibody prevalence in Pakistan; and 4) ascertainment of the prevalence of active HCV infection was not possible.[40]

Subsequently, recent global HCV estimates have been based on HCV ribonucleic acid (RNA) prevalence (i.e. HCV viraemia).[37, 43] A comprehensive study by The Polaris Observatory HCV Collaborators estimated the prevalence of viraemic HCV infection and genotype distribution at the end of 2015.[43] Globally, 71.1 million people (95% CI 62.5 – 79.4) were living with chronic HCV infection, representing a prevalence of 1.0% (95% CI 0.8 – 1.1).[43] This is lower than previous estimates,[37] due to use of HCV RNA rather than antibody prevalence, recent lower prevalence estimates in Africa (Nigeria and Cameroon) and high burden countries including China and India, and increased number of deaths.[43]

Although this new estimate suggests a decrease in global HCV prevalence, the prevalence of HCV infection has increased in a few countries due to foreign workforce migration from endemic countries (United Arab Emirates and Qatar), ongoing high levels of iatrogenic infection (India, Iraq, Syria), and escalating infection among PWID (Iran, Russia and Latvia).[43] The study also reported that 20 countries account for 80% of global HCV infections, with China, Pakistan, India, Egypt and Russia being in the top five countries with the highest number of infections.

The distribution of HCV infection varies substantially across regions (Table 2), with prevalence in countries ranging from <1% to 7%.[43] This variation reflects differences in patterns of the HCV epidemics and modes of transmission.[7, 10, 44] The highest prevalence of HCV infection was reported in Egypt; exceeding 6%.[43] The high prevalence of HCV in Egypt has been attributed to iatrogenic transmission during mass

treatment of schistosomiasis from the 1950s to the 1980s, in which shared, unsterile syringes and needles were used.[10, 45] This also represents the largest ever iatrogenic transmission of a blood-borne infection, with millions of people exposed to HCV, resulting in the high prevalence of HCV infection observed in Egypt today.[46]

Table 2. Regional HCV prevalence and number of people with HCV[43]

WHO region	HCV prevalence (95% CI)	HCV infected (millions; 95% CI)
African region	1.0 (0.7, 1.6)	10.3 (7.3, 15.9)
Region of the Americas	0.7 (0.6, 0.8)	7.2 (6.1, 8.0)
Eastern Mediterranean region	2.3 (1.9, 2.4)	15.2 (12.6, 15.5)
European region	1.5 (1.2, 1.5)	13.6 (10.9, 14.2)
South-East Asia region	0.5 (0.4, 0.9)	10.4 (8.0, 17.8)
Western Pacific region	0.7 (0.6, 0.8)	13.9 (10.3, 14.7)
Total	**1·0% (0·8, 1·1)**	**71·1 (62·1,79·0)**

Globally, the most common genotype is genotype 1 (44% of all infections), followed by genotype 3 (25%) and genotype 5 (15%).[43] Genotype 1 was predominant in high- and upper-middle income countries (60% of all infections), while genotype 3 was most common in low- and middle-income countries (LMIC) (36%), and genotype 4 was common in low-income countries (45%) (Figure 1).[43] In many countries, however, genotype distribution is unknown.

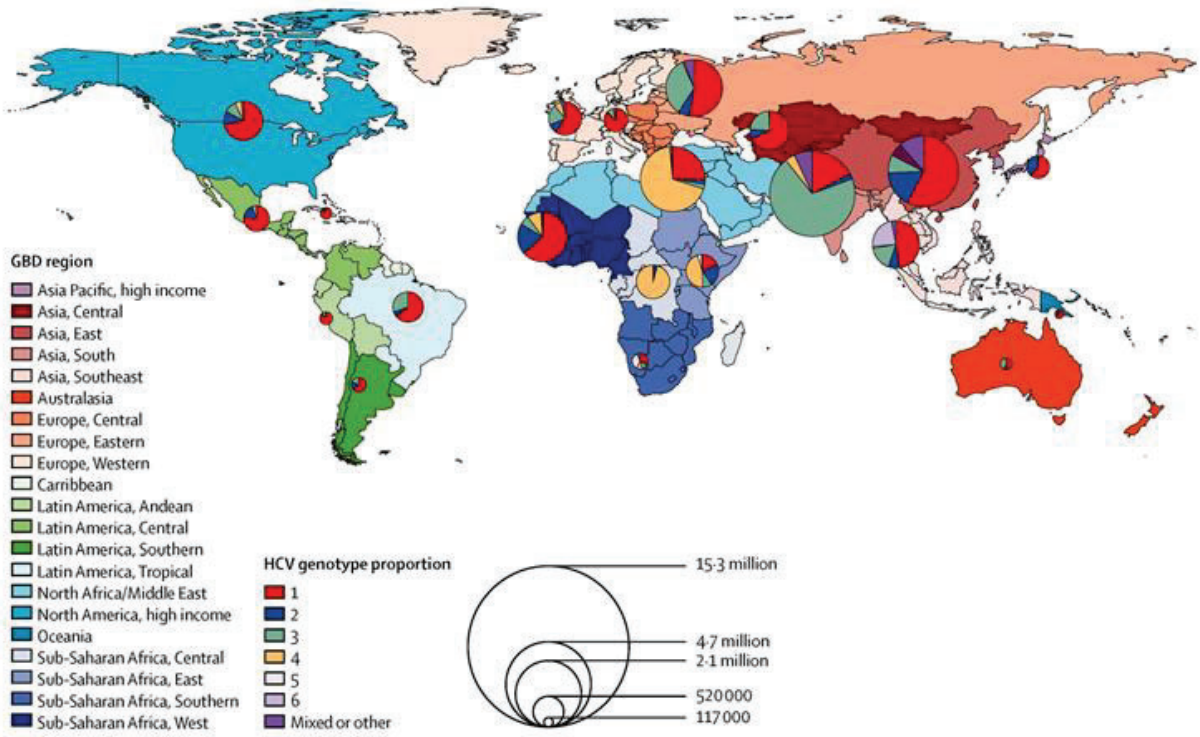

Figure 1. HCV genotype distribution and total infected by GBD region

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1.2.2 Routes of HCV transmission

HCV is a blood-borne virus transmitted by percutaneous exposure to infected blood or blood derived body fluids. The main routes of transmission are blood transfusions, medical procedures and injection drug use.[47] Understanding the routes of HCV transmission within a population are pivotal to the design and implementation of public health strategies in response to the epidemic.

In most high-income countries, injection drug use is the primary route of HCV transmission.[10, 48-52] The majority of existing (60%) and new (80%) HCV infections in high-income countries are attributable to injection drug use,[53] and data from the past decade indicate that injection drug use is becoming an important risk factor for new HCV infections in many low- and middle-income countries (LMIC).[54, 55] Sharing of used needles and syringes or other injection paraphernalia (e.g. spoons, filters, water) for injecting drugs is a major risk factor for HCV transmission among PWID.[48, 56, 57] Younger age and recent initiation of injection drug use have been shown to be associated with higher HCV incidence.[57-61] Other documented risk factors associated with HCV acquisition include higher injecting frequency, number of injecting partners, type of drug injected, unstable housing and human immunodeficiency virus (HIV) coinfection.[57, 58, 62]

Iatrogenic transmission of HCV infection has become uncommon in high-income countries, but remains a major driver of transmission in many LMIC.[47, 63-66] Iatrogenic

HCV transmission occurs through unsafe injection practices (reuse of unsterile injection devices) and procedures including renal dialysis, surgery, dental care and blood transfusions.[63, 64] Although data is limited, estimates indicate that 315,000 new HCV infections occur annually due to unsafe injection practices.[67] Strategies to address iatrogenic HCV transmission include enhanced education and awareness, introduction of reuse of single-use (disposable) prevention devices such as retractable syringes and reduction in unnecessary use of injectable medications.

There is paucity of data on other routes of HCV transmission such as tattooing and body piercing.[68] The risk of vertical transmission from mothers with chronic HCV infection to their children during pregnancy or delivery is also important and is around 6%.[69]

Sexual transmission of HCV occurs infrequently in heterosexual couples, but is recognised as a major route of transmission in men who have sex with men (MSM), particularly those with HIV infection.[70, 71] Permucosal risk factors for HCV transmission include mucosally traumatic sexual practices, mucosally administered recreational drugs and 'chemsex' (use of recreational drugs to enhance or prolong sexual interaction), and HIV infection (which may 'increase both infectiousness and susceptibility to HIV').[71] Globally, around 2.3 million people are estimated to be living with HCV/HIV co-infection, of whom, more than half are PWID.[72]

1.2.3 Incidence of HCV infection

Unlike data on prevalence, global HCV incidence estimates are limited.[4, 13, 73] HCV incidence is difficult to ascertain due to the asymptomatic nature of acute HCV infection, difficulty in identifying and following individuals at high-risk of HCV exposure, and lack of robust surveillance systems in many countries.[10, 40] Nonetheless, evidence from available age-specific seroprevalence studies, surveillance and biomarker surveys (as done in Egypt), suggests that global HCV incidence is generally declining.[3, 12, 13] This reduction in HCV incidence is likely attributed to improvement in injection safety in healthcare settings and harm reduction coverage. Despite this trend, estimates from mathematical modelling suggest that there were 1.75 million new HCV infections globally in 2015, representing an incidence rate of 24 per 100,000.[3]

The prevalence of HCV infection in high-income countries including United States, Western and Northern Europe, Australia and Japan is low (<2%).[10] However, patterns of HCV epidemics in these countries differ in relation to period of peak incidence and routes of transmission, reflected in differential age-specific HCV prevalence.

In the United States, based on estimates derived from the 2013 – 2016 National Health and Nutrition Examination Survey, 4.1 million people were HCV antibody positive and 2.4 million people who were HCV RNA detectable, representing a current HCV infection prevalence of 1.0%.[74-76] This figure is likely to be an under-estimate given that high-risk populations such as people who are incarcerated or homeless, people on active military duty and migrants were excluded from the survey, and PWID are likely under-

represented because of response bias.[76] According to HCV surveillance data from the US Centers for Disease Control and Prevention (CDC), a peak in HCV incidence occurred between 1982 and 1989 (7.4 per 100,000), after which a decline in incidence was observed between 1994 to 2005 (0.7 per 100,000), subsequently plateauing between 2006 and 2010.[13, 77] The decline in incidence in the 1990s was related to improvements in healthcare injection practices and screening of blood donors.[78] From 2005 to 2016, however; the number of new HCV infections increased four-fold, with a marked increase between 2011 and 2016 (0.6 per 100,000 in 2012 to1.0 cases/100,000).[13] This new wave of HCV infections has been attributed to the current opioid epidemic, particularly among people under the age of 30.[79-81] Injection drug use is the most common risk factor reported for HCV acquisition in the United States.[13]

Data on HCV incidence in Europe is somewhat limited.[2, 38, 73] In the majority of Western and Northern European countries, injection drug use is the predominant route of HCV transmission.[10, 73] A systematic review by Wiessing et al., showed that HCV incidence is highly heterogeneous across Europe with nine of 27 counties having HCV incidence data among PWID ranging from 5 to 42/100 person-years (median estimate of 26/100 person-years).[73] There is evidence of declining HCV incidence in Western Europe since the 1990s,[82, 83] but HCV incidence is increasing in Eastern European countries including the Czech Republic, Estonia and Russia.[84]

Australia has a similar HCV prevalence and routes of transmission as the United States.[10] In contrast to the US, high rates of HCV acquisition occurred during the 1980s

and 1990s.[85] Peak prevalence in Australia is observed in people aged 30 – 39 years, more than a decade younger than in the United States where rates of HCV acquisition were highest in the 1960s and 1970s.[10] Japan has a similar HCV prevalence, but 86% of infections are among people 40 – 69 years of age.[10] This is primarily attributed to iatrogenic transmission during the mid-1900s.[86]

In Australia, the prevalence of HCV infection is 1.0% with around 50% of infections being genotype 1 and 35 – 40% genotype 3.[87] There are approximately 600 newly acquired HCV infections notified each year in Australia;[88] however, mathematical modelling suggests a much higher number: HCV incidence peaked at 14,000 infections in 1999 then declined to 9,700 infections in 2005,[85] and 8,790 infections in 2013.[89] An increase in HCV notification rates between 2015 and 2016 after stable rates between 2012 and 2015 may reflect increased testing following access to government-subsidised DAA treatment from March 2016.[88]

The primary risk factor for HCV acquisition in Australia is receptive sharing of needles and syringes among PWID.[10, 44] Estimated HCV antibody prevalence in PWID is 55-75%,[53] of whom around 74% are HCV viraemic.[90] The reduction in notification rates among people under 25 years (who are likely to have acquired HCV more recently) between 2015 and 2016 suggests that HCV transmission may be declining at the population level, potentially related to some decline in the at-risk population (PWID).[88] However, there has been no decrease in the prevalence of receptive syringe sharing in the same period.[88] Furthermore, according to the Annual Needle and Syringe Program

Survey (ANSPS), the proportion of respondents reporting receptive sharing of needles and syringes has increased from 15% in 2013 to 17% in 2017.[91] Among a retrospective cohort of PWID attending a community health service in Sydney, incidence fluctuated between 2.1 and 15.8 per 100 person-years between 2010 and 2017, but with wide confidence intervals around these rates.[88, 92] Primary HCV incidence among PWID enrolled in a community-based prospective observational study – the Hepatitis C Incidence and Transmission Study-community (HITS-c) – was 7.9/100 person-years.[93] Increased primary HCV infection was observed among participants not receiving OST and who reported heroin as the main drug injected (26.9/100 person-years), those who reported unstable housing (22.7/100 person-years), and receptive syringe sharing (23.6/100 person-years) in the six months prior to baseline.[93]

Indigenous people are disproportionately affected by HCV infection compared to non-indigenous people.[88, 94, 95] For instance, in 2017, the rate of HCV notifications among Indigenous Australians was 4.4 times as high as non-indigenous people.[88] Indigenous Australians are also over-represented among PWID.[94] Data from the ANSPS showed the proportion of respondents who identified as Indigenous Australian increased from 14% in 2014 to 18% in 2017.[91] In addition, Indigenous Australians have higher rates of co-factors for liver fibrosis progression including heavy alcohol intake and metabolic disorders.[96] Other high-risk groups for HCV in Australia include prisoners, particularly those who inject drugs,[97] people with psychiatric illness,[98] people who are homeless,[99] and MSM.[100]

1.2.4 Global burden of HCV infection

Viral hepatitis is a leading cause of death worldwide,[5] causing an estimated 1.34 million deaths per year, comparable to death rates due to tuberculosis (1.37 million deaths), or HIV (1.06 million deaths).[3] The vast majority of viral hepatitis deaths are due to advanced liver disease-related complications, cirrhosis and hepatocellular carcinoma (HCC).[5] Of these deaths, 66% are attributed to HBV infection, 30% due to HCV infection, 0.8% due to hepatitis A, and 3.3% due to hepatitis E.[3] Among the deaths due to HBV and HCV, there were more deaths due to cirrhosis (720,000) than HCC (470,000).[3] Among people with HCV infection, the burden is further compounded by common co-morbidities, such as type-2 diabetes, and chronic renal disease, of which sizable proportions are extrahepatic manifestations of HCV infection.[101, 102]

Morbidity, mortality and associated costs due to viral hepatitis are increasing.[4, 7] Globally, the absolute number of deaths increased by 63% and disability-adjusted life-years (DALYs) increased by 34% between 1990 and 2013.[5, 89, 103] DALYs for HCV have more than doubled since 1990, with increases in age-specific rates due to both population growth and changes in age distribution.[104] In 2013, 39% of DALYs due to HCV were attributed to injection drug use, an increase from 23% in 1990.[104] Injection drug use-attributable HCV burden was highest in high-income countries.[104] As an example of the burden of HCV on healthcare resources, a study in Scotland showed a rising burden of inpatient hospital stays among Scottish HCV-diagnosed patients with decompensated liver disease.[103] Between 1996 and 2013 there was a 16-fold rise in

annual total admissions (from 112 to 1791) and an 11-fold rise in hospital bed days (719 – 8045).[103]

HCV is the predominant cause of HCC in Australia (41%). In addition, the proportion of people with HCV who had cirrhosis increased from 9% in 2004 to 19% in 2014.[105, 106] HCV infection is responsible for 23% of all adult liver transplants.[105, 106] Mathematical modelling indicated that under the interferon era low treatment uptake scenario, a threefold increase in HCV-related deaths was anticipated by 2030.[89]

1.3 HCV infection in PWID

1.3.1 Defining populations of PWID and prevalence of injection drug use

Knowledge of the size and characteristics of PWID populations is crucial in the development of public health strategies to address the HCV epidemic.[107-109] However, literature on the natural history of injection drug use is limited, leading to uncertain population estimates and inadequate understanding of the different sub-populations of PWID.[109-111] Estimating the prevalence of injection drug use is impeded by limited or imprecise estimates of the rates of initiation of injection drug use, transition to frequent injecting, and periods of cessation including long-term cessation of injecting.[109, 112] Various longitudinal studies have showed that injection drug use may persist for several decades, with periods of cessation of injecting, drug dependency treatment and incarceration.[113, 114] As such, PWID are a heterogeneous and dynamic population

comprised of various and overlapping sub-groups related to recency and frequency of injection drug use, as well as current and past OST.[109, 115]

In estimating the size of PWID populations related to HCV exposure, the following groups are of importance. 'Lifetime PWID' or people with a history of injection drug use refers to those reporting injecting an illicit drug at least once in their lifetime.[109, 115] Within this population are 'recent PWID' (with definitions of *recent* varying from one to 12 months), and 'former PWID' who have ceased injection drug use.[109, 115] Former PWID account for a substantial proportion of people living with HCV infection.[109] Given the complex nature of drug dependency, people can oscillate between these two groups with periods of cessation and injection drug use. Among the 'lifetime PWID', the population of people receiving OST may be former or recent injectors (Figure 2).

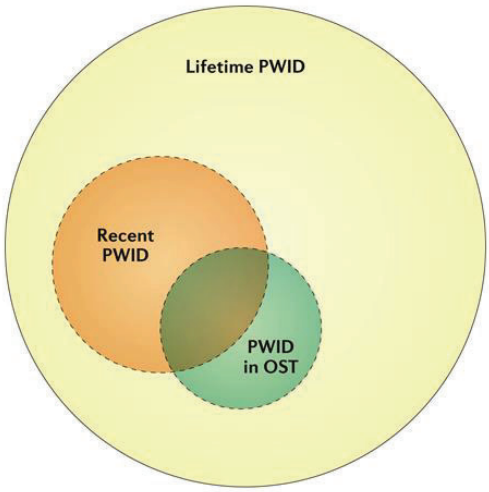

Figure 2. Overlap of different populations of people who inject drugs.

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In 2015, an estimated 15.6 million people globally aged 15 – 64 years injected drugs in the previous year, of whom 80% were male, and under a third were younger than 25 years.[116] Gender distribution varied across regions; women were estimated to comprise 30% of PWID in North America and 33% in Australasia, compared to 3% in south Asia.[117] The majority of PWID were in East and South-East Asia (~4 million), followed by Eastern Europe (~3 million) and North America (~2.6 million).[116] Russia, the United States and China contributed the largest proportions of the total PWID population.[116]

The sociodemographic and risk characteristics of PWID varied across regions and countries. Globally, estimates suggest that around 22% of PWID experienced homelessness or unstable housing in the previous year, and 58% had a history of incarceration. Approximately 6.7% of PWID experienced recent homelessness or unstable housing in Eastern Europe compared to 50% in North America.[116] The highest rate of history of incarceration estimated was in Puerto Rico (82%) (the only Caribbean country for which estimates could be calculated), and lowest in Eastern Europe (36%).[116] The proportion of PWID engaging in recent receptive needle and syringe sharing (defined as using a needle after someone else) ranged from 10% in Western Europe to 47% in central Asia and 54% in Latin America.[116]

Global estimates indicate that 18% of PWID are living with HIV and 9% are HBV surface antigen positive.[116] Opioids were the main drug injected among 83% of PWID globally in 2017.[116]

1.3.2 HCV prevalence in PWID and intersecting risk factors of incarceration and homelessness

Globally, among the estimated 15.6 million people who have recently injected drugs, around 52% are HCV antibody positive (~8.2 million)[116] and 39% have HCV infection (~6.1 million).[117] People with recent injection drug use make up an estimated 8.5% of all HCV infections globally.[117] HCV infection prevalence varied substantially across regions and countries, with prevalence of 60 – 80% in ten countries, 40 - <60% in 38 countries and <40% in 50 countries.[117] 'The highest estimated numbers of people with

recent injection drug use and HCV infection were in East and South-East Asia (~1.5 million), Eastern Europe (~1.5 million) and North America (~1.0 million).[117] People living with HCV infection in Russia, the United States, China, and Brazil accounted for 51% of people with recent injection drug use living with HCV infection (Table 3).[117]

Table 3. Top ten countries with greatest number of people with HCV infection*among people with recent injecting drug use globally[117]

Country	HCV prevalence (95% CI) among people with recent injecting drug use	Total population living with HCV infection 95% CI)	Population of people with recent injecting drug use living with HCV infection (95% CI)	Proportion of people with recent injecting drug use among the total population with HCV infection % (95%CI)
Russian Federation	51.6 (44.2, 58.9)	51.6 (44.2, 58.9)	4 748 000 (3,238 000, 4 960 000)	20.4 (9.3, 37.2)
United States	39.8 (28.4, 51.3)	895 000 (353 500, 1 601 500)	2 936 000 (2 231 000, 3 826 000)	30.5 (10.9, 58.9)
China	32.3 (20.8, 44.3)	828 000 (493 000, 1 228 500)	9 795 000 (6 675 000, 10 832 000)	8.5 (4.6, 14.3)
Brazil	47.9 (44.3, 51.5)	461 000 (336 500, 596 500)	1 787 000 (1 293 000, 1 896 000)	25.8 (17.2, 38.5)
Japan	48.6 (40.8, 56.3)	179 000 (130 500, 234 500)	857 000 (364 000, 1 024 000)	20.9 (11.7, 46.5)
Canada	52.9 (44.5, 61.2)	65 000 (50 000, 82 000)	212 000 (136 000, 246 000)	30.7 (20.2, 49.3)
Italy	43.4 (38.8, 48.1)	148 500 (98 500, 205 000)	680 000 (455 000, 1 641 000)	21.8 (7.6, 33.9)
Malaysia	50.3 (46.2, 54.5	142 000 (116 000, 169 500)	382 000 (240 000, 405 000)	37.1 (25.2, 59.2)
Ukraine	40.4 (36.3, 44.6)	129 000 (54 000, 222 000)	NK	NG
Indonesia	66.9 (62.2, 71.5)	127 500 (103 000, 153 000)	1 289 000 (443 000, 2 046 000)	9.9 (5.5, 24.9)

*HCV infection= current HCV infection (HCV RNA detectable); NK = no estimate of prevalence of that HCV was located, yet evidence of injecting drug use occurring in that country was identified; NG = no estimate of HCV among the general population was available.

A 2019 modelling study by Trickey et al., used data from 88 countries to estimate the contribution of injection drug use to HCV transmission globally.[118] Overall, the study estimated a population attributable fraction (PAF) of 39% over the period 2018-2019.[118] Estimated PAFs were higher in high-income countries (79%) than in in LMIC (38%).[118] For example, the PAF varied from 14% in sub-Saharan Africa to 96% in Eastern Europe.[118] The authors suggested that 43% of incident HCV infections could be averted over a 12 year period (2018-2030) if transmission associated with injection drug use was removed. This study highlights the urgent need to scale-up a combination of interventions to prevent onward HCV transmission among PWID in order to achieve the WHO incidence reduction (80%) target by 2030.

As mentioned previously, the major risk factor for HCV acquisition is receptive sharing of needles and syringes used to inject drugs. Studies have demonstrated that HCV incidence decreases with age probably due to decreasing risky injecting behaviour with age.[57, 119, 120] Furthermore, a majority of people with a history of injection drug use report injecting during the ages of 15 to 24 years, (Figure 3), highlighting the need to prioritise younger PWID for primary prevention interventions.[109]

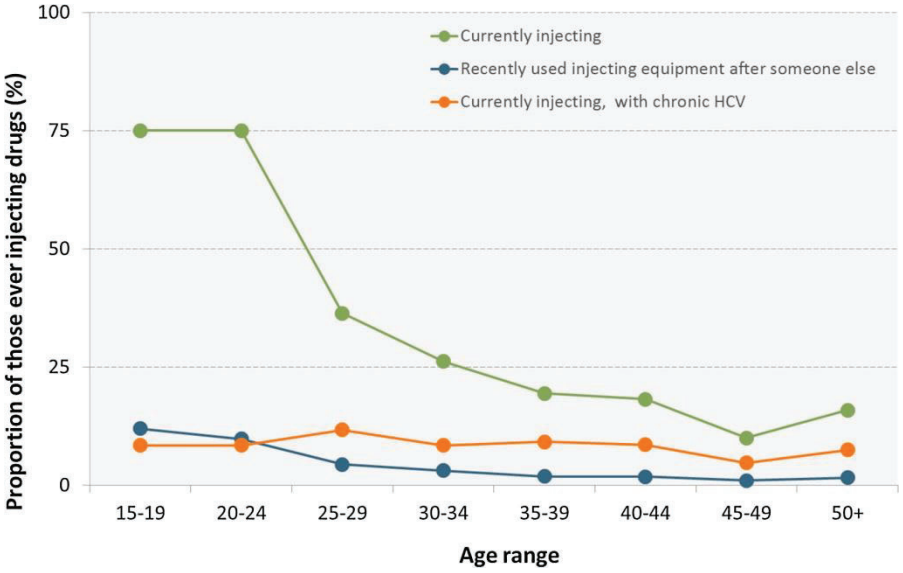

Figure 3. Age-related changes in current injecting and sharing of injecting equipment among people who have ever injected drugs.
Notes: 'Currently injecting' derived from proportion of lifetime PWID reporting injecting drug used in the previous 12 months in the 2013 National Drug Strategy Household Survey. 'Recently used injecting equipment after someone else' derived from Horyniak et al., 2012. 'Currently injecting, with chronic HCV' derived from 2013 Australian Needle and Syringe Program Survey.

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HCV infection is prevalent among people who are incarcerated[121] and people who are homeless.[122-124] Further, PWID who have a history of incarceration[125] or homelessness[93, 126, 127] are at increased risk of HCV infection. Global estimates suggest that HCV antibody prevalence among the 11 million of prisoner population is 26%, and 64% among prisoners with a history of injection drug use.[121] HCV incidence in prison has been estimated at 1.4 per 100 person-years, rising to 16.4 per 100 person-years in those with a history of injecting drug use.[121] Criminalisation of drug use is an important driver of prevalent HCV infection in prisoners, given that one-fifth are held in custody for drug-related charges, and 56 – 90% of PWID globally have been incarcerated at some stage in their lives.[116, 128] In addition, one of the primary risk factors for HCV

acquisition in prisons is injection drug use.[129] Despite the burden of HCV infection among PWID in prisons, provision of harm reduction in prisons has been a public health policy failure with OST available in prisons in only 52 countries (most with suboptimal access) and only eight countries have one or more NSPs in prison settings.[130] In addition, people who have been previously incarcerated are less likely to initiate DAA treatment than those who have not been incarcerated.[131]

Similar to the heterogeneity of the population of PWID, definitions of homelessness vary widely and are 'socially and culturally constructed'.[132] Homelessness comprises an array of living situations such as sleeping on the street, staying in temporary accommodation (e.g. hostels and shelter), or living in insecure accommodation lacking privacy.[132] Homelessness, or residential instability, can precipitate drug use, and the reverse is also important in that drug use may be an antecedent to homelessness.[133] Studies have demonstrated the relationship between high-risk populations of PWID and homeless and incarcerated people.[123] The prevalence of HCV infection among people who are homeless ranges widely from 4% to 36%.[122, 134] There are a number of factors contributing to increased HCV risk among people who are homeless including intense periods of drug consumption, hasty injecting practices in public spaces, and communal environments.[135, 136] PWID in qualitative research have reported that given the difficulty in injecting safely while living on the streets, HCV acquisition is inevitable.[137]

1.4 Natural history of HCV infection

1.4.1 Disease progression of chronic HCV infection

Acute HCV infection is typically characterised by the occurrence of HCV viraemia within 2 weeks of HCV acquisition, elevation of serum liver enzymes (alanine aminotransferase and aspartate a aminotransferase) and the development of HCV antibodies within 3 – 21 weeks of HCV acquisition.[10] Given that symptoms of acute HCV infection are only present in 15 – 30% of cases,[10] case definitions of acute HCV infection vary in the literature.[138] Nonetheless, there is a recognition that the acute-phase of HCV infection usually refers to the six months after HCV acquisition, after which *it* is referred to as chronic HCV infection.[10] Approximately 25% of individuals exposed will spontaneously clear the virus, and the remaining 75% will progress to chronic HCV infection.[139] Those who spontaneously clear the virus are at risk of reinfection in the context of subsequent HCV exposure.[140] People with chronic HCV infection are at risk of liver fibrosis progression,[141, 142] and long term liver-related sequelae including cirrhosis and HCC.[143]

There are a number of factors associated with fibrosis progression and risk of liver-related mortality among people with chronic HCV infection,[144] including: 1) duration of HCV infection;[144] 2) host factors – male sex,[145] ethnicity,[146] age >40 years of infection,[145] HIV co-infection,[147] chronic HBV co-infection,[148] insulin resistance and/or diabetes,[149, 150] obesity,[151] hepatic steatosis;[151] 3) behavioural factors – heavy alcohol intake;[152] and 4) absence of HCV therapy and subsequent virological response (i.e. cure).[153] Although some studies have shown an association between daily cannabis[154]

and cigarette smoking[155] and fibrosis progression, results remain inconclusive. Given the slowly progressive nature of chronic HCV infection, and limited advanced fibrosis in the first two decades of HCV infection, the duration of HCV infection and its surrogate, age, are key predictors of morbidity and mortality.[143, 144]

The rate of the development of cirrhosis varies substantially,[143] however, multiple studies demonstrate that 10 – 20% of people living with chronic HCV infection develop cirrhosis within 20 – 30 years of infection.[156] A systematic review showed an exponential relationship between duration of HCV infection and risk of cirrhosis, related to the generally protracted disease course, cumulative nature of cirrhosis prevalence and the possibility of more rapid fibrosis progression at > 40 years of age.[141, 144] Without effective intervention, compensated cirrhosis often progresses to decompensated cirrhosis defined by the presence of ascites, variceal bleeding and/or encephalopathy.[157]

Estimates of the rate of occurrence of HCC among people with chronic HCV infection are 1 – 3% after 30 years.[144] Predictors of HCV-related HCC include, age>55 years, heavy alcohol intake and male sex.[158] A previous study demonstrated that individuals with chronic HCV infection and liver stiffness measurement (LSM) (measured by transient elastography) greater than 25 kilopascals (kPa) were almost three times more likely to develop HCC than individuals with LSM of 10 – 25 kPa.[159]

1.4.2 Mortality among people with chronic HCV infection

Evidence from the literature has corroborated the categorisation of the causes of death in people with chronic HCV infection into three groups: 1) drug-related overdose and suicide; 2) HIV-related; and 3) HCV-related liver disease (i.e. decompensated cirrhosis and HCC).[144] The mortality distributions of these three main categories are contingent on the mode of HCV acquisition, age distribution, duration of HCV infection, and access to treatment which alters the natural history of the infection within a population.[144]

Studies on the natural history of HCV infection in PWID are limited. Given the majority of PWID in many settings acquired HCV infection 20 to 30 years ago, coupled with low treatment uptake, many have developed advanced liver disease. Disease progression is further compounded by co-occurring morbidities such as diabetes, obesity/steatosis, HIV co-infection, and excessive alcohol intake. Importantly, PWID have competing death risk due to drug-related harm.[160-163]

In a review which assessed the distribution of causes of deaths in large population-based HCV notification death registry linkage studies in Australia, Sweden, Scotland and Denmark, the proportion of liver-related deaths ranged from 19% to 24% and for drug-related deaths from 18% to 27%.[144] Injection drug use is a major route of HCV transmission in all four countries reflected in the high proportion of drug-related mortality. The proportion of HIV-related deaths was highest in Scotland (7.9%)[164] where 4% of the studies population were HIV co-infected, and lowest in Australia

(0.4%)[165] where only 0.5% of the diagnosed population had HIV co-infection. Countries in which the HIV co-infection rate is higher than in Scotland would be expected to have larger proportions of HIV-related mortality than found in Scotland.[10, 144]

An Australian data linkage study assessed cause-specific mortality trends among people with HCV notifications between 1993 – 2012 in New South Wales (NSW). Findings indicated that in the early 2010s, 33% of HCV-related deaths were liver-related, 17% were cancer-related (excluding liver cancer), and 15% were drug-related. In addition, between 2002 and 2012, HCV-related liver deaths increased substantially (111 to 284).[166] Results of the study suggested that at a population level, HCV-related liver disease burden is increasing. There was a strong association between older age and liver-related mortality, consistent with the ageing cohort effect in Australia.[166] Other predictors included male sex, HBV/HCV/HIV co-infection, and alcohol use disorder. Additionally, drug-related mortality remained a major cause of death between 2002 and 2012, highlighting the critical need to implement effective strategies to reduce drug-related harm. Small numbers of individuals were HCV treated during 2000s and early 2010s; however, increased uptake of DAAs is projected to lead to considerable reductions in mortality at the population-level.[89, 167]

In an inner-city cohort of illicit drug users in Vancouver, the major causes of death among HCV antibody positive younger individuals (<50 years of age) were HIV and drug-related harm, whereas the major cause of mortality among older HCV positive >50

years of age was liver-related.[168] This is again consistent with the ageing cohort effect of populations that have acquired HCV in 1970s and 1980s.

1.4.3 Liver disease staging in people with chronic HCV infection

International guidelines recommend the assessment of liver disease severity in individuals diagnosed with chronic HCV infection. The METAVIR (Meta-analysis of Histological Data in Viral Hepatitis) scoring system, designed specifically for HCV,[169] is the most common system used to assess the degree of inflammation and fibrosis of the liver. The activity grade indicates the degree of inflammation (A0 to A4) and fibrosis stage represents the extent of fibrosis scarring. The fibrosis stage is defined as: F0: no fibrosis/scarring; F1: mild fibrosis/portal fibrosis without septa; F2: portal fibrosis with rare septa; F3: numerous septa without cirrhosis; F4: cirrhosis or advanced scarring.[170]

Historically, liver disease staging using a liver biopsy was the gold standard to determine the risk vs benefit of treatment on a case-by-case basis.[171] As treatment efficacy improved, liver disease stage-based treatment initiation has become a less important aspect of clinical management and greater focus is given to identification of cirrhosis and HCC monitoring.[172] It has been well established that the invasive nature, cost, complications (e.g. bleeding), tissue sampling error and histopathological scoring of liver biopsy are barriers to liver disease assessment and linkage to care among PWID.[173, 174] However, liver biopsy has largely been replaced by non-invasive methods for staging the extent of liver fibrosis in people with chronic HCV infection.[175]

Non-invasive techniques include the measurement of liver stiffness using transient elastography and fibrosis biomarkers. FibroScan® (Echosens, Paris, France), is a novel non-invasive device that assesses the stiffness of the liver via transient elastography. By using an ultrasound-like probe, liver stiffness is evaluated by measuring the shear wave generated on the skin. Shear wave is determined by measuring the time the vibration takes to travel to a specific depth inside the liver, reflecting tissue stiffness.[176] Results are expressed in kPa and LSM (fibroScan score) range from 2.5 to 75kPa. A LSM 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 are taken.[176] There are some factors that may affect transient elastography, such as obesity, although use of an XL probe has partially addressed this limitation. In LMIC and in community-health services, where access to transient elastography may be limited due to cost, aspartate aminotransferase to platelet ratio index (APRI) or fibrosis-4 (FIB-4) are reliable, inexpensive and simple to administer biochemical surrogate methods to assess the extent of liver fibrosis. Notably, these methods are not recommended for post-treatment monitoring. A number of studies have shown that transient elastography is highly acceptable in the general population and among PWID.[177, 178]

1.5 From the interferon era to the DAA era: The evolution of HCV therapy

1.5.1 Overview of HCV therapeutic development

The shift in the management of people with chronic HCV infection from using interferon-based to all-oral, short duration DAA regimens has provided an unprecedented opportunity to curb the HCV epidemic and improve quality of life.

During the early to mid-1990s, the standard therapy for chronic HCV infection was interferon-alpha, administered subcutaneously three-times a week for 24 – 48 weeks. Successful treatment outcome was exceptionally low with sustained virological response (SVR) rates of 5 – 20%.[179-181] In addition, patients commonly experienced severe adverse effects, including flu-like symptoms (fatigue, headaches), myalgia, neuropsychiatric disorders (depression, anxiety), sleep disturbance and anaemia.[50, 182, 183] Although the subsequent pegylation of interferon (peginterferon alpha-2a and 2b) and co-administration with a weight-based purine analogue [ribavirin (RBV)] resulted in improved SVR rates of 30 – 55%,[184-187] the toxicity profile (anaemia, thrombocytopenia, neutropenia) impeded treatment adherence and often resulted in discontinuation.[188] Predictors of interferon-based induced SVR included female sex, genotype 2 or 3, and <40 years of age.[182, 185, 189] To this end, due to the toxicity profile, drug interactions, requirement of injection, long duration of treatment and limited successful treatment outcome, treatment uptake remained exceptionally low globally, ranging from <1% to 5% treatment of people with chronic HCV infection commencing treatment annually.[188]

Fortunately, a more comprehensive understanding of the HCV viral cycle has paved the way for rational drug design of small molecule inhibitors of various HCV proteins involved in HCV replication; most importantly: 1) NS3/4A protease; 2) NS5B RNA-dependent RNA polymerase; and 3) NS5A protein.[17] Protease inhibitors telaprevir and boceprevir were the first available of the first generation of DAAs marketed in 2011, followed by simeprevir in 2013, but these agents were used in combination with peginterferon/ribavirin and only for genotype 1 (Figure 3). The licence approval of sofosbuvir (nucleotide analogue) and evidence from the first phase 2 trial demonstrating SVR rates of 92 – 94% with a 12-week course of sofosbuvir plus simeprevir (with or without RBV) for genotype 1 signalled the beginning of interferon-free all-oral DAA management of HCV infection.[17, 190] Similarly, phase 3 trials of other interferon-free DAA regimens (daclatasvir or ledipasvir in combination with sofosbuvir) demonstrating SVR >95% including in treatment naïve patients with cirrhosis ushered in major milestones and optimism entering the DAA era (Figure 4).[191-195] FDA approval of the various DAAs relevant to the Australian context are presented in Table 4.

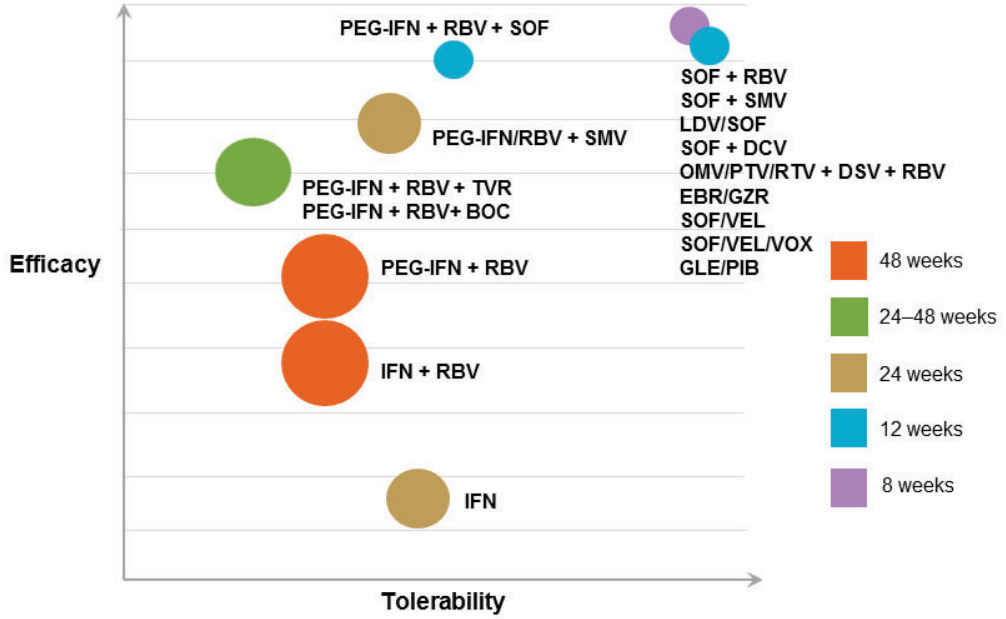

Figure 4. Advances in HCV therapy with respect to tolerability and efficacy

BOC: boceprevir DCV: daclatasvir; DSV: dasabuvir; EBR: elbasvir; GLE: glecaprevir; GZR: grazoprevir; LDV: ledipasvir; OMV: ombitasvir; PEG-IFN: pegylated interferon; PIB: pibrentasvir; PTV: paritaprevir; RBV: ribavirin; RTV: ritonavir; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir; VEL: velpatasvir; VOX: voxilaprevir

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Table 4. DAA drugs and their classes

Drug name & class	Year of FDA approval	HCV GT
NS3/4A Protease Inhibitors		
Boceprevir	2011	1
Telaprevir	2011	1
Simeprevir	2013	1
Grazoprevir	2016	1, 4
Glecaprevir	2017	1-6
Voxilaprevir*	2017	1-6
NS5B RNA-dependent RNA Polymerase Inhibitors		
Nucleotide		
Sofosbuvir	2013	1-6
Non-nucleotide		
Dasabuvir	2014	1
NS5A Inhibitors		
Daclatasvir	2015	1-6
Ledipasvir	2014	1
Ombitasvir	2014	1, 4
Elbasvir	2016	1, 4
Velpatasvir	2016	1-6
Pibrentasvir	2017	1-6

*In combination with sofosbuvir/velpatasvir for people previously treated with sofosbuvir or NS5A inhibitors

To date, major breakthroughs with the development of the new generation of DAAs included: 1) increasing SVR rates ≥95% in both treatment naïve and treatment experienced individuals across all genotypes; 2) short duration of treatment with the shortest being 8 weeks with the most recent pangenotypic regimen (glecaprevir/pibrentasvir) in treatment naïve individuals with no cirrhosis; 3) administered orally, and with pangenotypic regimens dosed once a day without the addition of RBV; 4) extremely high treatment completion rates of well-tolerated regimens, even with RBV inclusion; 5) extremely low rates of HCV resistance. Importantly, the DAAs can now be safely administered to patient populations historically poorly responsive to interferon-based treatment including those with genotype 1, cirrhosis, HIV-HCV coinfection, psychiatric illnesses, renal disease and prior experience with HCV treatment.[196-206] Further, a systematic review of clinical trials by Falade-Nwulia et al., found minimal loss to follow-up of <10% and treatment discontinuation <5%.[196]

An example of the evolution of Australian recommended treatment protocols for chronic HCV infection as of August 2017 and updated protocols as of September 2018 are presented in Tables 5 and 6.

Table 5. Brief outline of Australian recommended treatment protocols for people with HCV infection and compensated liver disease, including people with HCV-HIV coinfection (August 2017)

Regimen	HCV GT	Treatment duration				Efficacy (SVR)
		No cirrhosis		Cirrhosis		
		Treatment naïve	Treatment experienced	Treatment naïve	Treatment experienced	
Sofosbuvir 400mg/ledipasvir, 90mg daily	1	8 or 12 weeks	12 weeks	12 weeks	24 weeks	≥95%
Sofosbuvir 400mg/daclatasvir 60mg daily*	1	12 weeks	12 or 24 weeks	12 or 24 weeks	12 or 24 weeks	≥95%
	3	12 week	12 weeks	12 or 24 weeks	12 or 24 weeks	>85%
Sofosbuvir 400mg/velpatasvir, 100mg daily	1-6	12 weeks	12 weeks	12 weeks	12weeks	≥95%
Elbasvir 50mg/grazoprevir 100mg*	1,4	12 weeks	12 or 16 weeks	12 weeks	12 or 16 weeks	≥95%
Paritaprevir-ritonavir 150mg/100mg/ombitasvir 25mg/dasabuvir 250mg twice daily*	1	12 weeks	12 weeks	12 weeks	12 weeks	≥95%
Sofosbuvir 400mg/ribavirin 1000/1200mg daily (weight-based)	2	12 weeks	12 weeks	12 weeks	12 weeks	>90%

*+/- Ribavirin and dosing is weight-based; recommended dose is 1000 mg for people weighing < 75 kg and 1200 mg for people weighing ≥ 75 kg.

Table 6. Brief outline of Australian recommended treatment protocols for treatment-naïve people with HCV infection and compensated liver disease, including people with HCV-HIV coinfection (as of September 2018)

Regimen	Trade name	HCV GT	Treatment duration	
			No Cirrhosis	Cirrhosis
Sofosbuvir 400mg/velpatasvir 100m daily	Epclusa®*	1,2,3,4,5,6	12 weeks	12 weeks*
Glecaprevir 300mg, daily + Pibrentasvir 120mg, daily	Maviret®	1,2,3,4,5,6	8 weeks	12 weeks
Elbasvir 50mg, daily + Grazoprevir 100mg, daily	Zepatier®	1,4	12 weeks	12 weeks
Sofosbuvir 400mg daily + Ledipasvir 90mg daily	Harvoni®	1	8 or 12 weeks	12 weeks

* Addition of ribavirin may be considered for patients with genotype 3 HCV and compensated cirrhosis. Ribavirin dosing is weight-based; recommended dose is 1000 mg for people weighing < 75 kg and 1200 mg for people weighing ≥ 75 kg.

1.5.2 DAA treatment efficacy in PWID with chronic HCV infection

Although interferon-based HCV treatment outcomes in PWID populations were comparable to outcomes in the general population,[207-209] the arduous treatment profile impeded its uptake among PWID.[210] Despite the removal of toxicity-related barriers to treatment uptake, obstacles persist in the DAA era including physician reluctance[211] to provide HCV therapy to PWID and payer restrictions in some countries and jurisdictions based on ongoing drug use or receiving OST.[115, 212, 213] This arises from historical concerns about treatment adherence, poorer outcomes compared to the general population, and the risk of HCV reinfection.[211, 214]

PWID who have recently injected drugs were excluded from phase 2 and 3 DAA trials,[215] except for the inclusion of a small number of individuals stabilised on OST. Post-hoc analyses of these trials showed that SVR in individuals receiving OST was similar to those not receiving OST.[194, 216, 217] According to pooled analysis of people infected with HCV genotype 1 treated with ombitasvir/paritaprevir/ritonavir and dasabuvir with or without RBV,[218] and data from the ION trial of sofosbuvir/ledipasvir treatment[219] completion was 96–100% and SVR was 94–96% in people receiving OST.

The C-EDGE CO-STAR study was the first phase 3 trial designed to evaluate DAA treatment outcomes in people receiving OST.[115, 220] Individuals reporting concurrent injecting drug use were eligible to participate in the study.[220] Participants with HCV genotypes 1,4 or 6 were randomised to receive elbasvir/grazoprevir for 12 weeks (n=201) or placebo for 12 weeks, followed by deferred treatment of elbasvir/grazoprevir

for 12 weeks (n=100).[220] In an intent-to-treat (ITT) analysis, SVR was 91%. Further, drug use at baseline was not associated with SVR and adherence (>97% of participants completed treatment and >95% were adherent).[220]

In light of this existing evidence there are concerns over whether these favourable outcomes would be observed in 'real world' PWID populations.[115] Multiple observational studies showed treatment completion rates of 93 – 100% and SVR of 80 – 96% among PWID with or without recent injecting drug use.[221-223] A recent meta-analysis by Hajarizadeh et al., demonstrated favourable DAA treatment outcomes among people with recent drug use and those receiving OST.[224] The meta-analysis also demonstrated that among people receiving OST, treatment completion was 97.4% and ITT SVR was 90.7%. In people with recent drug use (injection and non-injection), treatment completion and ITT SVR was 97.5% and 87.7%, respectively. Clinical trials (vs observational studies) and older age were associated with higher ITT SVR. The study also highlighted that lower SVR observed among people who have recently used drugs (both injecting and non-injecting), is likely attributable to post-treatment loss to follow-up (i.e. between end-of-treatment and SVR12) and not virological failure. This underscores the need to improve retention in post-treatment care through innovative models of care tailored to the unique needs of PWID. For example, in two studies from Germany[225] and Canada[226] evaluating DAA treatment outcomes among individuals on OST, loss to follow-up was lower in those receiving OST and DAA therapy in the same centre than in those receiving these services in different centres. Integration of HCV care within drug user health services has been shown to be effective in engaging people in HCV testing and treatment. Importantly, OST should not be a pre-requisite to

receiving HCV treatment given many recent injectors are not opioid dependent (e.g. methamphetamine or other drug users) and therefore are not candidates for OST.

Several mathematical modelling studies suggest that HCV treatment of PWID can lead to significant reductions in HCV prevalence and incidence. Economic evaluations have also suggested that HCV DAA treatment of PWID is cost-effective.[23] In some settings HCV treatment of PWID could be more cost-effective than treating people at the same disease stage without ongoing risk of transmission.[23]

1.5.3 DAA pricing and access

The development of DAA therapy inspired the ambitious goal of HCV elimination by 2030. However, a major barrier to DAA access is payer (government and private entities) subsidy/funding restrictions due to exorbitant wholesale drug pricing. For example, in 2013, the initial market price of a 12-week course of sofosbuvir and simeprevir were US$ 66,000 and US$ 84,000, respectively.[227] Price negotiations between payers and pharmaceutical companies are usually made privately and rarely made public, although often include undisclosed rebates that can be around 30%.[228]

Studies have demonstrated that initial prices per course of DAA treatment varied massively between countries, particularly among high-income countries, and were incongruent with gross national incomes.[229] Additionally, LMIC may have been paying higher adjusted prices than high-income countries.[229, 230] High pricing of DAA can

place substantial strains on national health budgets.[231-233] A 2015 study by Iyenhar et al., assessing the price of originator sofosbuvir and sofosbuvir/ledipasvir across 30 countries found the prices varied markedly from US$ 56,123 in the United Kingdom to US$ 89,395 in Poland. Price disparity was especially observed when adjusted to local purchasing power.[230] The authors demonstrated that treating a tenth of individuals with ledipasvir/sofosbuvir would consume ≥ 10% of the total pharmaceutical expenditure in Poland (19.1%), Portugal (16.5%), Italy (12.3%), and Spain (11.2%).[228, 230] In contrast, this would consume < 5% of the total pharmaceutical expenditure in Norway (3.4%), the UK (3.3%), Finland (3.4%), Germany (2.6%), France (2.0%) and the Netherlands (1.4%).[228, 230] Further, in some countries the total cost of treating all individuals with HCV infection would exceed the total cost of all medicines.[230]

Hence, high DAA pricing and the potential impact on national health budgets led to the rationing and prioritisation by payers of treatment for people with advanced liver disease (F ≥ 3), which was in line with earlier international clinical guidelines from the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) (2014) and EASL (2015).[212, 213, 234] For example, in 2017 46% (n=16) countries or jurisdictions in Europe restricted DAA reimbursement to fibrosis stage of F2 or higher.[213] Further, consistent with the interferon-era, restrictions on drug and alcohol use have been imposed by payers in many countries and jurisdictions. Despite updated international guidelines with recommendations that remove fibrosis and drug use sobriety restrictions, funding restrictions persist in many countries.[228]

1.5.4 Access to and uptake of DAA treatment in Australia

With over 80% of the chronic HCV population diagnosed and a substantial number treated with DAA between 2016 and 2017,[235] Australia is one of 12 countries considered to be 'on-track' for HCV elimination by 2030.[236] Pivotal to this initial rapid DAA scale-up was the development of the Australian government-funded DAA access program, launched in March 2016.[237] Despite rapid uptake in the initial 16 months of unrestricted and subsidised access to DAA treatment, a drop-off has been observed, highlighting the need for enhanced efforts to maintain treatment uptake.[237]

At the core of the success of the HCV treatment program in Australia is the inception of National Hepatitis C Strategy, which is in its fifth strategy and 20th year. The strategy is underpinned by collaboration between government, clinical, academic and community organisations (including representation of people who use drugs). In addition, strategy developments have attracted bipartisan political support. Negotiations between the Australian government and pharmaceutical companies resulted in – what has been labelled the "Netflix model" – a risk-sharing agreement to spend AUS$1 billion over 5 years (i.e. 2016 -2020 inclusive) on DAA drugs in exchange for an unlimited supply of DAAs.[238] DAA regimens and year subsidised by the Pharmaceutical Benefits Scheme (PBS) (Australian government-funding of medicines program) are presented in Table 7. Key features of the government-funding DAA access program include: 1) no restrictions based on liver disease stage or drug/alcohol use; 2) minimal co-payment by patients (AUS$ 6.50 – 40.30/month); 3) broad prescribing by any registered medical practitioner (consultation with specialist was removed for experienced non-specialist

prescribers in late 2016); 4) retreatment of reinfection cases; 5) no cap on number treated per year.

Between March 2016 and March 2018, an estimated 58,280 people were treated with DAAs, equating to 26% treatment uptake among 227,310 Australians living with chronic HCV infection in 2015. An estimated 70% of people with HCV-related cirrhosis have been treated between 2014 and 2017.[235] However, treatment initiations have dropped in 2017 indicating enhanced efforts are required, particularly among high-risk populations such as PWID. Mathematical modelling suggests that around 20,000 people need to be treated annually in Australia to achieve HCV elimination by 2026.[167]

Table 7. Interferon-free DAA treatment regimens listed on the PBS in Australia

PBS listing	DAA regimen	HCV GT	Treatment duration (weeks)
March 2016	Sofosbuvir/ledipasvir	1	8 – 24
	Sofosbuvir/daclatasvir	1,3	12 – 24
	Sofosbuvir/ribavirin	2	12
	Sofosbuvir/peg-INF/ribavirin	1, 3, 4 – 6	12
May 2016	Paritaprevir/ritonovir/ombitasvir/dasabuvir	1	12 – 24
January 2017	Grazoprevir/elbasvir	1 – 6	12
August 2017	Sofosbuvir/velpatasvir	1 – 6	8 – 12

*In combination with sofosbuvir/velpatasvir for people previously treated with sofosbuvir or NS5A inhibitors

1.6 HCV care cascade

1.6.1 Global HCV care cascade

To achieve population-level impact of DAA therapy on morbidity and mortality and ongoing HCV transmission, high proportions of populations with HCV infection need to be tested and diagnosed, linked to care, treated and cured.

The cascade of care, first conceptualised by the HIV field, is a framework composed of the key stages of care for individuals who are living with a particular chronic disease. These stages typically include, testing and diagnosis, linkage to a healthcare provider, treatment initiation, and achieving a successful treatment outcome.[239] The main utility

of the care cascade is to monitor health outcomes at both the clinical and population-levels. Similar to the case of HIV, there is no consensus on definitions for stages along the HCV care cascade.[240] Nonetheless, the aim of the HCV care cascade is to: 1) monitor the prevalence of individuals tested and diagnosed for HCV antibodies and HCV RNA, linked to healthcare provider for HCV/liver disease assessment, initiated on treatment, and cured (SVR); 2) identify drop-offs along the care continuum; and 3) evaluate the impact of interventions and barriers in engaging individuals at each stage of the care continuum (Figure 5).

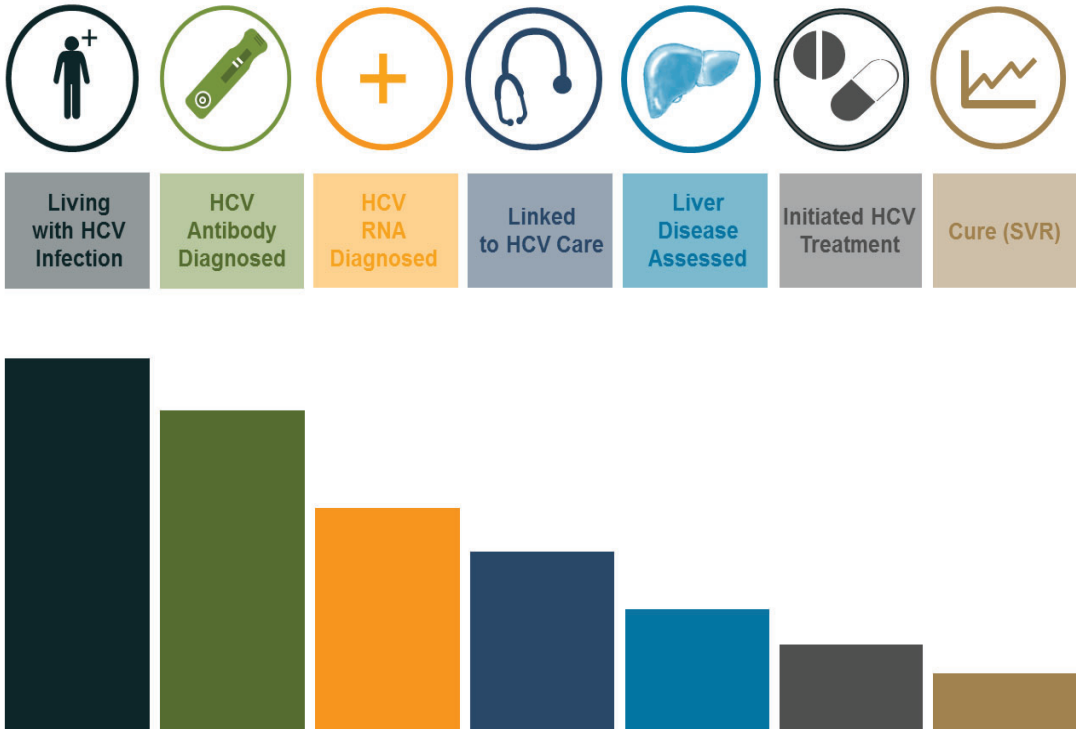

Figure 5. Illustration of a typical HCV care cascade

Estimates of the prevalence of people engaged at each stage of the global HCV care cascade do not exist. However, recent mathematical modelling of separate diagnosis and

treatment rates, demonstrated that of the 71 million people living with HCV infection globally in 2015, an estimated 20% (14 million) were aware of their diagnosis and 7% had initiated treatment (1.1 million) (Figure 6). Large disparities between regions in diagnosis rates persist, with 46% of infections diagnosed in high-income countries, compared with 17% in upper–middle-income and 14% in LMIC.[3] The highest proportion of people treated was estimated in the Eastern Mediterranean region owing to the massive scale-up of screening and DAA treatment in Egypt.[3, 241] About half of those treated in 2015 received DAA treatment, once again reflective of broad DAA access in Egypt. Most of those treated (n=843,000; 80%) were projected to have achieved SVR.[3]

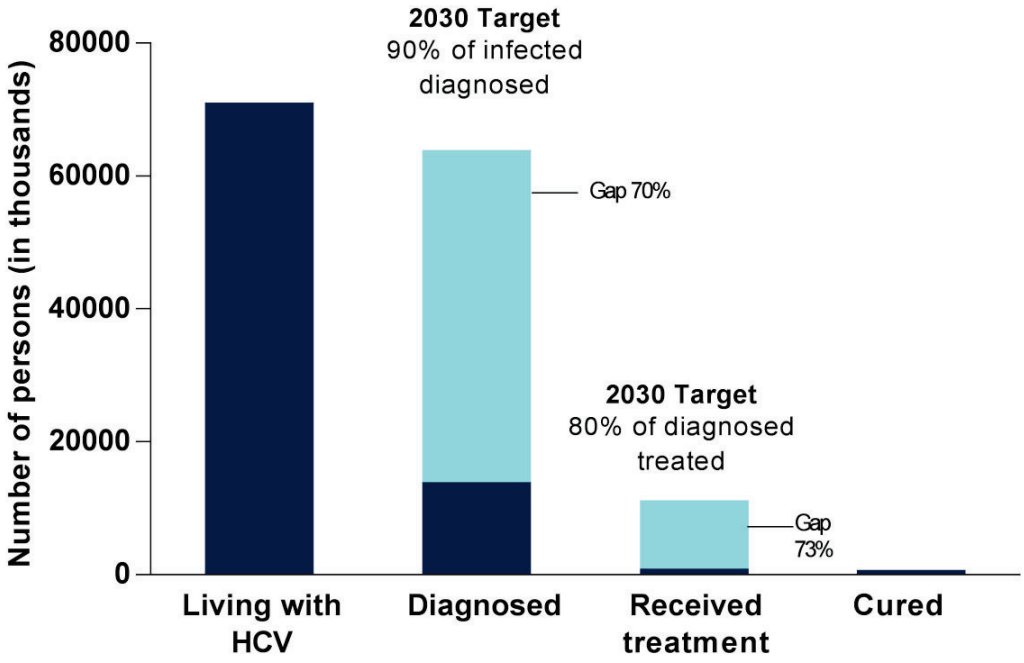

Figure 6. Global HCV care cascade in 2015

Variations in diagnosis rates across countries is consistent with previous work by Dore et al., with estimates in 2013 ranging from less than 20% in Egypt and Brazil to more than 80% in Australia and Sweden.[188] Diagnosis rates were lowest in LMIC that have generalised epidemics compared to high-income countries where the epidemics are concentrated in PWID populations.[188] The same study, also demonstrated that in the interferon era, annual treatment uptake was consistently low. Data from 16 countries revealed annual treatment uptake in 2013 ranging from 0.5% in Denmark, 0.6% in Brazil, 1.1% in Egypt to 1.7% in Australia, 4.7% in Germany and 5.2% in France.[188] Results suggested that socio-economic determinants of health may not be the major driver of treatment uptake rates.

There is also a dearth of studies in the interferon era that describe the HCV care cascade in the general population and in high-risk groups.[242-247] Nonetheless, the available literature has consistently shown significant deficits along the care cascade. A meta-analysis by Yehia et al.,[244] described the HCV care cascade in the Unites States between 2003 and 2013. Of the 3.5 million people estimated to have chronic HCV infection, 50% were estimated to be aware of their infection, 27% received a HCV RNA confirmatory test, 17% underwent liver fibrosis staging, 16% were prescribed treatment, and only 9% achieved SVR.

Similarly, a population-based linkage study by Janjua et al., of individuals receiving HCV testing or reporting HCV infection between 1990 and 2013 linked to

hospitalisation, cancer, medical visits, death and prescription data, described the HCV care cascade in British Columbia.[243] An estimated 73,203 people were HCV antibody positive in 2012 (undiagnosed: 18,301, 25%; diagnosed: 54,902, 75%). Of these, 56% (40,656) had HCV RNA testing; 34% (26,300) were genotyped. Of the estimated population with HCV, only a small proportion (12%, n=8532) received interferon-based therapy and 7% (5197) had documented SVR. Males, older birth cohorts (<1945), and those with HBV coinfection were less likely to undergo HCV RNA testing while those with a history of illicit drug use were less likely to be genotyped. People with HIV, cirrhosis, problematic drug or alcohol use were more likely to be in liver care while males and those with HBV coinfection were less likely to be retained in care.

According to national surveillance work in Australia, there were an estimated 182,144 people living with chronic HCV infection by the end of 2017. Of those, 80% (145,838) have been diagnosed, of whom 47% (68,544) had HCV RNA confirmatory test. Of those receiving confirmatory testing, 31% (21,530) had initiated treatment, of whom 95% (20,454) achieved SVR.[88]

1.6.2 Strategies to enhance the HCV care cascade in the general population

HCV testing and diagnosis

Strategies to improve the HCV care cascade for HCV infection need to be developed in accordance with local epidemiology, national health priorities and available resources.[46] In recognition of the analogy that ‘one size does not fit all’, innovative models of care tailored to the needs of high-risk populations such as PWID, HIV-coinfected, incarcerated and homeless people, are necessary.

Historically, strategies to enhance HCV testing have focused on screening high-risk populations, including PWID, people living with HIV, high-prevalence birth cohorts (e.g. the 'baby boomer generation'- people born between 1945 and 1965 – in the US),[248, 249] and MSM. Strategies were underpinned by recommendations such as those made by the CDC in 1998 involving risk-based approaches to screening PWID, persons who received intravenous blood clotting factor products before 1987, those with persistently abnormal ALT, and recipients of blood transfusion or organ transplant or on haemodialysis. These strategies were, however, impeded by multiple factors including physician hesitance to ask about risk factors and patient unawareness or unwillingness to disclose risk behaviour due to fears of being stigmatised and discriminated against.[171]

With the evolution of HCV therapeutics and launch of the WHO elimination targets, screening strategies also evolved with the first WHO guidelines on testing for chronic HBV and HCV infections being published in 2016. Recommendations also evolved from treating patients with significant liver disease to treating all people with chronic HCV infection through simplified models of care using pangenotypic DAAs. International Guidelines reinforced screening of high-risk populations as a priority (PWID, prisoners, MSM, sex workers, people living with HIV) in health facility and community-based settings. General population screening in settings with intermediate (≥2%) and high (≥5%) seroprevalence (e.g. in HIV, tuberculosis and antenatal clinics and primary health services) and in settings with poor injection safety remains relevant. Birth cohort screening of age-groups who may have been exposed to unscreened blood

products remains relevant in some countries. As an example, Egypt initially implemented screening programs of army recruits, university students and hospitalised inpatients, prior to generalised screening. Although broad screening programs can be cost-effective in some settings, the caveat is the potential of missing 'hard to reach' at-risk populations who remain undiagnosed.

Modelling studies have suggested that in order to reach elimination targets, frequent (e.g. annual) testing of high-risk populations, including PWID, is needed.[250] Multidisciplinary models of care for HCV infection integrated in a variety of settings including prisons,[251, 252] supervised injecting centres, centres for migrants and people who are homeless, OST[253, 254] and NSP services, and general practice[255] have been shown to be effective. A systematic review of interventions to enhance the HCV care cascade among PWID is presented in Chapter 2 of this thesis.

A meta-analysis by Zhou et al., demonstrated that clinician reminders to prompt HCV testing during clinical visits increased HCV testing rates almost four-fold compared to no clinician reminders (RR 3.70, 95% CI 1.81 – 7.57; n=52947).[256] The three studies evaluated were conducted in primary care clinics in New York City, and employed either physical reminder stickers or reminders incorporated into an electronic medical record system to prompt providers to ask patients about HCV related high-risk behaviours or order testing for patients born in a high-prevalence birth cohort.[255, 257, 258] Provision of educational sessions (group sessions and/or individual consultation), pre-test counselling, and on-site HCV testing at various services (including, shelters serving

people who are homeless and asylum seekers, psychiatric inpatient units) have shown increased HCV testing uptake compared to no intervention.[98, 259]

Strategies to enhance testing and diagnosis must address the complex high-cost diagnostic paradigm, requiring multiple patient visits for HCV diagnosis, with inadequate infrastructure to facilitate decentralisation. The current HCV testing algorithm requires the detection of antibodies against HCV to confirm exposure. In people testing HCV antibody positive, a confirmatory HCV RNA test is needed to confirm active infection. Evidence suggests that due to the number of visits needed to make a diagnosis, this two-step algorithm has resulted in a significant drop-off from antibody testing to diagnosis in the HCV care cascade.[260] Several studies from high-income countries have shown that between 46-73% of people testing HCV antibody positive received confirmatory HCV RNA testing.[243, 244, 260-263] There are a number of barriers to receiving confirmatory HCV RNA testing. First, individuals may need up to five clinical and pathology visits to receive confirmation of diagnosis.[260] Second, phlebotomists and pathology are usually off-site, and HCV RNA results may take weeks to return. This is particularly problematic in remote/rural settings and in LMIC where affordability is an issue, and among marginalised populations (PWID and those who are homeless or incarcerated) who infrequently access these services. Third, in some studies, inadequate knowledge and competence among primary healthcare providers in ordering HCV RNA tests to confirm active infection in HCV antibody positive patients led to confusion among patients in relation to their status.[264, 265] Fourth, poor knowledge among patients in relation to HCV testing and the difference

between HCV antibody and HCV RNA testing may contribute to defaulting on subsequent visits.[177, 266]

Strategies that have improved HCV testing include point of care testing and simplified diagnostic algorithms. A point of care test is defined as 'a diagnostic test that is performed near the patient or treatment facility, has fast turnaround time and may lead to a change in patient management' (Figure 7).[267] Point of care and dried blood spot (DBS) testing have been demonstrated to increase HCV testing uptake and linkage to care. The advantages of finger-stick capillary DBS testing include: 1) avoids the need for phlebotomy which is particularly favourable in settings where these services are unavailable, or where venous access may be difficult, such as in PWID; 2) allows reflex HCV RNA testings for those testing HCV antibody positive by using additional spots on the same filter paper thereby avoiding additional patient visit; 3) does not require cold-chain storage and once dried is easy to transport and store which is important in resource-limited settings; 4) allows for task-shifting as it can be performed by lower-skilled workforce such as peer workers and community health workers thereby allowing decentralisation and expansion of testing.

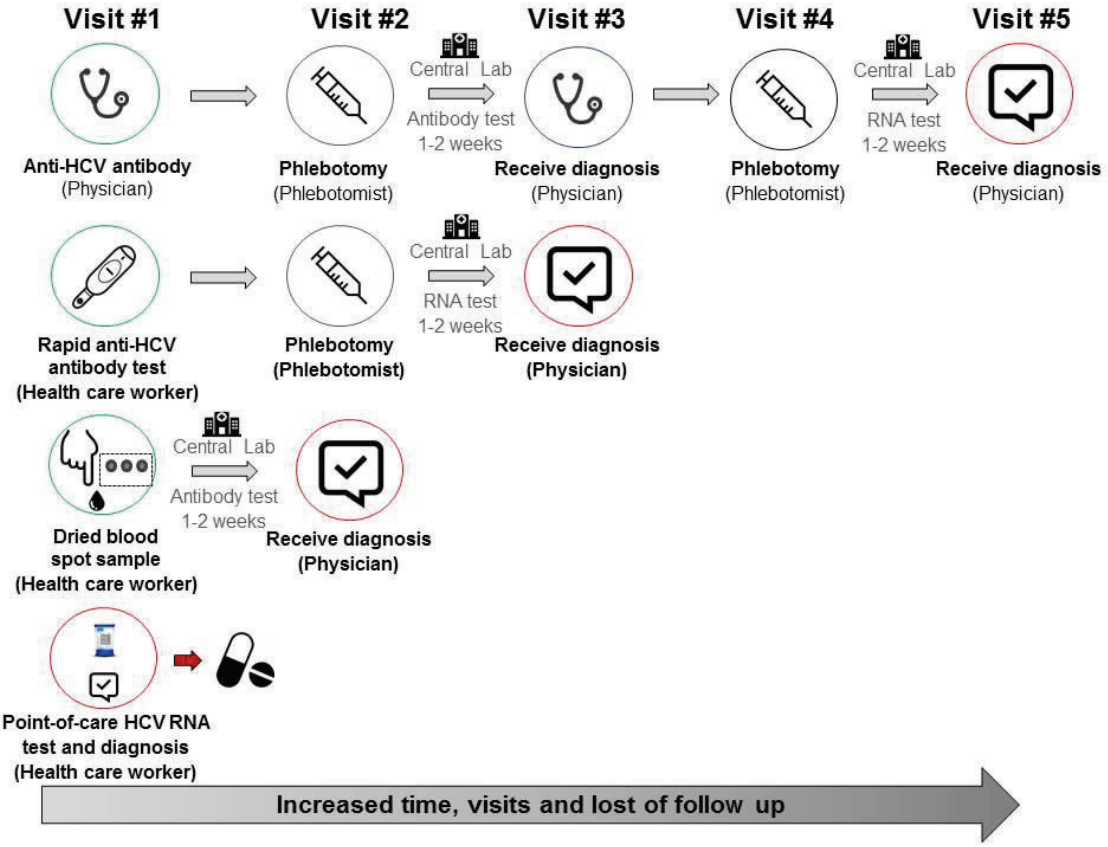

Figure 7. Point of care diagnostics paving the way to a single visit HCV diagnosis
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Liver disease assessment and linkage to HCV care

Historically, liver biopsy was needed for liver fibrosis staging and guided interferon-based therapy but was a barrier to linkage to care and treatment. Painless and rapid non-invasive methods, such as transient elastography, for liver disease assessment have been shown to facilitate linkage to care and treatment.[177, 178, 268] Advantages of transient elastography include: 1) allows task-shifting to lower-skilled health professionals; 2) portable and easy to incorporate in outreach mobile clinics for 'hard to reach' populations (e.g. PWID, homeless people), and can be integrated into various settings such as general practice, prisons, OST clinics, mobile outreach and other services; 3) provides liver fibrosis staging in less than 5 minutes.

In the interferon era, nurse-led models of care have been shown to enhance linkage to care and treatment among marginalised populations. A study by Lloyd et al., evaluated the effectiveness and safety of specialist telemedicine-supported nurse-led model of care for inmates with chronic HCV infection across three prisons.[269] Key features included protocol-driven liver disease assessment (using liver function tests and conservative clinical assessment or ultrasound), risk behaviour, and treatment suitability. Based on these assessments, the nurse triaged patients to initiating treatment or requiring face-to-face consultation with specialist before treatment was initiated. Following specialist assessment patients were initiated on treatment and monitored for adverse events and treatment outcomes by the nurse. Among 391 patients with HCV infection, 36% completed assessments and 28% initiated interferon-based treatment.

HCV treatment uptake

Few evaluations of interventions to enhance treatment uptake and SVR in the general population have been performed and the vast majority were performed in the interferon era. Project ECHO (Extension for Community Healthcare Outcomes) used a model of primary care physician–based HCV treatment with specialist mentorship and demonstrated equivalent cure rates between primary care physicians and specialists.[270] In the DAA era, expansion of HCV treatment to community-based non-specialist providers (nurses and primary care physicians) has been shown to be successful. In a recent non-randomised clinical trial in the United States, patients were assigned in a specified manner to receive sofosbuvir/ledipasvir from nurse practitioners, primary care

physicians, or specialists (infectious diseases physician and hepatologist). SVR rates were consistent across the three provider types: nurse practitioner (89.3%); primary care physician (86.9%); and specialists (83.8%);[271] adding to growing evidence of prescriber diversity in a variety of settings.

1.6.3 HCV care cascade among PWID

Studies describing the HCV care cascade in PWID are scarce and largely limited to high-income countries and the interferon era,[272, 273] although more research is beginning to emerge in the DAA era. Evidence from these studies shows significant gaps along the care cascade. For example, a study by Iversen et al., used national surveillance data to estimate the HCV care cascade among PWID in Australia in 2015 (prior to DAA access). The study demonstrated of the 93,000 PWID in Australia, 89% were estimated to have been screened, 57% were HCV antibody positive, of whom 46% received confirmatory HCV RNA test, 31% received a specialist assessment and 8% were treated (Figure 8).[263] Among participants with current or past active HCV infection, those who had received confirmatory testing were more likely to have a history of past (OR 2.12, 95% CI 1.27– 3.67, p = 0.007) or current (OR 2.69, 95% CI 1.64–4.43. p < 0.001) OST, and to have received their last HCV test at a primary health clinic that provided services specifically for PWID (OR 2.00, 95% CI 1.06–3.76, p = 0.032).

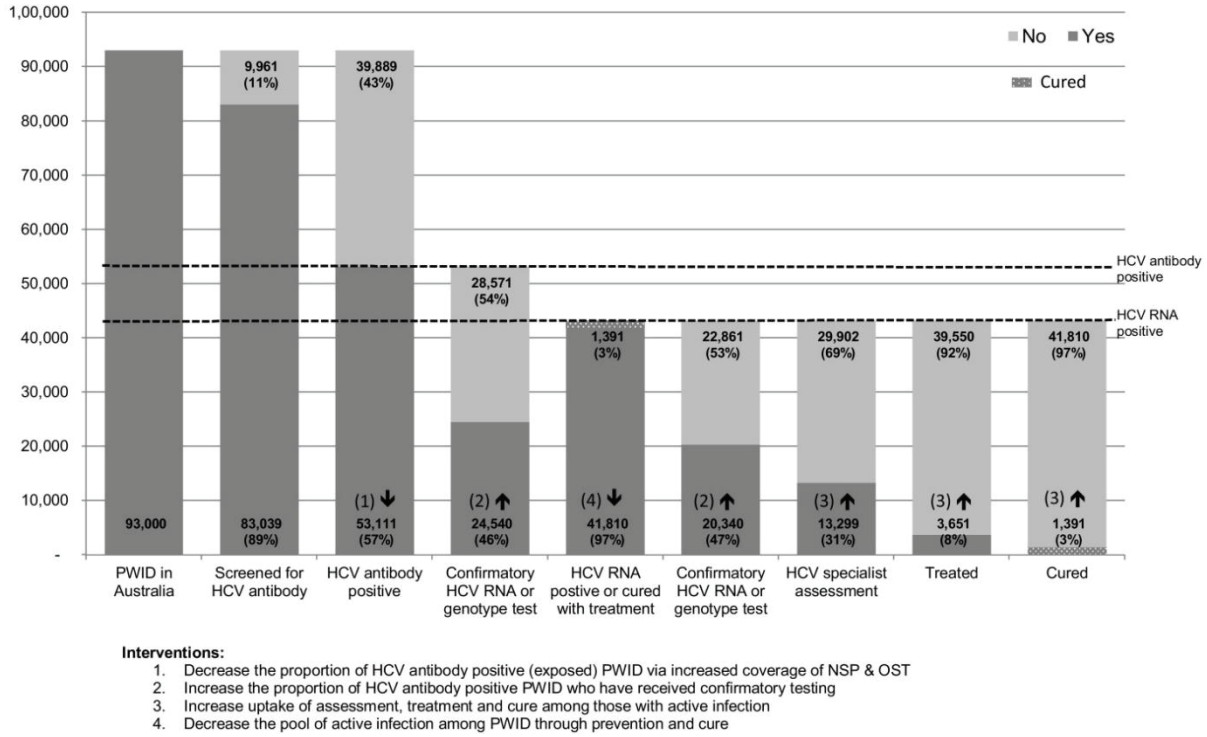

Figure 8. Estimate of the cascade of HCV care among PWID in Australia in 2015[263]

Reprinted from Iversen J et al. Int J Drug Policy. 2017 https://doi.org/10.1016/j.drugpo.2017.05.022 with permission from Elsevier

Data derived from three prospective cohort studies of PWID in Canada, between 2005 and 2015, also demonstrated major drop-offs along the HCV care cascade.[274] Among 1571 PWID with chronic HCV infection, 87% (n=1359) were linked to care, 80% received liver disease assessment (n=1257), of whom 38% either had a liver biopsy or transient elastography, 10% (n=163) initiated treatment and only 5% (n=71) completed interferon-based HCV treatment.[274] Predictors of having undergone liver disease assessment were HIV positivity (adjusted hazard ratio [AHR]=1.75, 95% CI 1.50 - 2.05), use of methadone maintenance therapy (AHR=1.42, 95% CI 1.23 -1.64), and hospitalization (AHR=1.50, 95% CI 1.25 - 1.81). Reasons for declining HCV treatment

included concerns about side effects (35%), perceptions that symptoms were not severe enough (23%) and HCV not being a priority (11%).

Data on the HCV care cascade in LMIC is lacking.[275] Available data from LMIC demonstrate a less populated HCV care cascade than high-income countries, with the vast majority of PWID with HCV unaware of their status.[275] In a large cross-sectional study in India using respondent-driven sampling for recruitment, PWID demonstrated abysmal HCV diagnosis and treatment uptake rates. Of the 5,777 PWID testing HCV antibody positive, only 5.5% were aware of their status, 3% had sought medical advice for their HCV and just 1.4% initiated HCV treatment.[275] Predictors of HCV antibody positive status awareness were higher education, HIV testing history, awareness of HIV positive status, and higher prevalence of antiretroviral therapy in the community. These data highlight the urgent need for the scale-up of education, literacy and testing campaigns, and effective context-specific linkage to care and treatment strategies.

1.6.4 Barriers to HCV care among PWID

A myriad of barriers to HCV testing and diagnosis, linkage to care and treatment uptake among PWID in the interferon era have been identified.[173, 174, 211, 214, 266, 276-289] Barriers have typically been categorised at the patient- provider- and system-levels. This section provides a brief account of these barriers, some of which – as discussed in subsequent chapters of this thesis – remain in the DAA era.

Patient-level barriers

PWID face a complex set of interrelated barriers to accessing HCV services and care, underpinned by economic marginalisation and social exclusion.[214, 280, 289] Lack of HCV-related knowledge among PWID has been cited as a reason for not accessing testing or treatment services.[173, 266, 278] Previous studies have demonstrated that high knowledge scores are associated with receiving HCV assessment and treatment uptake.[266, 290] Receipt of a positive HCV diagnosis can be either distressing or of limited concern or prompt urgency to seek treatment (particularly because of the lack of physical symptoms).[291] This is largely contextual and depends on hardship, normalization within a peer/social network and seeing other people's experiences with HCV care.[291] PWID in a number of studies reported not wanting to present to health services due to fears of being stigmatised by health providers.[280, 292-294] Additional barriers include cost of transportation to appointments and medication.[136] PWID may also have competing priorities such as maintaining financial and drug supply and avoiding overdose, drug withdrawals, homelessness and incarceration.[295, 296]

As previously mentioned, venous access difficulties for blood collection have been cited as barriers to accessing HCV testing services.[295, 297] Drop-off at the testing and diagnosis stages of the cascade of care has been shown to be is related to the number of times that individuals need to access phlebotomy services and to see health providers for test results.[260] In the prison setting, prisoners with chronic HCV infection feel 'double stigma' due to their HCV status and being identified as prisoners when, for instance, attending out-patient appointments in handcuffs.[298]

A number of studies have reported high levels of treatment willingness among PWID.[177, 299, 300] However, fear of side-effects and moderate success rates of interferon-based treatment were major barriers to initiating treatment in the interferon era,[278] and these fears may persist in the DAA era.

Health provider-level barriers

Despite the increasing burden of HCV infection in PWID and current international guidelines endorsing HCV treatment for this population,[301-303] many physicians continue to be reluctant to prescribe HCV treatment to PWID due to concerns about patient non-adherence, ongoing drug use, reinfection, and limited resources (due to the cost of therapy).[211, 288] Evidence indicates that treatment adherence is comparable between PWID and the general population,[224] and that the risk of reinfection is relatively low.[304] In a nationwide survey of hepatologists, gastroenterologists and infectious diseases specialists in Canada, only 20% indicated that they would consider prescribing interferon-based HCV treatment to recent PWID.[288] Furthermore, lack of confidence and inadequate knowledge in initiating interferon-based treatment among general practitioners have been cited as barriers to provide testing and treatment.[305]

Health system-level barriers

Evidence suggests that high DAA pricing and treatment restrictions based on fibrosis staging and drug/alcohol use are barriers to HCV care among PWID.[213, 215, 228]

Integration of HCV care in existing infrastructures providing drug user health services has been shown to successfully facilitate linkage to care and treatment uptake.[306] For example, OST clinics, community-based clinics, and decentralised models of care harnessing peer-based strategies have been successful.[254, 307, 308]

Due to high DAA drug pricing, treatment restrictions on the basis of current alcohol and illicit drug use remain in many countries and jurisdictions.[213] For example, in a review of DAA reimbursement restrictions in the United States, drug and alcohol abstinence for a minimum of six months is required to be eligible for treatment in the majority of states.[215]

There are additional barriers to care among PWID in prison settings. Due to the criminalisation of drug use and involvement in illegal activity to support drug use, PWID are over-represented among prisoner populations. Barriers to accessing HCV treatment in this setting include delays in accessing blood tests, HCV screening and receiving results.[298, 309]

1.6.5 HCV Prevention among people who inject drugs

The WHO, United Nations Office on Drugs and Crime (UNODC) and UNAIDS have endorsed a set of interventions for the prevention of viral hepatitis B and C among

PWID.[310] This guidance endorses five essential health interventions: needle and syringe programs, opioid substitution therapy for people with opioid dependence, risk reduction communication and education, HBV vaccination, and treatment of chronic HCV infection.

'Harm reduction refers to policies, programmes and practices that aim to minimise negative health, social and legal impacts associated with drug use, drug policies and drug laws. Harm reduction is grounded in justice and human rights - it focuses on positive change and on working with people without judgement, coercion, discrimination, or requiring that they stop using drugs as a precondition of support'.[311] Harm reduction policies and programmes gained traction as a response to the HIV epidemic in the 1980s. Several terms are used interchangeably, including 'harm minimisation' and 'risk minimisation' and 'risk reduction'. Harm reduction strategies particularly relevant to HCV prevention are NSP and OST. A recent Cochrane Systematic Review found high coverage of NSP was associated with 56% risk reduction in HCV acquisition, but when combined with high coverage of OST (>40 per 100 PWID) the reduction in risk of HCV acquisition is 76%.[312]

Modelling studies have demonstrated that OST and NSP need to be implemented at high levels of coverage and in combination in order to substantially reduce HCV transmission at the population-level.[34, 313-315] Current recommendations include the distribution of 300 needle-syringes per PWID per year, and OST to more than 40 per 100 PWID. However, global and national coverage of harm reduction strategies remains

drastically inadequate. A recent systematic review demonstrated that less than 1% of PWID live in countries with high coverage of both NSP and OST.[316] Further, only nine countries (e.g. including Australia, Norway and Scotland) had high NSP coverage (e.g. Australia, Austria, Netherlands; i.e. distributed more than 200 needles/syringe per PWID annually) and 20 countries provided high coverage OST.[316] Renewed efforts to enhance harm reduction strategies and increase coverage of these essential health interventions is crucial in order to achieve HCV elimination targets.

1.7 Thesis rationale and objectives

Chronic HCV infection is a leading cause of morbidity and mortality globally. Further, this burden is expected to rise due to ageing populations who were infected during periods of high HCV transmission two to four decades ago. HCV infection is highly prevalent among marginalised populations, including PWID and people who are homeless, many of whom inject drugs. While the development of highly efficacious (>95% cure rates) and tolerable interferon-free DAAs has provided an unprecedented opportunity to eliminate HCV by 2030, large proportions of people living with chronic HCV infection need to be diagnosed, linked to care, treated and cured.

In most high-income countries, HCV infection is predominantly concentrated in PWID. However, even in these settings, most PWID have not been diagnosed or treated for HCV infection. PWID face a multitude of socio-economic and systemic barriers to accessing HCV care. Novel strategies tailored to the needs of PWID are required to

engage them along the HCV care cascade in order to reach the WHO HCV elimination goals by 2030.

This thesis consists of an overview of the literature (Chapter 1) and four other chapters (Chapters two to five), including original research findings. The overall aim of this thesis is to assess the feasibility and outcomes of strategies to enhance HCV testing and diagnosis, liver disease assessment and treatment uptake in PWID and people who are homeless pre- and post-access to DAA therapy. The specific objectives of the studies described in this thesis are:

1. To systematically evaluate the effectiveness of interventions to enhance HCV testing, linkage to care, and treatment uptake among PWID.

2. To assess the acceptability and preferences for point of care finger-stick whole-blood and venepuncture HCV RNA testing among PWID in Australia.

3. To assess HCV RNA prevalence, liver disease burden, linkage to care and treatment uptake and outcomes among people attending homelessness service in Sydney, Australia.

4. To a) describe the HCV care cascade 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) identify factors independently associated with significant liver fibrosis; c) examine HCV

treatment uptake in the pre-DAA and DAA eras, and determine factors independently associated with DAA treatment uptake.

Chapter 2: Interventions to enhance testing, linkage to care and treatment uptake for hepatitis C virus infection among people who inject drugs: A systematic review

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Declaration

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2.1 Abstract

Background: The burden of hepatitis C virus (HCV) infection is escalating among people who inject drugs (PWID), yet testing and treatment remains suboptimal. The aim of this systematic review was to evaluate the effectiveness of interventions to enhance HCV testing, linkage to care, and treatment uptake among PWID. **Methods:** A systematic literature search of Medline (Ovid 1946 – present), Embase, Global Health, Cochrane Central Register of Controlled Trials, PsycINFO, Clinical Trials Registry, and Web of Science was conducted covering interventional studies published before 20 July 2016. Studies evaluating interventions to enhance HCV testing, linkage to care or treatment among PWID were included. Data from included studies was extracted by one reviewer and checked by a second reviewer with disagreements discussed until consensus was reached. Relative risk ratios and corresponding confidence intervals were generated for studies included in analysis. **Results:** After adjusting for duplicates, 10,116 records were identified. A total of 14 studies were included for analysis, of which 57% were randomised controlled trials. Interventions to enhance HCV testing included on-site testing with pre-test counselling and education; and dried blood spot testing. Interventions to enhance linkage to care included facilitated referral for HCV assessment and scheduling of specialist appointments for clients. Interventions to enhance HCV treatment uptake included integrated HCV care, drug use and psychiatric services delivered by a multidisciplinary team with case management services, with or without non-invasive liver disease assessment. All studies were conducted in the interferon treatment era and there were no studies conducted in low- and middle-income countries. **Conclusions:** In the direct acting antiviral treatment era, well-designed

studies evaluating interventions to enhance a simplified care cascade are crucial in facilitating treatment scale-up.

Key words: HCV, drug use, interventions, testing, treatment, linkage to care

2.2 Background

Globally, 71 million people were estimated to be living with chronic hepatitis C virus (HCV) infection in 2015, of which 5.6 million (8%) were 'currently' injecting drugs.[3] In addition, there is also a large, undetermined fraction of those with chronic HCV infection that have ceased injecting drugs.[53] Despite the increasing global burden of HCV infection, in the era of interferon-based HCV therapy, testing, diagnosis and treatment were low in the general population [317-320] and in PWID. [73, 210, 321] Estimates suggest that 14 million (20%) of people living with chronic HCV infection were diagnosed, with 1.1 million (7%) having received treatment.[3] Global estimates of HCV treatment uptake among PWID remain unquantified.

The availability of highly effective, interferon-free, short-course direct acting antiviral (DAA) treatment has transformed the clinical and public health management of HCV infection.[322] However, the impact of these new therapies in decreasing HCV burden at the population-level is contingent on the level of testing, diagnosis and treatment uptake.[32, 34, 323] Evidence-based interventions to improve testing, linkage to care and treatment uptake among PWID are urgently needed to reduce HCV- related morbidity and mortality among this population.

The care cascade, popularised by the HIV field, is a tool comprised of the key stages of care for individuals who are living with a particular disease: tested and diagnosed, linked to a healthcare provider, started on treatment, and achieved a successful treatment outcome.[239] The main purpose of this cascade is to provide a framework to

monitor population-level clinical and public health outcomes, and to identify gaps in the continuum of care. The HCV care cascade is a valuable tool which enables estimation of the prevalence of chronic HCV, testing and diagnosis, linkage to care and treatment uptake.[244, 324]

Interventions aimed at optimising the HCV care cascade have been evaluated in the general population. Interventions to enhance HCV testing include clinician reminders to prompt testing in high-risk populations [255-257], on-site testing with counselling and education [98, 256, 259, 325, 326], rapid HCV testing [252, 327, 328] and dried blood spot (DBS) testing.[329, 330] Interventions to enhance linkage to HCV care and treatment include patient navigation programs [331, 332], telemedicine [270], and non-invasive liver disease assessment using transient elastography with referral to an HCV practitioner.[177, 268] However, PWID face unique health systems and social barriers to accessing healthcare services resulting in limited or poor engagement in HCV care.[173, 266, 278, 287]

To date, there has been no systematic review of evidence-based interventions targeting PWID at the various stages of the HCV care cascade. The aim of this review was to synthesise data on the effectiveness of interventions to improve HCV testing, linkage to care, and treatment uptake among PWID.

2.3 Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[333] Methods of analysis and inclusion criteria were specified in advance and documented in a protocol. The study was registered in PROSPERO (42016042546).

2.3.1 Eligibility criteria

Interventional studies were considered eligible for inclusion if they met all of the following criteria:

1. *Population:* Intervention(s) targeted people who use drugs or at least 50% of the study sample were comprised of people who reported recent injection drug use or on opioid substitution therapy (OST). The assumption is that people who use drugs who are being tested for HCV consist primarily of PWID. Similarly, people who use drugs with chronic HCV infection are assumed to have acquired HCV through injecting drugs.
2. *Intervention:* Intervention(s) were aimed at improving engagement of the study population at any (or combination) of the following stages along the chronic HCV care cascade:
    a) testing for HCV antibodies and/or HCV ribonucleic acid (RNA)
    b) linkage to HCV care, defined as clinical assessment of HCV infection or liver disease
    c) treatment uptake, including interferon-containing and interferon-free regimens

3. *Comparison:* Comparative group composed of participants allocated to no intervention or receiving care as usual or routine care. For non-randomised studies, comparative groups include historical comparisons or before and after intervention implementation, or control groups derived by convenience sampling
4. *Outcomes:* The primary or secondary outcomes were:

    a) proportion of the study population tested and/or,

    b) proportion of study population with chronic HCV linked to care and/or,

    c) proportion initiating treatment as defined by the study authors

Exclusion criteria included studies that were not presented as peer-reviewed scientific articles or conference abstracts, review articles including systematic reviews and non-comparative studies. However, non-comparative studies were identified and reviewed. Public health interventions targeting health care providers as opposed to individuals were excluded.

2.3.2 Information sources

The following electronic databases of literature were searched for full-text and abstract entries published before 20/07/2016: Medline (Ovid 1946 – present), Embase, Global Health, Cochrane Central Register of Controlled Trials, PsycINFO, and Web of Science. In addition, ClinicalTrials.gov was searched for registered studies. The International Liver Congress 2016, American Association for the Study of Liver 2016, and International Network on Hepatitis in Substance Users 2016 conference archives

were searched for accepted abstracts. Reference lists of selected articles and relevant review articles retrieved during the initial search were hand-searched and forward citation checks were performed to identify additional studies.

2.3.3 Search strategy

A comprehensive list of search terms related to each of the investigated care cascade components was used to develop a search strategy for each electronic database. Search strings for each database were developed in consultation with a librarian at the UNSW Sydney. Search strings were formulated using a combination of keywords and indexed subject headings (MeSH and EMTREE terms). Terms within each of the population and hepatitis C disease groups were combined using the 'AND' operator, and the terms within groups belonging to each of the three components of the HCV care cascade were combined using the 'OR' operator. Indexed subject heading were broadened using the 'explode' operator. The detailed list of search terms used to search all the electronic databases and full search strategies used for the database are included in the supplementary material (Supplementary Data 1 and 2). Abstracts from the selected scientific conferences were screened for review eligibility.

2.3.4 Study selection

Data retrieved through the search strategy were imported into EndNote X7 (Thomson Reuters, New York, NY, USA) and duplicates removed. Titles obtained from the initial search strategy were screened by two reviewers (S.B. and E.C.) and irrelevant citations were removed if appropriate. Abstracts were then examined according to eligibility

criteria by one reviewer (S.B.) for further review. Full texts for all abstracts identified for further review were then assessed independently by two reviewers (S.B. and B.H.) for inclusion. In the event of a disagreement, two reviewers determined final inclusion (G.D. and J.G.). Reasons for exclusion were reported.

2.3.5 Data collection process and data items collected

Data from studies included for analysis were extracted by one reviewer author (S.B.) using a pre-piloted standardised data extraction form (Microsoft Excel 2010 Redmond, WA, USA). A second reviewer (B.H.) checked the extracted data, and disagreements were resolved by discussion between the two reviewers until consensus was reached. The following variables were collected: first author, title, publication year, study design, study location, setting, population characteristics (% reporting recent drug injection, % with a history of injecting drug use, % receiving OST), intervention description, comparator description, sample size (including in intervention and control arms), duration of intervention, outcome description, number of participants achieving the outcome of interest (and proportions if applicable) in each intervention and control arms.

2.3.6 Risk of bias assessment in individual studies

Risk of bias in individual studies were assessed by one reviewer (S.B.) using the Cochrane Collaboration's risk of bias tool for randomised studies [334] and the ROBINS-I tool (Risk Of Bias In Non-randomized Studies - of Interventions) [335] for non-randomised studies. If a single study reported outcomes at multiple stages of the care

cascade, risk of bias was assessed for each stage independently. For randomised studies, outcomes were evaluated along six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. The number of domains deemed as 'high risk' of bias for each study per outcome was identified. Outcomes of non-randomised studies were evaluated along seven domains: bias due to confounding, bias in selection of participants into study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result. The overall risk of bias for each outcome was classified into five categories: low risk of bias, moderate risk of bias, serious risk of bias, critical risk of bias or no information.

2.3.7 Data analysis

Study designs, participants, interventions and reported outcomes varied significantly, and meta-analyses were unlikely to be informative, therefore they were not performed. The characteristics and findings of the included studies were summarised and structured using tables and forestplots. Risk ratio (RR) and corresponding 95% confidence interval (95% CI) was calculated for each study outcome, using the initial number of eligible participants included and the number achieving the outcome of interest in each arm. Analyses were conducted using statistical package Stata v14.0 (College Station, TX, USA).

2.4 Results

2.4.1 Study Selection

The numbers of studies identified, reviewed and selected and the reasons for exclusion are summarised in Figure 1. The initial electronic databases search retrieved 16,404 records. After adjusting for duplicates, 10,116 records remained. Of these, 8,539 records were excluded on the basis of non-relevant titles. An additional 1,338 abstracts were excluded (reasons depicted in Figure 1). The remaining 239 studies were retained for full-text review. Eight additional studies were added through backward/forward citation check. Following the full-text review, 233 studies were excluded for the following reasons: non-relevant studies (n=18), repeated/duplicate result (n=17), ineligible methodologies (n=27), ineligible outcomes (n=63), unavailable data (n=3), no comparator group (n=27), no population of people who use drugs (n=14), and no intervention (n=64). The non-comparator studies (n=27) identified throughout this process evaluating interventions to enhance HCV testing, linkage to care and treatment are described in Box 1. A total of 14 studies were identified for inclusion in the review and analysis.

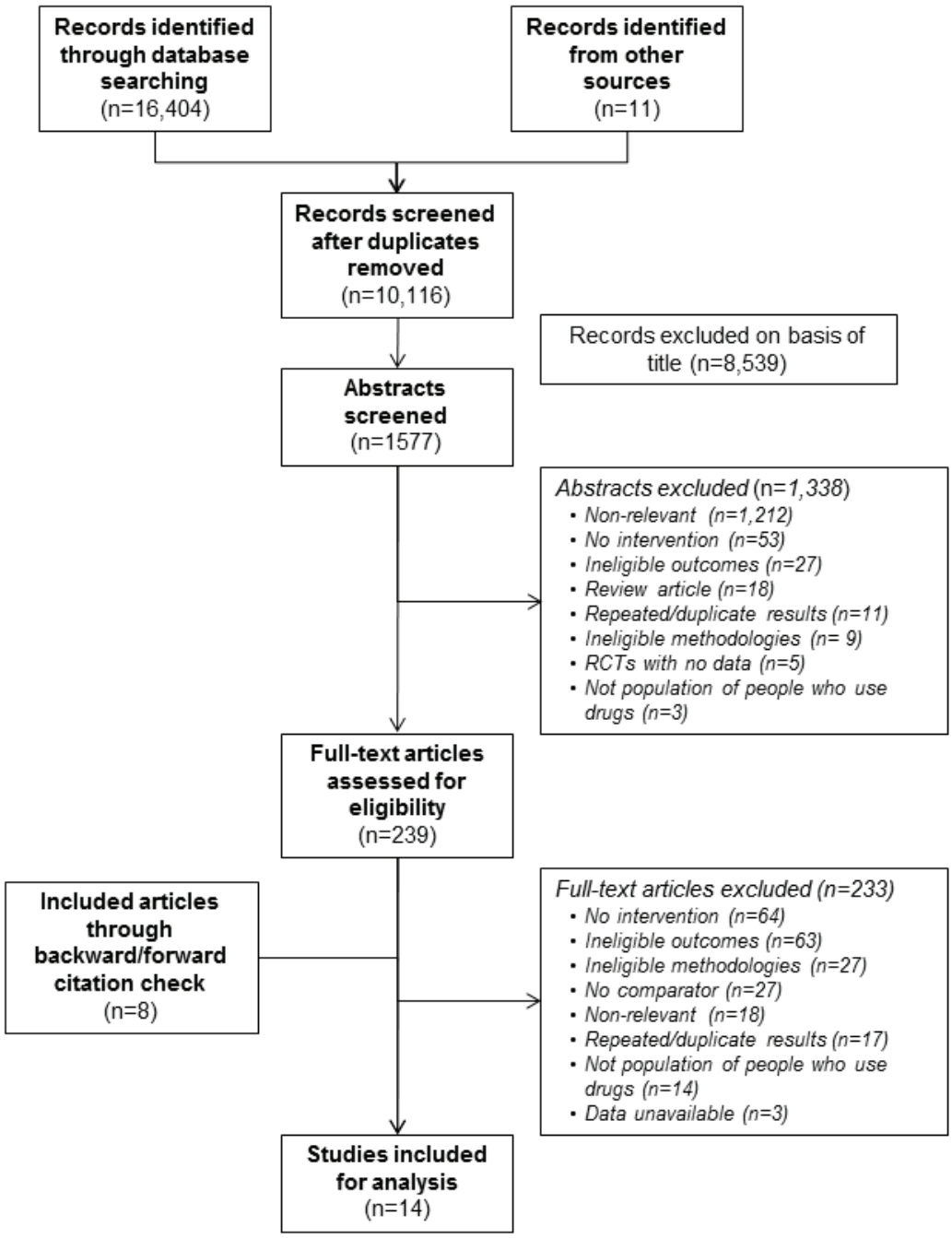


Figure 1: Study selection process

Box 1: Strategies to enhance the chronic HCV care cascade among people who inject drugs (non-comparative studies)

HCV testing

- Peer-delivered outreach HCV testing and counselling [307]
- Prison-based outreach testing and counselling [336]
- Patient referral contact tracing programme with monetary incentive for testing [337]
- Rapid HCV antibody testing at community pop-up/mobile clinics or low threshold settings [338-340]
- DBS testing [341, 342]
- Integrated on-site testing, counselling and education [343, 344]

HCV linkage to care

- Patient navigation and facilitated referral for HCV evaluation [331, 345, 346]
- Nurse-led pre-treatment assessment in prison with specialist support via telemedicine [269]
- Non-invasive liver disease assessment using transient elastography with facilitated referral to care [177, 178, 341, 347]
- Integrated HCV care in drug & alcohol setting/primary care, including on-site HCV assessment with/without peer support [254, 308, 348-351]
- Community-based nurse-led HCV evaluation and liver disease assessment using transient elastography; and subsequent referral to specialist for treatment [242]
- HCV bridge counsellor employed to provide education, scheduling of specialist appointments, home visits to locate individuals, incentives and transportation [344]
- Multidisciplinary mobile clinic offering point of care testing, counselling and liver disease assessment using transient elastography [340]

HCV treatment uptake

- Integrated HCV care in drug & alcohol setting/primary care, including on-site HCV assessment with/without peer support [308, 348, 352]
- Integrated HCV care and drug use care in primary care, with/without onsite treatment [350, 351, 353, 354]
- Community-based nurse-led HCV evaluation, including ordering of blood tests and disease assessment using transient elastography; and subsequent referral to specialist for treatment [242]
- Patient navigation including motivational interviewing and treatment readiness counselling [346]

2.4.2 Study characteristics and results of individual studies by outcome

The characteristics and results of included studies for each of the three outcomes of the care cascade are summarised in Tables 1 to 3. Forest plots for each of the three outcomes stratified by intervention type are shown in Figure 2.

Of the 14 studies included in the review, three (21 %) investigated the effect of interventions at multiple stages of the care cascade. Eight (57%) of the 14 studies were randomised controlled trials (RCT), of which two were cluster RCTs, and six were non-randomised studies. All included studies were conducted in high income countries and published in English. Seven on-going clinical trials were retrieved from the clinical trials register but contained no data and were therefore excluded from review and analysis.

HCV testing

Ten studies evaluated interventions to enhance HCV testing uptake (Table 1 and Figure 2A).[98, 325, 355-362] Six (60%) of the included studies were RCTs (one cluster and one pilot) and four non-randomised studies. There were four distinct intervention types: on-site testing with education and counselling, DBS testing, education with facilitated off-site liver disease assessment, and harm reduction focused education.

Table 1: Characteristics and results of included studies investigating interventions to enhance HCV testing

HCV Testing

Author (year)	Study Design	Location	Setting	Population (Ever inject %; recent inject %; OST %)	Intervention description	Comparator Description	Outcome Description	Intervention n (%)	Control n (%)	RR (95% CI)
On-site HCV testing, pre-test counselling and education										
Cullen (2006)	RCT (Cluster)	Ireland	General practice	OST clients (100%; NA; 100%)	Offer OST clients on-site testing and nurse-led pre-test counselling	No implementation of HCV care guidelines which offers on-site testing and counselling (usual care)	HCV testing uptake	104 (49%)	92 (27%)	1.80 (1.22,2.66)
Hagedorn (2007)**	NRS	USA	Drug & alcohol clinic	People who use drugs (NA; NA; NA)	Offer HCV testing to all new clients at clinic intake	HCV testing not offered routinely (usual care)	HCV testing uptake	171 (66%)	104 (72%)	0.91 (0.78,1.08)
Lacey (2007)	NRS	Australia	Hospital	Psychiatric inpatients (50%; NA; NA)	On-site testing, pre-test-counselling and education	No screening (usual care)	HCV testing uptake	402 (18%)	430 (9%)	1.90 (1.32,2.73)
Merchant (2014)	RCT	USA	Hospital	People who use drugs attending ED (4%; 1%; NA)	On-site testing; Motivational interview and education; self-administered	Self-administered HIV/HCV risk assessment alone	HCV testing uptake	198 (65%)	197(65%)	1.01 (0.87,1.17)

					HIV/HCV risk assessment					
Merchant* (2015)	RCT	USA	Hospital	People who use drugs attending ED (NA; 8%; NA)	On-site testing; Motivational interview and education ; self-administered HIV/HCV risk assessment	Self-administered HIV/HCV risk assessment alone	HCV testing uptake	431 (37%)	432 (43%)	0.87 (0.74,1.02)
Rosenberg (2010)	RCT	USA	Community mental health clinic	People who use drugs with Psychiatric disorder (NA; NA; NA)	Integrated care: On-site testing (venepuncture), education and pre-test counselling	Provision of information about blood-borne diseases and referral to local services for testing	Self-reported HCV testing uptake	81 (86%)	69 (15%)	5.96 (3.34,10.65)
Dried Blood Spot Testing										
Hickman (2008)	RCT (Cluster)	UK	Drug & alcohol clinic/NSP/Prison	People who use drugs/prisoners (NA; NA; NA)	DBS	Venepuncture (usual care)	HCV testing uptake	3840 (21%)	4500 (5%)	3.81 (3.32,4.38)
Radley * (2017)	NRS	UK	Community pharmacy	OST clients (NA; NA; 100%)	DBS	DBS testing at other services	HCV testing uptake	143 (30%)	561 (13%)	2.24 (1.62,3.12)
A combination of provider-led and peer-led education, and off-site liver disease assessment										

Arain (2016)	RCT (pilot)	Belgium	Drug & alcohol clinic	OST clients (69%; 49%; 100%)	Formal group information session followed by peer-led education; off-site non-invasive liver disease assessment using transient elastography at hepatology clinic	Information brochures available in waiting rooms; referral of anti-HCV positive clients to hepatologist (usual care)	HCV testing uptake	25 (20%)	27 (7%)	2.70 (0.57,12.68)
Harm reduction education										
Roux* (2016)	NRS	France	NSP	People who use drugs (100%; 100%; 72%)	Injection-focused face-to-face education	No education sessions (usual care)	Self-reported HCV testing uptake	75 (85%)	120 (78%)	1.10 (0.95,1.24)

DBS= Dried Blood Spot; ED= Emergency Department; NA= Not Available; NRS= Non-Randomised Studies; NSP=Needle and Syringe Programs; OST= Opioid Substitution Treatment; RCT= Randomised-Controlled Trials ±In half total sample surveyed *Proportions of uptake calculated as per protocol **Per protocol proportions 98% intervention vs 72% control

Table 2: Characteristics and results of included studies investigating interventions to enhance HCV linkage to care

Linkage to Care

Author (year)	Study Design	Location	Setting	Population (Ever inject %; recent inject %; OST %)	Intervention description	Comparator Description	Outcome Description	Intervention n (%)	Control n (%)	RR (95% CI)
Facilitated referral and scheduling of appointment with specialist										
Cullen (2006)	RCT (Cluster)	Ireland	General practice	HCV antibody positive clients receiving OST (100%; NA; 100%)	Nurse-facilitated referral to hepatology clinic	Usual care	Hepatology specialist appointment attendance	73 (51%)	41 (22%)	2.31 (1.24,4.29)
Hagedorn* (2007)	NRS	USA	Drug & alcohol clinic	People who use drugs with chronic HCV infection (NA; NA; NA)	Scheduling of an appointment with hepatology clinic by nurse	Usual care	Hepatology clinic appointment attendance	9 (78%)	6 (50%)	1.56 (0.65,3.72)
Masson (2013)	RCT	USA	Drug & alcohol clinic	HCV antibody positive clients receiving OST (70%; NA; 100%)	Hepatitis care coordination: motivational-interviewing styled education and counselling; case management; appointment at hepatology clinic scheduled directly by case manager	Post-test counselling without motivational interviewing; off-site referral for hepatitis evaluation	Adherence to HCV clinical evaluation appointment within 6 months of the date of referral	149 (65%)	137 (37%)	1.75 (1.37,2.24)
Rosenberg (2010)	RCT	USA	Community mental health service	HCV antibody positive people who use drugs with	Facilitated referral	Information provided; directed to seek care from	Self-reported medical	21 (81%)	16 (75%)	1.08 (0.76,1.53)

				psychiatric disorder (NA; NA; NA)		health provider or local clinic providing free testing	visit for HCV care			
Tait (2010)	NRS	UK	Hospital/ general practice/ Drug & alcohol clinic/prison	HCV antibody positive individuals in a geographical region (people who use drugs=86%)	Non-medical and outreach nurse-led facilitated referral to hepatitis specialist	Medical-led referral only (usual care)	Hepatitis Specialist appointment attendance	875 (82%)	430 (66%)	1.26 (1.17,1.35)

DBS= Dried Blood Spot; ED= Emergency Department; NA= Not Available; NRS= Non-Randomised Studies;
RCT= Randomised-Controlled Trials; OST= Opioid Substitution Treatment; *Proportions of uptake calculated as per protocol

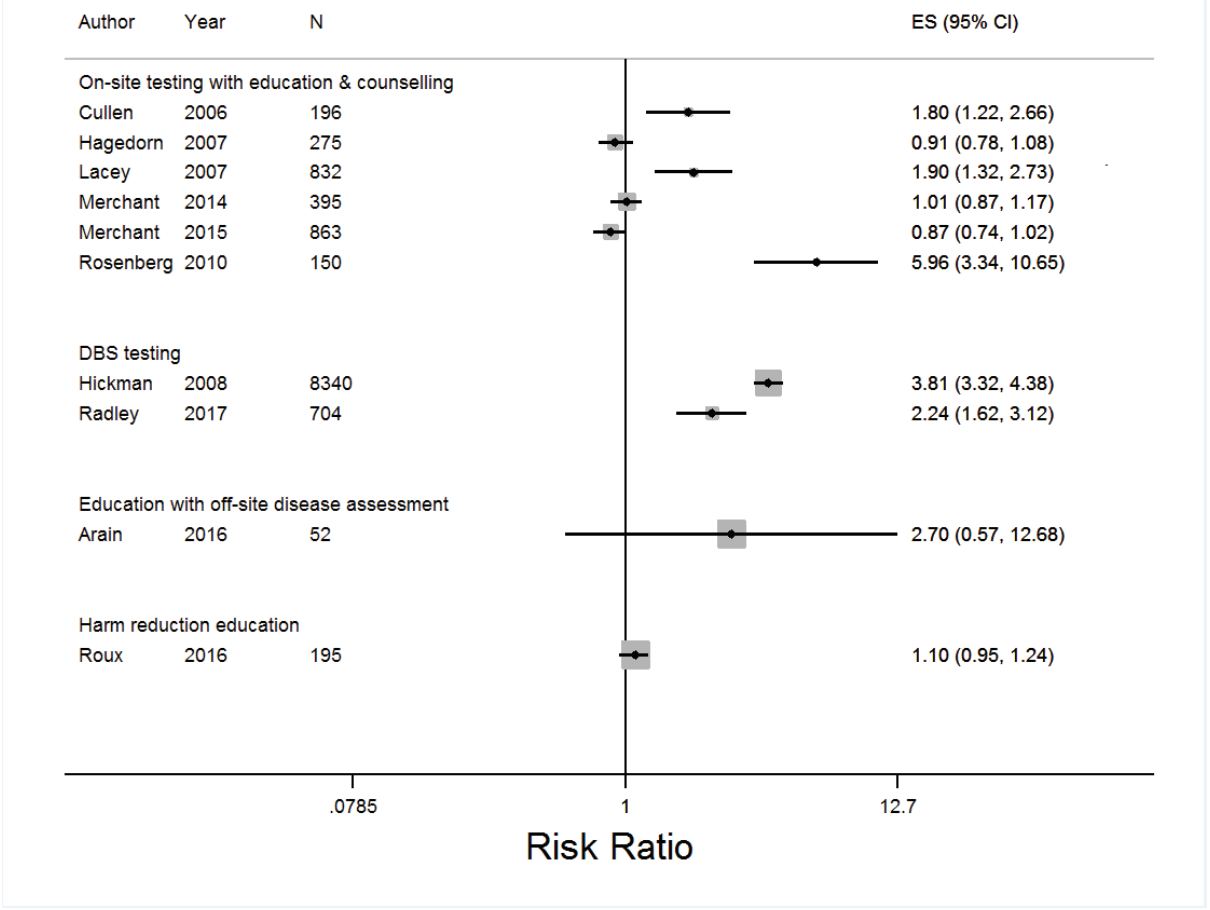
Table 3: Characteristics and results of included studies investigating interventions to enhance treatment uptake

Treatment Uptake

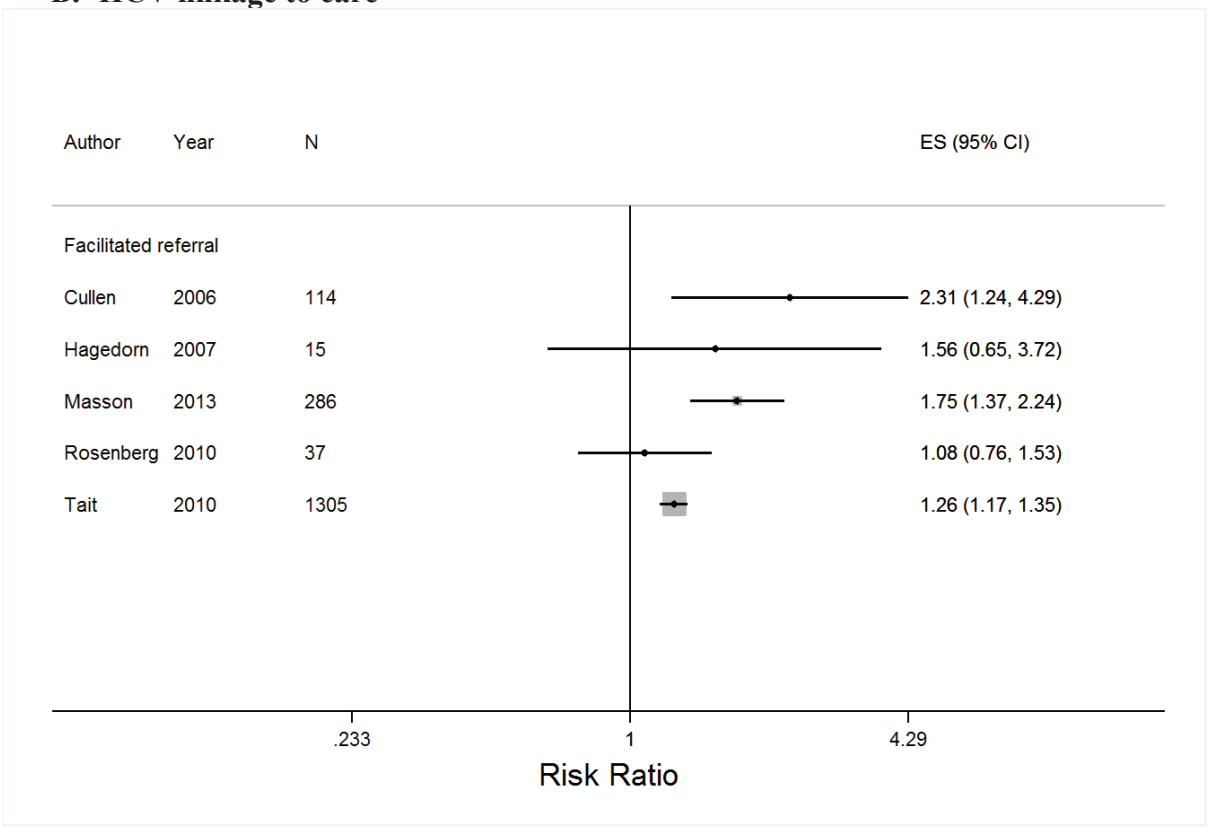
Author (year)	Study Design	Location	Setting	Population (Ever inject %; recent inject %; OST %)	Intervention description	Comparator Description	Outcome Description	Intervention n (%)	Control n (%)	RR (95% CI)
Nurse-facilitated referral to hepatology clinic										
Cullen (2006)	RCT (Cluster)	Ireland	General practice	OST clients (100%; NA; 100%)	Nurse-facilitated referral to hepatology clinic	Usual care	Treatment uptake	73 (7%)	41 (3%)	2.81 (0.34,23.23)
Integrated mental health, substance use disorders and hepatitis services										
Ho (2015)	RCT	USA	HCV clinic	Chronic hepatitis C clients with psychiatric disorder and/or drug use (People who use drug use=65%)	Integrated mental health, substance use disorders and hepatitis services, including case management	Clients were referred for mental health/substance use services elsewhere (usual care)	Treatment uptake	182 (32%)	181 (19%)	1.70 (1.17,2.46)
On-site non-invasive liver disease assessment and motivational education										
Moussalli (2010)	NRS	France	Drug & alcohol clinic	Chronic hepatitis C clients receiving OST (NA; NA; 69%)	On-site multidisciplinary team, non-invasive liver disease assessment; motivation and therapeutic education provided by nurse before treatment initiation	HCV clients referred to hospital (usual care)	Treatment uptake	224 (38%)	113 (2%)	21.44 (5.37,85.54)

DBS= Dried Blood Spot; ED= Emergency Department; NA= Not Available; NRS= Non-randomised studies;
RCT= Randomised-controlled Trials; OST= Opioid Substitution Treatment

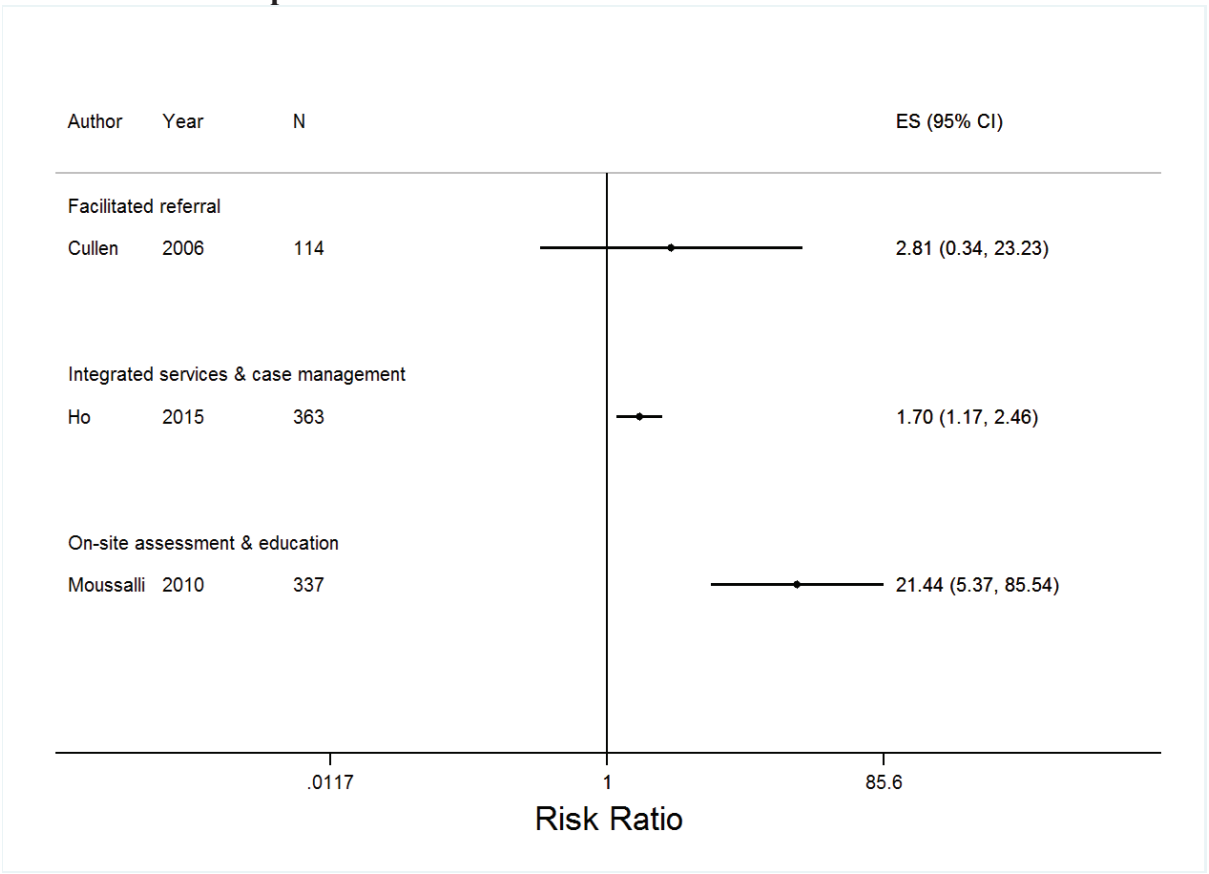
A. HCV testing



B. HCV linkage to care



C. Treatment uptake



**The size of the shaded box around each point estimate is based on the inverse of the standard error. A small standard error (narrow confidence interval) yields a larger shaded box*

Figure 2: Forest plot of included studies by outcome and stratified by intervention type

On-site testing with pre-test counselling and education was evaluated in six studies.[98, 325, 358-362] The interventions were evaluated in a number of settings including a general practice providing OST services, a drug and alcohol clinic, a hospital setting (emergency department and psychiatric inpatient ward) and a community mental health clinic. The study populations varied across the studies and included people who use drugs with or without known psychiatric co-morbidities. Further, injecting drug use and OST characteristics were either undocumented or inadequately defined in most studies. The total sample size ranged from 150 to 863 clients.

In one study, integrated on-site HCV testing with counselling and education in a mental health service significantly increased the proportion tested for HCV infection compared to referrals for testing at other services (86% vs 15% in control group, N=150, RR 5.96, 95% CI 3.34 – 10.65).[325] Similarly, integrated on-site HCV testing with counselling and education conducted in a psychiatric inpatient ward showed an increase in HCV testing (18% vs 9% in control group, N=832, RR 1.90, 95% CI 1.32 – 2.73).[98] In contrast, on-site testing with motivational interviewing and self-administered HIV/HCV risk assessment conducted within emergency departments, did not increase testing compared to self-administered risk assessment alone.[360, 361] Both studies by Merchant *et al.* were unsuccessful in engaging PWID, with less than 10% of the study sample reporting 'ever injecting drugs'.

On-site DBS HCV testing was evaluated in two studies.[355, 356] DBS testing was evaluated in drug and alcohol clinics, needle and syringe programs, community pharmacies and prisons. The main inclusion criteria across the studies entailed people who use drugs with varying populations including those 'ever injecting drugs', 'recent injecting drug use' (with various or no definitions) and those receiving OST. Both studies were multicentre, and the total sample sizes ranged from 704 to 8340 individuals. In the study by Hickman *et al*., the comparator group was usual care (venepuncture), while in the study by Radley *et al*., DBS testing in community pharmacies was compared to DBS testing offered in other services.

DBS testing provided to drug users in drug and alcohol clinics and prisons increased the proportion tested by four-fold compared to venepuncture (21% vs 5% in control group, N=8,340, RR 3.81, 95% CI 3.32 – 4.38).[355] A non-randomised study evaluated the uptake of DBS testing among OST clients in a group of six pharmacies in comparison with DBS testing in other health services.[356] While DBS testing offered in pharmacies increased testing uptake (N=704, RR 2.24, 95% CI 1.62 – 3.12), this study was subject to high risk of selection bias and performance bias.

HCV education provided by a health care professional and a peer worker with off-site non-invasive liver disease assessment using transient elastography did not increase proportion tested in comparison to the control group (N=52, RR 2.70, 95% CI 0.57 – 12.68).[357] However, this study was a pilot study and not powered appropriately to evaluate the primary study outcome.

Lastly, face-to-face training and education about HIV and HCV transmission risk reduction in volunteer harm reduction centres did not increase self-reported testing in comparison to no education in unadjusted analysis (N=195, RR 1.10, 95% CI 0.95 – 1.25).[362] However, after adjusting for two factors associated with HCV testing (crack and buprenorphine use), participants exposed to the intervention at least once during follow-up were more likely to have been subsequently tested for HCV [odds-ratio (OR) (95% confidence interval (CI) = 4.13 (1.03; 16.60)].

HCV linkage to care

Five studies evaluated interventions to enhance linkage to care (Table 2 and Figure 2B).[253, 325, 358, 359, 363] Three of the five studies were RCTs (of which one was a cluster RCT). The total sample size ranged from 15 to 1,305 participants. Facilitated referral for HCV assessment and scheduling of specialist appointments for clients was evaluated in all studies.

In one RCT conducted in drug and alcohol clinics, the intervention included motivational style interviewing and counselling, and case management sessions to facilitate HCV clinical evaluation at an off-site hepatology clinic.[253] Case managers scheduled hepatologist appointments, accompanied participants to appointments, facilitated access to psychiatric services, and provided follow-up reminder phone calls. The study showed that participants in the intervention group were significantly more

likely to attend an HCV evaluation appointment at a hepatology clinic within six months of referral than participants in the control group (RR 1.74, 95% CI 1.37 – 2.24). In a large retrospective cohort study, facilitated referrals by non-medical and outreach nurse officers of HCV antibody positive individuals in a geographical region in Scotland was evaluated.[363] The intervention increased hepatologist appointment attendance (82% vs 66% in control group, N=1305, RR 1.26, 95% CI 1.17 – 1.35). Facilitated referral in another RCT showed self-reported attendance to HCV clinical evaluation appointments was not statistically different between the two groups (N=37, RR 1.08, 95% CI 0.76 – 1.53).[325]

HCV treatment uptake

Three studies evaluated interventions to enhance interferon-based treatment uptake (Table 3 and Figure 2C).[358, 364, 365] Two of the studies included in the analysis were RCTs (one cluster) and one was a non-randomised study. A cluster RCT evaluated a nurse-facilitated referral to a hepatology clinic on treatment uptake among current and PWID receiving OST.[358] Injection drug use characteristics of the study population were not defined. Overall, treatment uptake was low and the intervention did not significantly increase treatment initiation (7% vs 3% in control group, N=114, RR 2.81, 95% CI 0.34 – 23.23).

Integrated HCV care, drug use and psychiatric services delivered by a multidisciplinary team with case management services, increased the proportion initiating treatment (32% vs 19% in control group, N=363, RR 1.70, 95% CI 1.17 – 2.46).[364] Sixty-five percent of

the study population reported drug use within one year of enrolment; however, information on injecting drug use was not reported. An on-site total care concept, provided by a multidisciplinary team, included non-invasive liver disease assessment, psychiatric evaluation, motivational interviewing and education provided by a nurse to initiate treatment was also evaluated.[365] Over the two year intervention period, a greater proportion of clients initiated treatment compared to one year before the intervention (38% vs 2% before intervention, N=337, RR 21.44, 95% CI 5.37 -85.54). Sixty-nine percent of the study sample were receiving OST; however, drug injecting characteristics were not described. Of note, the study was subject to selection and performance biases.

2.4.3 Risk of bias assessment in individual studies

Risks of bias assessment for each outcome of the included studies were performed and available in the supplementary material (Supplementary Data 3). The risk of bias varied between studies particularly for non-randomised studies.

Half of the HCV outcomes of the RCTs assessed had one domain at high risk of bias. Those domains were attrition bias, detection bias and other bias. One third of HCV linkage to care RCTS had one domain at high risk of bias (detection bias) and none of the HCV treatment RCTs exhibited high risk of bias at any of the domains.

All outcomes of the non-randomised studies included were classified as having an overall critical risk of bias. Seventy-five percent of the non-randomised studies evaluating HCV testing were classified as critical risk of bias in the confounding

domain. Studies either did not report or adjust for demographic (injecting drug use, housing) and clinical characteristics which could potentially confound the outcome. Selection bias was classified as critical risk in 50% of HCV testing non-randomised studies, where researcher and participant knowledge of the intervention or the retrospective inclusion of participants (in one or both groups) may have biased selection. In addition, 75% of HCV testing non-randomised studies were classified as no information in the bias due to missing data, which made it difficult to ascertain the impact of lost-to-follow up on outcome. Both linkage to care non-randomised studies were classified as critical risk of bias due to confounding. Similarly, the one non-randomised study for treatment uptake was classified at critical risk of bias at the confounding and selection bias domains.

2.5 Discussion

We have taken a comprehensive systematic review to evaluate interventions to improve testing, linkage to care and treatment uptake among PWID. Interventions to enhance HCV testing included on-site testing with pre-test counselling and education and DBS testing. Interventions to enhance linkage to care included facilitated referral for HCV assessment and scheduling of specialist appointments for clients. Interventions to enhance HCV treatment uptake included integrated HCV care, drug use and psychiatric services delivered by a multidisciplinary team with case management services, with or without non-invasive liver disease assessment. Results highlight the paucity of well-designed RCTs or comparative studies evaluating interventions to enhance HCV testing, linkage to care and treatment. Further, there were no studies evaluating interventions to enhance components of the HCV care cascade in low- and middle- income countries or in the DAA era. This review identifies important research gaps and the need for well-powered RCTs which compare well-characterised interventions, including better characterisation of drug injecting population, to evaluate strategies to enhance HCV testing, linkage to care and treatment in the DAA era.

On-site testing with pre-test counselling and education was identified as an intervention to enhance HCV testing among PWID. This is consistent with a recent systematic review of interventions in the general population, which also included studies identified in this review, and revealed similar improvement in HCV testing.[256] The success of this intervention is likely due to the integration and co-location of HCV services within OST services in primary care, and community-based mental health clinics, making testing

more accessible to PWID. DBS testing provided on-site within drug and alcohol clinics, needle and syringe programs and prisons was also identified as an intervention to enhance HCV testing. This is consistent with a previous systematic review demonstrating that DBS testing may enhance HCV testing in high-risk populations.[329] There are a number of additional reasons for the success of DBS testing in enhancing HCV testing among PWID. DBS is a blood collection method which does not require venepuncture, usually performed by a capillary finger-stick.[366] Difficult venous access is a major barrier to obtaining blood samples by venepuncture among PWID [367], which could be a reason for why PWID may not present for testing . Conversely, finger-stick dried blood spot testing has been shown to be highly acceptable among PWID.[368] Given that 25% of people spontaneously clear HCV infection [369], HCV antibody testing only measures previous exposure, while HCV RNA testing can indicate active infection. DBS provides the opportunity to perform both HCV antibody testing and confirmatory HCV RNA testing using additional spots on the same filter paper. This circumvents the need for further blood draws and additional visits, hence reducing the risk of loss to follow-up. Further, DBS testing enables the expansion of on-site HCV testing services in community-based settings (e.g. peer-led settings), and in remote areas, particularly in low- and middle-income countries, where central laboratories are inaccessible. DBS collection is relatively easy to perform which is an advantage for use by lower-skilled cadres of health workers in low- and middle-income countries.[370] DBS also has the potential to enable home-based testing which may appeal to PWID who may wish to know their HCV status but remain anonymous. Nonetheless, further research would be needed to explore the effectiveness of this model.

However, the caveat of DBS testing is the requirement of laboratory-based assays for sample processing, and the need for patients to return for results increasing loss to follow-up. This is particularly problematic among PWID who experience difficult social determinants of health (e.g. homelessness and incarceration) and may not present for follow-up. Rapid point-of-care HCV antibody tests have also been shown to be acceptable to PWID [371] and point-of-care HCV testing could increase testing and diagnosis, and linkage to care among marginalised populations such PWID.[327] Point-of-care HCV RNA tests have recently become commercially available which could allow individuals to receive their test results within hours and subsequently started on treatment.[370] High sensitivity and specificity of the Xpert HCV Viral Load test for HCV RNA detection in finger-stick samples has been reported among people attending drug health and homelessness services in Australia [372], with this assay now having a turnaround time of 108 minutes. Point-of-care HCV RNA assays potentially provide an important tool to enhance HCV testing and linkage to care, hence reducing loss to follow-up. However, further studies are needed to evaluate the performance of novel assays in different settings and populations, and whether they would improve treatment uptake.

A number of other strategies to expand HCV testing have been examined including peer-led outreach testing, rapid testing in mobile pop-up clinics, and low threshold services and HCV contact tracing programs (Box 1). However, studies to date have employed non-comparative designs, making it difficult to measure impact.

Facilitated referral for HCV assessment and scheduling of specialist appointments for clients was identified as an intervention which may enhance linkage to care among PWID. This is consistent with findings from the systematic review by Zhou et al, which also reported the effectiveness of this intervention in the general population.[256] Due to structural and social barriers, PWID have reported difficulties in navigating tertiary care settings and are often not linked to HCV care, even when tested for HCV.[287] Poor knowledge of HCV and its treatment, the fear of treatment side effects, and the asymptomatic nature of HCV infection are often cited by PWID as the main reasons for not considering HCV treatment.[254, 278] The success of facilitated referral interventions may relate to a proactive approach of health providers in engaging with people in discussions about HCV, its treatment, and the potential long-term consequences of HCV-related liver disease if left untreated. However, the interventions used in all the studies were evaluated in comparison to 'care as usual' or before intervention implementation arm (i.e. historical comparison). Therefore, it was unsurprising that the interventions were shown to be effective. In addition, the confidence intervals around the RRs in some of the studies were wide, and in some studies the RR were not statistically significant.

Increasing the capacity for DAA prescribing by general practitioners, addiction medicine specialists, and nurses should improve the capacity for facilitated on-site testing, linkage to care, and treatment (e.g. test and treat strategies), given that PWID may be less likely than other populations to attend off-site specialist appointments. The need for referral to an off-site specialist could then be limited to situations where people have advanced liver disease and require assessment by a specialist. Interventions focused on linking chronic HCV patients to specialists in tertiary settings will become

less relevant as the transition to simplified, primary care-based HCV care occurs in the interferon-free DAA era.

Integrated HCV, drug user health and psychiatric care, which includes multidisciplinary care coordination and patient case management, was identified as an intervention to enhance interferon-based treatment uptake, consistent with interventions in the general population.[256] Integrated care including on-site non-invasive liver disease assessment using transient elastography was also identified as an intervention to enhance treatment uptake. As with testing, the co-location and embedding of health services, provided by a multidisciplinary team, who treat individuals holistically, may be a key reason for the success of this intervention. In addition, the provision of on-site HCV evaluation which circumvents the need for referral to a specialist allows for this 'one-stop shop' model of care. As we transition into the DAA treatment era, providing appropriate services to ensure a strong foundation for drug user health (e.g. needle and syringe programs, OST, etc.) will remain crucial to the care of chronic HCV among PWID. However, while integrated models will remain important for managing drug user health, the availability of simple, well-tolerated and highly effective DAA therapies have changed HCV management, providing the opportunity to evaluate less-intensive, integrated models of care for the delivery of DAA therapy, including models of care led by general practitioners, addiction medicine specialists, and nurses. Further research is needed to evaluate simplified models of DAA therapy delivery among PWID.

This review has several limitations. First, due to the diversity of interventions and limited definition of populations (i.e. former, recent, and current injection drug use), meta-analyses were unlikely to be informative and were not performed. However, estimates of the size of effect and confidence intervals were generated to evaluate individual studies providing an overview of the effectiveness of interventions. Second, all interventions were evaluated in the interferon era and no studies were identified in low- and middle-income countries. Third, the quality of studies was limited with almost half of all studies included for review being non-randomised studies. Most studies were small in sample size with high risk of bias and confounding. Further, almost all studies evaluated the impact of interventions in comparison to 'care as usual' or before and intervention arm (i.e. historical arm) which had little in the way of providing an enhanced service for PWID. Therefore, it is highly probable that a statistically significant difference would be observed between the intervention and control groups, although some with wide confidence intervals. Fourth, publication bias was likely given that studies with less favourable outcome are less likely to be published. Finally, the review excluded interventions focused on treatment adherence and cure. However, given the recent introduction of DAA treatment, treatment uptake studies conducted in the interferon era are becoming less relevant.

This review has several clinical management and policy implications. First, DAA treatments offer an opportunity to simplify the HCV care cascade. Integrated, on-site HCV testing and diagnosis, co-located in the primary care setting as described by interventions in this review will remain important in the DAA era. Second, the new DAA treatment era has increased treatment uptake, but this will continue to be

contingent on first diagnosing chronic HCV infection and ensuring that people are linked to HCV care and DAA treatment. Interventions to link people to specialist care should become less important (except for advanced/complicated cases with co-morbidities) and on-site HCV testing and DAA treatment will be crucial. Third, the clinical management of HCV infection requires advanced laboratory capacity to perform HCV RNA confirmatory tests, viral genotyping, liver function tests and monitoring of drug side-effects. This is of importance in low- and middle-income countries, and in remote areas, where sophisticated laboratory services are inaccessible due to cost and availability. However, as pangenotypic DAAs become available, those laboratory requirements may be further reduced. Simplified diagnostics, such as DBS, will continue to be important in the expansion of HCV services in the community. Further, the development of point of care HCV RNA diagnostics may facilitate a real 'test and treat' model of care. A simplified 'two-step' care cascade enabling a 'test and treat' model will enhance HCV treatment scale-up. Fourth, the provision of harm reduction and mental health services will remain vital in the care of PWID with chronic HCV; however, these services should not be pre-conditions to DAA treatment access. Finally, the World Health Organization's (WHO) global strategy aims to eliminate viral hepatitis as a public health threat by 2030. However, DAA treatment access remains restricted due to high drug pricing; even lower-cost generic forms are relatively expensive for many patients in low- and middle-income countries, where the majority of HCV burden lies. While the simplification of the care cascade is in process, prohibitive pricing represents a threat to treatment uptake and scale-up.

The review suggests several future research priorities. First, future studies evaluating interventions among PWID should clearly define study populations (including sociodemographic characteristics such as incarceration) and injecting drug use characteristics. Future studies should clearly indicate if the interventions being evaluated are targeting people with a history of injecting drug use, receiving OST, or recent PWID. Evaluation of interventions among different PWID populations is necessary, given that former injectors may access certain services more frequently than recent injectors. Second, studies evaluating the impact of simplified point-of-care HCV RNA diagnostics, which removes the need for serological testing and provides the detection of active infection, on testing uptake are required. Third, well-designed RCTs powered to evaluate interventions to enhance HCV testing, linkage to care, and DAA treatment among PWID in the DAA era are needed. Interventions should be clearly characterised and compared to other interventions as opposed to 'care as usual' to ascertain if the interventions truly have a significant clinical and potentially public health impact. Fourth, studies evaluating interventions among PWID in low- and middle-income countries settings are urgently needed. Interventions that may have been shown to be effective in high-income countries could be modified and adapted to different contexts and evaluated for efficacy. Finally, evaluation of interventions that target multiple components of a simplified cascade of care (i.e. 'test and treat' integrated model) will be critical in our quest for HCV elimination.

Conclusion

In order to achieve the WHO hepatitis elimination targets by 2030, high proportions of people with chronic HCV infection need to be diagnosed and successfully treated. This review demonstrates the importance of integrated, on-site HCV testing and treatment of

PWID in the primary care setting. As we transition from the interferon era to DAA treatment era, this review calls for well-designed studies evaluating interventions for a simplified care cascade. Evidence for their efficacy will be crucial for treatment scale-up among PWID to achieve HCV elimination.

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2.6 Supplementary material

Supplementary Data 1: Search terms

Population:
(Hepatitis C OR
HCV OR
CHC)

AND

(PWID OR
People who inject drugs OR
IVDU OR IDU
Drug dependent OR
Inject drug*
Injecting drug*
Injection drug
Drug inject*
Drug use*
Substance use/misuse
Opioid substitution*
OST*
Opioid agonist treatment or OAT*
Medication assisted treatment or MAT
Methadone therapy*
Methadone treatment*
Buprenorphine treatment*
MMT*)

AND

Outcome:
(Screen* OR
Test* OR
Anti-HCV* OR
Anti-HCV antibodies* OR
HCV RNA OR
HCV-RNA OR
Diagnos* OR
HCV PCR)

OR

Outcome:
(Care* OR
Link*
Refer* OR
Liver disease assessment OR
Assess* OR
Follow-up OR
Specialist visit OR
Fibroscan OR
Hepatic elastography OR
Liver biopsy)

OR

Outcome:
(Treat* OR
Treatment uptake OR
Treatment initiation OR
Direct acting antiviral OR
DAA OR
Interferon)

Note: Specific Mesh terms and key words were formulated for each database.

Supplementary Data 2: Full search strategy for each database

Medline search Strategy (20 July 2016 – 4274 records)

1. exp Hepatitis C/
2. hcv.mp.
3. chc.mp.
4. Hepatitis C/ or hepatitis c.mp.
5. exp Substance Abuse, Intravenous/
6. exp Substance-Related Disorders/
7. (ivdu or idu).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8. people who inject drug*.mp.
9. exp Drug Users/
10. injecting drug*.mp.
11. drug inject*.mp.
12. exp Opiate Substitution Treatment/
13. (opioid agonist treatment or OAT).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
14. ost.mp.
15. methadone therap*.mp.
16. methadone treatment.mp.
17. buprenorphine treatment.mp.
18. methadone maintenance.mp.
19. mmt.mp.
20. pwid.mp.
21. drug dependent.mp.
22. exp Mass Screening/
23. screen*.mp.
24. testing.mp.
25. exp Point-of-Care Testing/
26. exp Dried Blood Spot Testing/
27. test*.mp.
28. exp Hepatitis C Antibodies/
29. HCV RNA.mp.
30. exp Diagnosis/
31. HCV PCR.mp.
32. linkage to care.mp.
33. exp "Referral and Consultation"/
34. liver disease assessment.mp.
35. liver disease assess*.mp.
36. exp "Continuity of Patient Care"/
37. transient elastography.mp.
38. fibroscan.mp.
39. liver biopsy.mp.
40. treatment uptake.mp.

41. treat*.mp.
42. exp Treatment Outcome/
43. exp Antiviral Agents/
44. DAA.mp.
45. direct acting antiviral*.mp.
46. interferon*.mp.
47. exp Liver Cirrhosis/
48. inject drug*.mp.
49. liver disease stag*.mp.
50. (liver adj4 assess*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
51. treatment initiation.mp.
52. 1 or 2 or 3 or 4
53. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 48
54. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
55. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 47 or 49 or 50
56. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 51
57. 52 and 53
58. 54 or 55 or 56
59. 57 and 58

Embase Search Strategy (20 July 2016 – 6878 records)

1. exp hepatitis C/
2. exp Hepatitis C virus/
3. hcv.mp.
4. chc.mp.
5. exp chronic hepatitis C/
6. exp intravenous drug abuse/
7. exp substance abuse/
8. exp addiction/
9. exp opiate substitution treatment/
10. exp drug dependence/
11. exp methadone treatment/
12. pwid.mp.
13. (ivdu or idu).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
14. people who inject drug*.mp.
15. injecting drug*.mp.
16. drug inject*.mp.
17. ost.mp.
18. exp opiate addiction/
19. buprenorphine treatment.mp.
20. exp mass screening/

21. exp diagnosis/
22. exp dried blood spot testing/
23. exp "point of care testing"/
24. testing.mp.
25. screen*.mp.
26. exp hepatitis C antibody/
27. HCV RNA.mp.
28. HCV PCR.mp.
29. anti-HCV.mp.
30. exp follow up/
31. "linkage to care".mp.
32. exp patient referral/
33. liver disease assessment.mp.
34. (liver disease adj3 assess*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

35. exp liver cirrhosis/
36. exp liver fibrosis/
37. exp liver biopsy/
38. transient elastography.mp.
39. exp elastograph/
40. fibroscan.mp.
41. exp antiviral therapy/
42. treatment uptake.mp.
43. treat*.mp.
44. DAA.mp.
45. direct acting antiviral.mp.
46. exp antivirus agent/
47. interferon.mp.
48. 1 or 2 or 3 or 4 or 5
49. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
50. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
51. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
52. 41 or 42 or 43 or 44 or 45 or 46 or 47
53. 48 and 49
54. 50 or 51 or 52
55. 53 and 54
56. exp ultrasound/
57. 51 or 56
58. 48 and 49 and (50 or 57 or 52)

Global Health search strategy (20 July 2016 - 1861 records)

1. exp hepatitis c virus/
2. chronic hepatitis c.mp.

3. CHC.mp.
4. exp injecting drug users/
5. exp injecting drug abuse/
6. drug inject*.mp.
7. people who inject drug*.mp.
8. exp substance abuse/
9. (ivdu or idu).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
10. inject drug*.mp.
11. exp methadone maintenance/
12. opioid substitution.mp.
13. (buprenorphine adj treatment).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
14. exp screening/
15. testing.mp.
16. test*.mp.
17. exp diagnosis/
18. diagnos*.mp.
19. "point of care test".mp.
20. exp diagnostic techniques/
21. hepatitis c antibodies.mp.
22. anti-HCV antibodies.mp.
23. HCV RNA.mp.
24. HCV PCR.mp.
25. "linkage to care".mp.
26. exp physicians/
27. exp hepatic fibrosis/
28. liver disease staging.mp.
29. (liver disease adj3 assess*).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
30. hepatic cirrhosis.mp.
31. transient elastography.mp.
32. fibroscan.mp.
33. liver biopsy.mp.
34. exp antiviral agents/
35. treatment uptake.mp.
36. exp treatment/
37. direct acting antiviral.mp.
38. DAA.mp.
39. interferon*.mp.
40. treatment.mp.
41. 1 or 2 or 3
42. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
43. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
44. exp health care/
45. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 44
46. 34 or 35 or 36 or 37 or 38 or 39 or 40
47. 41 and 42

48. 43 or 45 or 46
49. 47 and 48

PsychInfo Search Strategy (20 July 2016 – 1011 records)

1. "hepatitis C".mp.
2. (hcv or chc).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
3. chronic hepatitis C.mp.
4. exp intravenous drug usage/
5. exp drug abuse/
6. exp drug dependency/
7. people who inject drug*.mp.
8. injecting drug*.mp.
9. (ivdu or idu).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
10. exp methadone maintenance/
11. opioid substitution treatment.mp.
12. exp maintenance therapy/
13. pwid.mp.
14. drug inject*.mp.
15. exp narcotic agonists/
16. oat.mp.
17. test*.mp.
18. screen*.mp.
19. exp diagnosis/
20. diagnos*.mp.
21. anti-HCV.mp.
22. HCV RNA.mp.
23. exp "continuum of care"/
24. exp health care services/
25. "linkage to care".mp.
26. exp professional referral/
27. exp liver disorders/
28. exp "cirrhosis (liver)"/
29. fibroscan.mp.
30. liver biopsy.mp.
31. (liver adj3 assess*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
32. treatment uptake.mp.
33. treatment.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
34. treatment initiat*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
35. treatment outcome.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

36. direct acting antiviral*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
37. interferon.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
38. 1 or 2 or 3
39. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
40. 17 or 18 or 19 or 20 or 21 or 22
41. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
42. 32 or 33 or 34 or 35 or 36 or 37
43. 38 and 39
44. 40 or 41 or 42
45. 43 and 44

Cochrane register of clinical trials search strategy (20 July 2016 – 137 records)

1. exp Hepatitis C/
2. (hcv or chc).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3. "people who inject drug*".mp.
4. exp Substance Abuse, Intravenous/
5. (ivdu or idu).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6. exp Substance-Related Disorders/
7. drug use*.mp.
8. injecting drug*.mp.
9. drug inject*.mp.
10. exp Opiate Substitution Treatment/
11. methadone maintenance.mp.
12. exp Opioid-Related Disorders/
13. buprenorphine treatment.mp.
14. Dried Blood Spot Testing/
15. exp Mass Screening/
16. screen*.mp.
17. exp Point-of-Care Systems/
18. test*.mp.
19. Hepatitis C Antibodies/
20. exp RNA, Viral/
21. HCV RNA.mp.
22. diagnos*.mp.
23. linkage to care.mp.
24. "Referral and Consultation"/
25. Liver Cirrhosis/
26. (liver adj3 assess*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
27. transient elastography.mp.
28. fibroscan.mp.

29. liver biopsy.mp.
30. treatment initiation.mp.
31. treatment uptake.mp.
32. Antiviral Agents/
33. Interferons/
34. treatment.mp.
35. Treatment Outcome/
36. 1 or 2
37. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
38. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
39. 23 or 24 or 25 or 26 or 27 or 28 or 29
40. 30 or 31 or 32 or 33 or 34 or 35
41. 36 and 37
42. 38 or 39 or 40
43. 41 and 42

Web of Science search strategy (20 July 2016 – 2236 records)

TOPIC:("hepatitis c" OR HCV) *AND* **TOPIC:**("people who inject drug*" OR "injecting drug use*" OR "drug inject*" OR "opioid substitut*" OR "methadone maintenance" OR MMT OR OAT OR "buprenorphine treatment" OR "substance inject*" OR "intravenous substance abuse" OR "opioid agonist treatment" OR "drug depend*" OR OST OR "drug abuse") *AND* **TOPIC:**(test* OR screen* OR "dried blood spot" OR "HCV RNA" OR "anti hcv" OR "HCV antibod*" OR "linkage to care" OR assess* OR diagnos* OR treatment OR referral OR consultation OR "liver disease staging" OR fibroscan OR "transient elastography" OR "liver cirrhosis" OR "liver fibrosis" OR DAA OR interferon OR "direct acting antiviral")

Supplementary Data 3: Risk of bias assessment of included studies

A. HCV testing

Risk of bias assessment for included randomised studies using the Cochrane Collaboration's risk of bias tool								
	Selection bias (random sequence)	**Selection bias (allocation concealment)**	**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**	**Number of domains of high risk of bias**
Arain 2016	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk	Unclear risk	1
Cullen 2006	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	0
Hickman 2008	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	High risk	1
Merchant 2014	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	0
Merchant 2015	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	0
Rosenberg 2010	Unclear risk	Unclear risk	Low risk	High risk	Unclear risk	Low risk	Low risk	1

Risk of bias assessment for included non-randomised studies using the ROBINS-I assessment tool								
	Bias due to confounding	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Risk of bias judgement**
Hagedorn 2007	Critical	Serious	Serious	Moderate	No information	Low	Moderate	Critical
Lacey 2007	Critical	Moderate	Moderate	Moderate	No information	Low	Serious	Critical
Radley 2017	Critical	Critical	Serious	Serious	No information	Moderate	Serious	Critical
Roux 2016	Moderate	Critical	Serious	Moderate	Serious	Critical	Moderate	Critical

B. HCV linkage to care

Risk of bias assessment for included randomised studies using the Cochrane Collaboration's risk of bias tool								
	Selection bias (random sequence)	**Selection bias (allocation concealment)**	**performance bias**	**detection bias**	**attrition bias**	**reporting bias**	**other bias**	**Number of domains of high risk of bias**
Cullen 2006	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	0
Masson 2013	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	0
Rosenberg 2010	Unclear risk	Unclear risk	Low risk	High risk	Unclear risk	Low risk	Low risk	1

Risk of bias assessment for included non-randomised studies using the ROBINS-I assessment tool								
	Bias due to confounding	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Risk of bias judgement**
Hagedorn 2007	Critical	Serious	Moderate	Serious	No information	Low	Moderate	Critical
Tait 2010	Critical	Serious	Low	Serious	Serious	Low	Moderate	Critical

C. HCV treatment uptake

Risk of bias assessment for included randomised studies using the Cochrane Collaboration's risk of bias tool								
	Selection bias (random sequence)	**Selection bias (allocation concealment)**	**performance bias**	**detection bias**	**attrition bias**	**reporting bias**	**other bias**	**Number of domains of high risk of bias**
Cullen 2006	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	0
Ho 2015	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	0

Risk of bias assessment for included non-randomised studies using the ROBINS-I assessment tool								
	Bias due to confounding	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Risk of bias judgement**
Moussalli 2010	Critical	Critical	Serious	Critical	No information	No information	Serious	Critical

Chapter 3: Acceptability and preferences of point-of-care finger-stick whole-blood and venepuncture hepatitis C virus testing among people who inject drugs in Australia

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Declaration

I certify that this publication was a direct result of my research towards this PhD and that reproduction in this thesis does not breach copyright regulations.

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3.1 Abstract

Background: Uptake of hepatitis C virus (HCV) testing remains inadequate globally. Simplified point-of-care tests should enhance HCV diagnosis and elimination. We aimed to assess the acceptability of finger-stick and venepuncture HCV RNA testing among people who inject drugs (PWID). **Methods:** Participants were enrolled in an observational cohort study with recruitment at 13 sites between June 2016 and February 2018. Capillary whole-blood collected by finger-stick and plasma collected by venepuncture were performed for Xpert® HCV viral load testing. Participants completed a questionnaire on acceptability of, and preferences for, blood collection methods. **Results:** Among 565 participants (mean age, 44 years; 69% male), 64% reported injecting drugs in the last month, and 63% were receiving opioid substitution treatment. Eighty three percent reported that finger-stick testing was very acceptable. Overall, 65% of participants preferred finger-stick over venepuncture testing, with 61% of these preferring to receive results in 60 minutes. The most common reason for preferring finger-stick over venepuncture testing was it was quick (62%) followed by venous access difficulties (21%). The main reasons for preferring venepuncture over finger-stick testing were that it was quick (61%) and accurate (29%). Females were more likely to prefer finger-stick testing than males (adjusted OR 1.96; 95% CI 1.30, 2.99; p=0.002). Among people with recent (previous month) injecting drug use, Aboriginal and/or Torres Strait Islander people were less likely than non-Aboriginal people to prefer finger-stick testing (adjusted OR 0.57; 95% CI 0.34, 0.9; p=0.033). **Conclusions:** Finger-stick whole-blood collection is acceptable to people who inject drugs, with males and Aboriginal and/or Torres Strait Islander people with recent injecting drug use less likely to prefer finger-stick testing. Further research is needed to evaluate

interventions integrating simplified point-of-care HCV testing to engage people in care in a single-visit, thereby facilitating HCV treatment scale-up.

Key words: Hepatitis C virus, screening, linkage to care, HCV RNA, point-of-care test, acceptability

3.2 Background

Globally, over one-third of people who report injecting drugs in the previous year are estimated to be living with hepatitis C virus (HCV) infection, equating to 6.1 million people globally.[116, 117] However, the majority have not received testing and are unaware of their status.[3, 244, 263, 373] While Australia has a high proportion of people with HCV infection who have been diagnosed, 20% of individuals remain undiagnosed [92] and only 26% of those with chronic HCV infection have initiated direct-acting antiviral (DAA) therapy.[235, 237, 374] People who inject drugs (PWID) often face a multitude of barriers to diagnosis and linkage to HCV treatment, including the requirement for multiple visits to a medical practitioner and often, referral to an external/off-site phlebotomist for venepuncture.[260] Innovative and simplified point-of-care testing strategies are needed to enhance timely HCV diagnosis and facilitate treatment uptake.[260, 370]

PWID are a key population in the global HCV response.[370, 375] Although in many settings, PWID report testing for HCV antibody, the majority have not received confirmatory HCV RNA testing.[262, 263] Data from a recent Australian surveillance report indicated that only 46% of PWID with positive HCV antibodies received confirmatory HCV RNA testing.[263] Barriers to HCV testing among PWID include social marginalisation[287], anxiety and fear of positive results[367], and difficulties in relation to venous access for blood collection.[367] Further, PWID with venous access difficulties may perceive blood collection as distressing due to several factors including feelings of being stigmatised by healthcare workers (including phlebotomists), inexperience of phlebotomists in collecting blood from PWID or restriction on which veins to use, and access to a phlebotomist at services preferred by PWID.[279]

As emphasised by the recent World Health Organization (WHO) guidance on HCV testing, gaps remain in the availability of simple, reliable and affordable testing strategies.[370] Finger-stick rapid diagnostic tests for HCV infection are available[376-378] and have been shown to increase testing[326, 355, 379] and linkage to care.[327, 328, 380] Point-of-care assays are also now available that facilitate HCV RNA confirmation and diagnosis in a single visit.[260, 381] This is particularly important for PWID. An evaluation of the redesigned Xpert HCV Viral Load Finger-stick point-of-care test for HCV RNA detection in finger-stick whole-blood and venepuncture samples of PWID showed very high sensitivity (100%) and specificity (100%).[381] This assay uses 100 μL of capillary whole-blood and provides confirmatory HCV RNA results in one hour, which could simplify the HCV care pathway and allow individuals to be linked to treatment the same day of diagnosis.

Previous studies have shown that rapid HCV antibody testing utilising saliva or capillary whole-blood specimen collection is acceptable among PWID.[368, 382] However, the acceptability of finger-stick point-of-care HCV RNA testing has not been evaluated. The aim of this study was to determine the acceptability of finger-stick whole-blood and venepuncture HCV RNA testing, and to assess factors associated with the preference for finger-stick HCV testing among a cohort of PWID in Australia.

3.3 Methods

3.3.1 Study design and participants

LiveRLife is an observational cohort study evaluating an intervention integrating a liver health promotion campaign and non-invasive liver fibrosis assessment on linkage to care and HCV treatment uptake among people with a history of injecting drug use and people who are homeless. Participants were enrolled between 12 August 2014 and 22 February 2018 from 17 sites in Australia (n=14, New South Wales) including 11 drug and alcohol clinics, one homelessness service, one needle and syringe program, one medically supervised injecting centre, one primary health clinic and one Aboriginal Medical Service.

Inclusion criteria were age ≥18 years, written informed consent, and history of injecting drug use (participants recruited from the homelessness service were exempt from this criterion). Current pregnancy was the only exclusion criterion.

Questions evaluating the acceptability and preferences for HCV testing were added to the enrolment survey after a protocol amendment which was approved on 14 January 2016. As such, for the current analysis, participants recruited between 27 June 2016 and 22 February 2018 from 13 sites (nine drug and alcohol clinics, one homelessness service, one needle and syringe program, one medically supervised injecting centre, and one Aboriginal Medical Service) were eligible for inclusion. Also, only participants with a history of injecting drug use were included. The study protocol is provided in the Supplementary material.

All participants provided written informed consent before study procedures commenced. The study protocol was approved by the Human Research Ethics Committee at St. Vincent's Hospital, Sydney.

3.3.2 Study procedures

In the weeks preceding 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 clinic staff provided information about the study to the participants while they were accessing services. Eligible participants were then consecutively enrolled into the study. Each clinic site held four LiveRLife 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 LiveRLife campaign coffee mug, and liver health promotion and education booklet) and an AUS$20 voucher for their time. Enrolment assessments included finger-stick capillary whole-blood sample collection using dried blood spots for HCV RNA testing, self-reported behavioural survey on tablet computers, transient elastography (FibroScan®), clinical nurse assessment (including standard of care assessment), and venepuncture blood samples for standard of care clinical testing and storage for HCV RNA testing. Finger-stick capillary whole-blood point-of-care HCV RNA testing (using the Xpert HCV Viral Load Fingerstick assay) was added to the study procedures after a protocol amendment approval on 14 Jan 2016.

Following finger-stick blood collection, participants completed a self-administered survey on tablet computers collecting demographic information, injecting drug use history, other drug use history, drug injecting behaviour, alcohol consumption, liver disease knowledge, HCV knowledge, health service utilisation, quality of life indicators, and FibroScan® and point-of-care HCV testing acceptability and preferences. High risk alcohol consumption was assessed using the AUDIT-C, a 3- item alcohol screen that can help to detect persons who are hazardous drinkers or who have active alcohol use disorders. The AUDIT-C is scored on a scale of 0-12 with scores of ≥4 in men and ≥3 in women considered as hazardous drinking levels.

After the survey, participants received transient elastography assessment. Liver fibrosis stage was assessed using the FibroScan®, which uses transient elastography to measure liver stiffness. FibroScan® 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).[176]

Liver disease assessment was followed by a clinical HCV assessment by a general practitioner or a nurse. This involved a standard health check and a review of medical history, FibroScan® result, and in some cases, a blood test was ordered for routine clinical care. Where applicable, a referral was made to a specialist for follow-up.

3.3.3 Study outcomes

The primary study endpoint was preference for finger-stick whole-blood collection in comparison to venepuncture blood collection for HCV RNA testing. Secondary

endpoints included the acceptability of finger-stick whole-blood testing compared to venepuncture testing, preferences for time to HCV test results, and reasons for preferring either testing method. Questions were asked following finger-stick whole-blood collection, and before venepuncture blood collection.

Participants were asked about previous experience with both finger-stick whole-blood collection and venepuncture HCV collection methods: "Have you ever been tested for hepatitis C by taking a sample of blood from a vein?" and "have you ever been tested for hepatitis C by a finger-prick blood test" with three options to choose from: yes; no; unknown. Participants were asked "would you prefer to get your hepatitis C test results on the same day?" with response options: yes, no, does not matter.

Preference for time to HCV test results was measured by asking participants "How long would you be willing to wait if you could get your results on the same day?" with 30; 45; 60; 90; 120 minutes; 'I would not be willing to wait' options to choose from. Participants were asked "If each of the following ways of collecting blood for hepatitis C testing was greater than 99% accurate, how acceptable they would be to you?" Participants rated testing methods on a Likert Scale as follows: very acceptable; somewhat acceptable; neither acceptable nor unacceptable; somewhat unacceptable; not at all acceptable. To examine the reasons underlying participants' rating of a testing method as somewhat unacceptable or not acceptable, participants were asked "Why do you feel that taking a sample of blood from a vein/finger prick test is somewhat unacceptable or not acceptable?" Response options included: it takes too much time; I feel the results will not be accurate; I do not want to get my blood taken for hepatitis C;

I have poor veins and it is difficult for the nurse to get blood from me; it is painful; other (please specify).

For preferences of HCV testing methods participants were asked "Which method of testing for hepatitis C would you prefer?" with six response options to choose from: a blood sample from a vein with results in two weeks; 120 minutes; or 60 minutes, respectively; or finger-stick test with results in two weeks; 120 minutes; or 60 minutes, respectively. For major reason for preference of either testing method participants were asked "What is the major reason for why you would prefer this method of testing for hepatitis C? with response options including: it is quick; I know the results will be accurate; it does not hurt; the nurse has trouble taking my blood; or other (please specify).

3.3.4 Statistical analysis

The proportion of participants preferring either finger-stick or venepuncture HCV testing methods was assessed. Factors hypothesised *a priori* to be associated with preference for finger-stick HCV testing were assessed, including age, sex, Aboriginal and/or Torres Strait Islander self-identification, formal education, housing stability, incarceration (including having been in prison or juvenile justice centre ever and in the previous 12 months), recent injecting drug use (including in the last six months and in the last month), current opioid substitution treatment (OST), previous testing by venepuncture and previous testing by finger-stick. Unadjusted analyses were performed using univariate logistic regression model with odd ratios (OR) and 95% confidence intervals (CI). Following unadjusted analyses, multivariable logistic regression was

performed, considering all potential variables. In addition, a more parsimonious model considering factors significant at the $p \leq 0.20$ level in the unadjusted analyses was also assessed by multivariable logistic regression. Model selection was then performed according to a stepwise backwards elimination, subject to a likelihood ratio test. Statistically significant differences were assessed at $P<0.05$; *P* values were two-sided. Further logistic regression analyses to evaluate factors associated with preference for finger-stick HCV testing was also performed among people with recent injection drug use (defined as injection drug use in the previous month; n=364). Factors hypothesised *a priori* to be associated with preference for finger-stick HCV testing were assessed, including age, sex, Aboriginal and/or Torres Strait Islander self-identification, formal education, housing stability, incarceration (having ever been in prison or juvenile justice centre vs. never), frequency of injection drug use (< daily use vs. > daily use), current opioid substitution treatment (OST), previous testing by venepuncture and previous testing by finger-stick. All analyses were performed using the statistical package Stata v14.0 (College Station, TX, USA).

3.4 Results

3.4.1 Participant characteristics

Baseline characteristics of participants are summarised in Table 1. The mean age was 44 years, 69% (n=387) were male, and 23% (n=132) identified as being of Aboriginal and/or Torres Strait Islander descent. Seventy-four percent (n=416) of participants injected drugs in the last six months, 64% (n=364) injected drugs in the past month, and 63% (n=357) were receiving OST. Overall, 36% (n=203) of participants had detectable HCV RNA.

3.4.2 Time to HCV test results

Prior to enrolment, 85% (n=480) reported testing for HCV by venepuncture and 51% (n=288) by finger-stick whole-blood collection. HCV sero-surveillance among PWID in Australia has been undertaken through finger-stick dried blood spot testing for more than 20 years. The majority (63%) indicated that they would prefer to receive same-day HCV test results, with 6% preferring not to receive same-day results, and 31% indicating that it did not matter. Over a third (43%) of participants reported that they would be willing to wait up to 30 minutes for test results, while 17% would be willing to wait up to 60 minutes, 8% for up to 45 minutes, 4% for up to 90 minutes, 16% for up to 120 minutes, and 12% reported that they would not be willing to wait for same-day test results.

Table 1: Baseline characteristics of participants with a history of injecting drugs and a complete enrolment survey, stratified by sex*, in the LiveRLife study (n=565)

Characteristic	Overall (n=565), n (%)	Male (n=387), n (%)	Female (n=172), n (%)
Age, mean (SD)	44 (9.7)	44 (9.8)	43 (9.8)
Age groups			
18 – 35	112 (20%)	67 (17%)	42 (24%)
36 – 45	221 (39%)	152 (39%)	67 (39%)
46 – 55	160 (28%)	114 (29%)	45 (26%)
≥ 56	72 (13%)	54 (14%)	18 (10%)
Age at first injection, mean (SD)	20 (6.4)	20 (6.7)	19 (5.6)
Sex			
Male	387 (69%)	-	-
Female	172 (30%)	-	-
Transgender	6 (1%)	-	-
Aboriginal/Torres Strait Islander self-identification			
Yes	132 (23%)	76 (20%)	54 (31%)
No	427 (76%)	307 (79%)	116 (67%)
Unknown	6 (1%)	4 (1%)	2 (1%)
Completed high school or higher education			
Yes	172 (30%)	116 (30%)	54 (31%)
No	393 (70%)	271 (70%)	54 (31%)
Main source of income			
No income	20 (4%)	13 (3%)	5 (3%)
Full-time/part-time/casual	40 (7%)	29 (7%)	11 (6%)
Government assistance	486 (86%)	332 (86%)	150 (87%)
Other	19 (3%)	13 (3%)	6 (3%)
Housing			
Stable	378 (67%)	245 (63%)	132 (77%)
Unstable	187 (33%)	142 (37%)	40 (23%)
Incarceration			
Ever (not in past 12 months)	273 (48%)	197 (51%)	73 (42%)
In past 12 months	107 (19%)	82 (21%)	23 (13%)
Never	185 (33%)	108 (28%)	76 (44%)
Injected drugs in past 6 months	416 (74%)	290 (75%)	120 (70%)
Frequency of injection in past 6 months[1]			
Daily or more	154 (27%)	112 (29%)	40 (23%)
<Daily	262 (47%)	178 (46%)	80 (47%)
None in past 6 months	149 (26%)	97 (25%)	52 (30%)
Injected drugs in past month	364 (64%)	257 (66%)	101 (59%)
Frequency of injection in past month[2]			
Daily or more	131 (31%)	89 (31%)	39 (33%)
<Daily	233 (56%)	168 (58%)	62 (52%)
None in past month	52 (13%)	33 (11%)	19 (16%)
Drug last injected[3]			
Heroin	125 (34%)	84 (33%)	40 (40%)
Other opioids (morphine, oxycodone)	48 (13%)	35 (14%)	13 (13%)
Methamphetamine	156 (43%)	114 (44%)	37 (37%)
Cocaine	6 (2%)	4 (2%)	3 (3%)

Methadone	17 (5%)	9 (4%)	8 (8%)
Buprenorphine/Buprenorphine-naloxone	11 (3%)	11 (4%)	-
High risk alcohol consumption (AUDIT-C)			
High risk male/female	196 (35%)	143 (37%)	53 (31%)
Low risk male/female	125 (22%)	93 (24%)	32 (19%)
Never drinks	238 (42%)	151 (39%)	87 (51%)
Missing[4]	6 (1%)	-	-
Opioid substitution treatment			
Current treatment	357 (63%)	240 (62%)	114 (66%)
Previous treatment, not current	74 (13%)	52 (13%)	21 (12%)
Never	134 (24%)	95 (25%)	37 (22%)
HCV RNA test result			
Positive	203 (36%)	142 (37%)	58 (34%)
Negative	312 (55%)	210 (54%)	101 (59%)
Invalid result	43 (8%)	-	-
Missing	7 (1%)	-	-
FibroScan® Liver disease staging			
F0/F1 – No/mild fibrosis	398 (71%)	278 (72%)	116 (68%)
F2 – Moderate fibrosis	69 (12%)	44 (11%)	24 (14%)
F3 – Severe fibrosis	25 (4%)	15 (4%)	9 (5%)
F4 – Cirrhosis	41 (7%)	32 (8%)	9 (5%)
Invalid	21 (4%)	-	-
Not performed	11 (2%)	-	-

Percentages indicate column percentages
*Stratified by female/male sex; transgender (n=6, 1%) excluded
[1]Among participants with a history of injection drug use (n=565)
[2]Among participants who injected drugs in the past 6 month (n=416)
[3]Among participants who injected drugs in the past month (n=364)
[4]Transgender excluded from the AUDIT-C

3.4.3 Acceptability of testing methods

The large majority (83%) indicated that finger-stick testing was 'very acceptable', while 12% felt it to be 'somewhat acceptable', 3% 'neither acceptable nor unacceptable', <1% 'somewhat unacceptable', and 1% 'not at all acceptable'. Fewer participants (72%) indicated that testing by venepuncture was 'very acceptable', 17% felt that it was 'somewhat acceptable', 4% 'neither acceptable nor unacceptable', 3% 'somewhat unacceptable', and 3% 'not at all acceptable'.

Among participants who felt that venepuncture testing was somewhat unacceptable or not at all acceptable (n=34), the majority (71%) cited venous access difficulties as the major reason for unacceptability, 9% reported that it takes too much time, 10% reported that it is painful, 10% did not want to have their blood taken for an HCV test. In contrast, among participants who felt that finger-stick testing was somewhat acceptable or not at all acceptable (n=12), four reported that it takes too much time, three reported that it is painful, two felt that the results would not be accurate or large volume of blood was required, and one did not want to have their blood taken for an HCV test.

3.4.4 Preferences for HCV testing methods

Overall, 65% of participants preferred finger-stick testing over venepuncture (35%). A greater proportion of females preferred finger-stick testing compared to males (74% vs. 61%, p=0.002). There was no difference in the preference for finger-stick testing among female participants by Aboriginal and/or Torres Strait Islander self-identification (74% vs.75% p=0.9).

Among those who preferred finger-stick testing (n=366), 61% preferred finger-stick testing with results in 60 minutes, 8% preferred results in 120 minutes, and 31% preferred results in two weeks. Among participants who preferred venepuncture testing (n=199), 37%, 13%, and 50% preferred testing with results in 60 minutes, 120 minutes, and two weeks, respectively.

Among those preferring finger-stick testing, the most common reasons for preferring this method were that it was quick (62%), venous access difficulties (21%), that it did not hurt (9%), and knowing that the results would be accurate (6%). Among those preferring venepuncture, reasons were because it was quick (61%), accurate (29%), did not hurt (5%), and venous access difficulties (3%) (Figure 1). Reasons for the preference of finger-stick and venepuncture testing, stratified by sex are shown in Supplementary Tables 1 and 2. Reasons for the preference of finger-stick and venepuncture testing among people with recent injection drug use (in the past month), stratified by Aboriginal and/or Torres Strait Islander self-identification, are presented in Supplementary Tables 3 and 4.

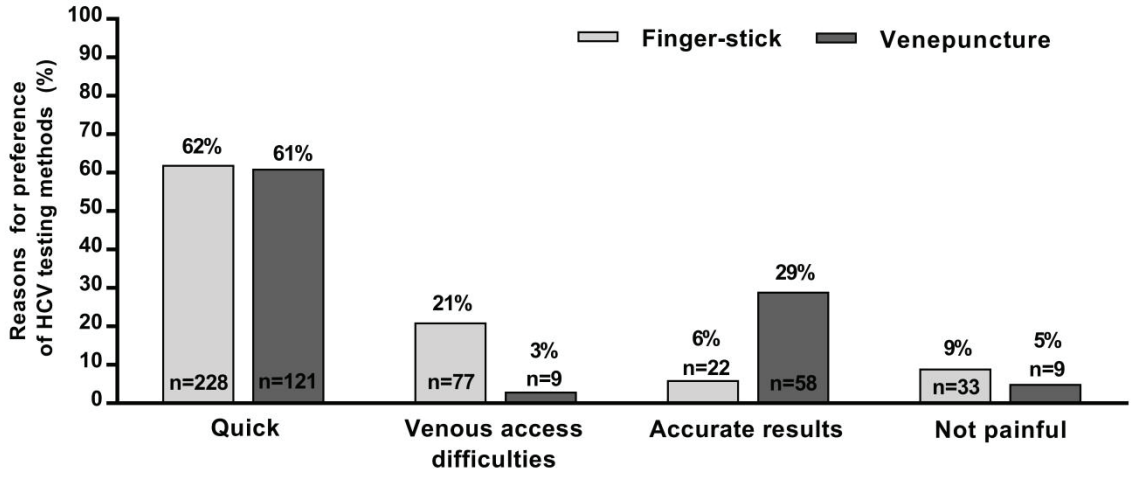

Figure 1. Reasons for the preference of either venepuncture or finger-stick HCV testing methods in the LiveRLife Study (n=565)

In unadjusted logistic regression analyses, preference for finger-stick HCV testing was associated with female sex (Table 2). In a logistic regression analysis adjusting for potential confounders, females had twice the odds of expressing a preference for finger-stick over venepuncture testing compared to males (adjusted odd ratio (aOR) 1.96; 95% CI 1.30, 2.99; p=0.002). In a more parsimonious logistic regression model including only factors associated with $p \leq 0.20$ in unadjusted analyses and subject to backwards stepwise elimination, female sex was the only factor associated with a preference for finger-stick testing.

In additional analyses among people with recent (previous month) injecting drug use, unadjusted logistic regression analyses demonstrated that preference for finger-stick HCV testing was associated with female sex, Aboriginal and/or Torres Strait Islander

self-identification and previous testing by venepuncture (Table 3). After adjusting for all potential confounders, females with recent injecting drug use had twice the odds of reporting a preference for a finger-stick over venepuncture testing compared to males (aOR 1.92; 95% CI 1.11, 3.30; p=0.019). Aboriginal and/or Torres Strait Islander people with recent injecting drug use were less likely to prefer finger-stick testing over venepuncture compared to non-Aboriginal and/or Torres Strait Islander self-identified participants (aOR 0.57; 95% CI 0.34, 0.9; p=value 0.033) (Table3). However, it should be noted that over a half (56%) of Aboriginal and/or Torres Strait Islander participants still preferred finger-stick testing compared to venepuncture testing. The adjusted logistic regression also demonstrated higher preference for finger-stick testing among those with previous testing with venepuncture, but this was not statistically significant (aOR 2.15; 95% CI 0.97, 4.80; p=0.060) (Table 3).

Table 2. Unadjusted and adjusted logistic regression models assessing factors associated with preference of participants for finger-stick HCV testing method in the LiveRLife study (n=565)

	Finger-stick preference, n (%)	Unadjusted model		Adjusted model	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Age[a]					
18 – 35 years	72 (64%)	1.00		1.00	
36 – 45 years	137 (62%)	0.91 (0.57, 1.45)	0.682	0.87 (0.54, 1.42)	0.575
46 – 55 years	107 (67%)	1.12 (0.68, 1.86)	0.658	1.05 (0.62, 1.80)	0.847
≥56 years	50 (69%)	1.26 (0.67, 2.38)	0.470	1.13 (0.57, 2.22)	0.733
Sex					
Male	236 (61%)	1.00		1.00	
Female	128 (74%)	1.89 (1.27, 2.82)	0.002	1.96 (1.30, 2.99)	0.002
Aboriginal/Torres Strait Islander self-identification					
No	280 (66%)	1.00		1.00	
Yes	82 (62%)	0.87 (0.58, 1.29)	0.487	0.81 (0.53, 1.23)	0.317
High school or higher education					
No	249 (63%)	1.00		1.00	
Yes	117 (68%)	1.23 (0.84, 1.79)	0.286	1.26 (0.84, 1.89)	0.263
Housing					
Stable	251 (66%)	1.00		1.00	
Unstable	115 (62%)	0.81 (0.56, 1.16)	0.251	0.98 (0.66, 1.45)	0.927
Incarceration (ever)					
No	120 (65%)	1.00		1.00	
Yes	246 (64%)	0.99 (0.68, 1.43)	0.976	1.12 (0.75, 1.68)	0.592

Recent injecting[b]					
Not in the past 6 months	99 (66%)	1.00		1.00	
In the past 6 months	8 (67%)	1.01 (0.29, 3.52)	0.987	0.99 (0.27, 3.59)	0.990
In the past month	259 (65%)	0.90 (0.60, 1.34)	0.610	0.99 (0.65, 1.50)	0.954
OST[c]					
Never	77 (57%)	1.00		1.00	
Yes, previously received	50 (68%)	1.54 (0.85, 2.79)	0.154	1.52 (0.81, 2.84)	0.188
Yes, currently receiving	239 (67%)	1.49 (0.99, 2.25)	0.051	1.47 (0.94, 2.29)	0.089
Previous testing by venepuncture[d]					
No	28 (55%)	1.00		1.00	
Yes	313 (65%)	1.53 (0.85, 2.74)	0.152	1.33 (0.72, 2.48)	0.364
Unknown	25 (76%)	2.57 (0.97, 6.76)	0.056	2.49 (0.86, 7.16)	0.091
Previous testing by finger-stick[e]					
No	158 (65%)	1.00		1.00	
Yes	185 (65%)	1.00 (0.70, 1.43)	0.987	0.96 (0.66, 1.39)	0.835
Unknown	23 (66%)	1.04 (0.50, 2.20)	0.911	0.87 (0.38, 1.99)	0.742

OR: Odds Ratio; CI: Confidence Interval; OST: Opioid Substitution Treatment

[a] Overall unadjusted and adjusted *p* values: 0.622, 0.771, respectively

[b] Overall unadjusted and adjusted *p* values: 0.869, 0.998, respectively

[c] Overall unadjusted and adjusted *p* values: 0.132, 0.203, respectively

[d] Overall unadjusted and adjusted *p* values: 0.137, 0.239, respectively

[e] Overall unadjusted and adjusted *p* values: 0.993, 0.939, respectively

Table 3. Unadjusted and adjusted logistic regression models assessing factors associated with preference of participants for finger-stick HCV testing method among people with recent injection drug use± in the LiveRLife study (n=364)

	Finger-stick preference, n (%)	Unadjusted model		Adjusted model	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Age[a]					
18 – 35 years	41 (60%)	1.00		1.00	
36 – 45 years	94 (61%)	1.05 (0.58, 1.88)	0.872	1.10 (0.60, 2.03)	0.751
46 – 55 years	74 (69%)	1.43 (0.76, 2.70)	0.265	1.27 (0.65, 2.50)	0.475
≥56 years	25 (71%)	1.65 (0.68, 3.97)	0.267	1.32 (0.52, 3.40)	0.557
Sex					
Male	159 (61%)	1.00		1.00	
Female	75 (74%)	1.87 (1.13, 3.14)	0.015	1.92 (1.11, 3.30)	0.019
Aboriginal/Torres Strait Islander self-identification					
No	184 (67%)	1.00		1.00	
Yes	50 (56%)	0.61 (0.38, 0.99)	0.047	0.57 (0.34, 0.9)	0.033
High school or higher education					
No	158 (62%)	1.00		1.00	
Yes	76 (70%)	1.47 (0.91, 2.39)	0.117	1.47 (0.90, 2.46)	0.148
Housing					
Stable	148 (67%)	1.00		1.00	
Unstable	86 (60%)	0.72 (0.47, 1.11)	0.142	0.90 (0.56, 1.44)	0.659

Incarceration (ever)					
No	74 (67%)	1.00		1.00	
Yes	160 (63%)	0.83 (0.52, 1.33)	0.434	0.94 (0.56, 1.59)	0.831
Injecting frequency					
< Daily	152 (65%)	1.00		1.00	
>Daily	82 (63%)	0.89 (0.57, 1.39)	0.614	0.96 (0.60, 1.55)	0.879
Current OST					
No	91 (60%)	1.00		1.00	
Yes	143 (67%)	1.39 (0.90, 2.14)	0.137	1.38 (0.86, 2.21)	0.182
Previous testing by venepuncture[b]					
No	13 (43%)	1.00		1.00	
Yes	206 (65%)	2.47 (1.15, 5.28)	0.019	2.15 (0.97, 4.8)	0.060
Unknown	15 (79%)	4.91 (1.13, 18.32)	0.018	5.09 (1.24, 21.00)	0.024
Previous testing by finger-stick[c]					
No	92 (61%)	1.00		1.00	
Yes	125 (66%)	1.25 (0.80, 1.96)	0.326	1.28 (0.79, 2.06)	0.311
Unknown	17 (65%)	1.19 (0.50, 2.85)	0.695	1.00 (0.39, 2.58)	1.000

OR: Odds Ratio; CI: Confidence Interval; OST: Opioid Substitution Treatment;

± Injection drug use in the past month

[a] Overall unadjusted and adjusted *p* values: 0.622, 0.879, respectively

[b] Overall unadjusted and adjusted *p* values: 0.023, 0.056 respectively

[c] Overall unadjusted and adjusted *p* values: 0.613, 0.576 respectively

3.5 Discussion

This study demonstrated that finger-stick whole-blood HCV RNA testing was acceptable among PWID in Australia. Participants reported a preference for finger-stick HCV RNA testing over venepuncture, with most of these preferring to receive results within 60 minutes. The most common reasons for preferring finger-stick testing over venepuncture testing were that it was quick and having a history of venous access difficulties. Females were more likely than males to prefer finger-stick testing. Among people with recent injecting drug use, Aboriginal and/or Torres Strait Islander people were less likely to prefer finger-stick testing to venepuncture testing compared to non-Aboriginal and/or Torres Strait Islander people. This study provides important data to guide future implementation of point-of-care testing as a strategy to enhance HCV testing and diagnosis among PWID.

Findings are consistent with previous studies demonstrating acceptability of, and preferences for, finger-stick whole-blood HCV antibody testing over venepuncture among PWID.[368, 382] Similar to previous studies [367], we observed that a major reason for preferring finger-stick testing over venepuncture was related to venous access difficulties. Similarly, rapid saliva HCV antibody testing has been found to be a preferred method of testing due to being pain-free and non-invasive.[368] However, to our knowledge, this is one of the first studies to evaluate the acceptability of finger-stick HCV RNA testing.

Consistent with previous studies, one of the reasons for preferring venepuncture over finger-stick testing among this population is the perception that this testing method is

more accurate.[367] However, there are now data demonstrating very high sensitivity and specificity for detection of both HCV antibodies and HCV RNA in samples collected via finger-stick testing.[376, 381, 383] In the Australian context, it is not surprising that there are concerns about the accuracy of these tests, given that these assays are novel and not the current standard of care. If there is a perception that a finger-stick capillary whole blood-based testing is inaccurate, this could be a potential barrier to testing uptake among PWID, indicating a need for further education about the accuracy of finger-stick testing methods for HCV infection.

We also observed that females were more likely to prefer finger-stick testing than males. Although White et al., found that women who inject drugs were more likely to prefer saliva testing over venepuncture and capillary blood testing, this was not associated with venous access difficulties, age, recruitment site, incarceration history or frequency of injection.[368] However, our data indicate that one of the reasons that female participants preferred finger-stick testing is related to venous access difficulties. It is plausible that this preference is underpinned by the experiences of women who inject drugs with injection-related skin, vascular and soft tissue injuries and disease, such as vein sclerosis, skin abscesses and sepsis.[384, 385] Previous studies have demonstrated that women who inject drugs are at higher risk of injection-related injuries and complications compared to men who inject drugs.[386-388] This increased risk among women who inject drugs is most likely due to factors such as having less prominent peripheral veins resulting in venous access difficulties, including resorting to injecting into central veins (e.g. femoral or jugular veins), and being more likely to be injected by others including with a previously used syringe.[386, 388] Several studies have also shown

that women who inject drugs are more likely to inject into a central vein than men.[384, 389, 390]

Although over a half of Aboriginal and/or Torres Strait Islander participants who recently injected drugs indicated a preference for a finger-stick testing, they were less likely to prefer finger-stick testing over venepuncture compared to non-Aboriginal and/or Torres Strait Islander people. Data on the acceptability of point-of-care testing among Indigenous communities in Australia, and in other countries, is limited. However, a recent evaluation of the national Quality Assurance for Aboriginal Medical Services (QAAMS) point-of-care testing for haemoglobin A1c performed for diabetes management in 65 Aboriginal medical services found that point-of-care finger-stick testing highly acceptable among Aboriginal and/or Torres Strait Islander patients.[391] Most patients in the haemoglobin A1c study reported that finger-stick testing was less stressful than venepuncture, convenient by allowing for immediate results, and understood what the point-of-care test machines were being used for.[391] Further qualitative research is needed to better understand the barriers and facilitators to HCV point-of-care testing uptake, and best practice in the culturally-appropriate implementation of HCV point-of-care testing in Aboriginal and/or Torres Strait Islander communities.

While a study by Morano et al. showed that vulnerable populations, including PWID, equally preferred point-of-care and venepuncture testing methods, participants who received point-of-care HCV antibody testing were significantly more likely to be linked to treatment than those who received standard of care testing.[328] Finger-stick dried

blood spot testing and point-of-care testing have also been shown to increase HCV testing and linkage to care in other settings.[327, 342, 379] Currently patients often require multiple visits for HCV antibody and HCV RNA confirmatory tests and the final receipt of results.[260] If phlebotomy is performed off-site, this further increases the number of visits and provides considerable opportunity for patients, including PWID, to be lost-to-follow-up. This is particularly complicated in remote/rural settings and in low- and middle-income countries where phlebotomy services are often inaccessible or under-resourced. Additionally, inadequate knowledge among primary healthcare providers about HCV testing requirements contributes to the confusion among patients/clients regarding the need for further visits for confirmatory HCV RNA testing following a HCV antibody positive result.[264-266] Finger-stick whole-blood collection for point-of-care HCV RNA testing presents an opportunity to provide same day diagnosis, circumventing the need for return visits and providing an opportunity to enhance linkage to care and treatment. In addition, finger-stick whole-blood collection for point-of-care HCV RNA testing provides an opportunity to engage PWID in drug user health counselling and education.

This study has limitations. Participants were likely already linked to healthcare services; thus this sample may not be representative of the broader population of PWID. Similarly, while participants were recruited from 13 sites, the majority of these (68%, n=385) were in New South Wales and results may not be generalisable to PWID living in other areas of Australia. The majority of participants also reported previously testing for HCV, and the findings may not be generalisable to testing-naïve PWID. Given that dried blood spot is not currently approved for HCV diagnostic testing in Australia, the

reported high previous exposure to finger-stick testing likely reflects high levels of participation in the Australian Needle and Syringe Program Survey (ANSPS)[263] which collects dried blood spots from PWID nationwide for HIV and HCV surveillance purposes. Our robust adjusted logistic regression models showed weak or no association between previous exposure to venepuncture or finger-stick testing and preference for finger-stick testing. The potential for social desirability bias was minimised by the use of self-administered surveys on computer tablets.[392, 393]

PWID are a key population to test and treat in order to achieve the WHO viral hepatitis elimination targets of 80% reduction in HCV incidence and 65% reduction in HCV-related mortality by 2030.[3] Finger-stick whole-blood collection is acceptable to PWID. Further evaluation of simplified point-of-care HCV testing as a single-visit opportunity to engage people in care is crucial for treatment scale-up and HCV elimination.

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Declaration of interests

GD is a consultant/advisor and has received research grants from AbbVie, Bristol Myers Squibb, Gilead, Merck, Janssen and Roche. MM has received speaker payments from AbbVie. JG is a consultant/advisor and has received research grants from AbbVie, Cepheid, Gilead Sciences and Merck/MSD.

3.6 Supplementary material

Supplementary Table 1. Reasons for the preference of finger-stick HCV testing in the LiveRLife study, stratified by sex (n=366)

	Quick	Venous access difficulties	Accurate results	Not painful	Other
Male	159 (66%)	45 (19%)	11 (5%)	18 (8%)	5 (2%)
Female	69 (54%)	32 (25%)	11 (9%)	15 (12%)	1 (<1%)

Supplementary Table 2. Reasons for the preference of venepuncture HCV testing in the LiveRLife study, stratified by sex (n=199)

	Quick	Venous access difficulties	Accurate results	Not painful	Other
Male	99 (64%)	2 (1%)	43 (28%)	6 (4%)	5 (3%)
Female	22 (50%)	4 (9%)	15 (34%)	3 (7%)	-

Chapter 4: Hepatitis C virus testing, liver disease assessment and direct-acting antiviral treatment uptake and outcomes in a service for people who are homeless in Sydney, Australia: The LiveRLife homelessness study

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Running title: HCV DAA treatment among homeless people

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Declaration

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4.1 Abstract

People who are homeless have increased hepatitis C virus (HCV) infection risk and are less likely to access primary healthcare. We aimed to evaluate HCV RNA prevalence, liver disease burden, linkage to care and treatment uptake and outcomes among people attending a homelessness service in Sydney. Participants were enrolled in an observational cohort study with recruitment at a homelessness service over eight liver health campaign days. Finger-stick whole-blood samples for Xpert® HCV Viral Load and venepuncture blood samples were collected. Participants completed a self-administered survey and received transient elastography and clinical assessment by a general practitioner or nurse. Clinical follow-up was recommended 2-12 weeks after enrolment. For participants initiating direct-acting antiviral (DAA) therapy, medical records were audited retrospectively, and treatment outcome data were collected. Among 202 participants (mean age, 48 years), 82% were male (n=165), 39% (n=78) reported ever injecting drugs, of whom 63% (n=49) injected in the previous month. Overall, 23% (n=47) had detectable HCV RNA and 6% had cirrhosis. HCV RNA prevalence among participants with either injecting or incarceration history was 35% (37/105), compared to 4% (3/73) among participants without these risk factors. Among those with detectable HCV RNA, 23 (49%) commenced therapy, of whom 65% (n=15) achieved sustained virological response, while the remainder had no available treatment outcome. No participant had documented virological failure. HCV DAA treatment uptake among people attending a homelessness service was encouraging, but innovative models of HCV care are required to improve linkage to care and treatment uptake among this highly marginalised population.

Keywords: Hepatitis C virus, treatment uptake, direct-acting antiviral, linkage to care, homelessness

4.2 Background

In 2015, the World Health Organization (WHO) set a goal to eliminate hepatitis C virus (HCV) infection as a major global public health threat by 2030.[3] Strategies for achieving the WHO HCV elimination targets of reductions of new HCV infections by 80% and number of HCV-related deaths by 65%, include increased HCV diagnosis from 20 to 90%, increasing treatment uptake from less than 5% to 80%, and enhanced blood safety and harm reduction.[3] People who are homeless are at increased risk of HCV infection, [122, 394-397] and have poorer access to primary healthcare services and treatment than people with stable housing.[394, 398, 399] Estimates of HCV antibody prevalence in the homeless population range from 4% to 36%.[122]

Definitions of homelessness differ across and within countries.[394] The Australian Bureau of Statistics defines a person as homeless when they do not have suitable accommodation alternatives and their current living arrangement is in a dwelling that is inadequate; or has no tenure, or if their initial tenure is short and not extendable; or does not allow them to have control of, and access to space for social relations.[400] In 2016, there were 116,427 homeless people in Australia, an increase from 89,728 in 2006; predominantly male (58%).[400] Numerous complex and intersecting individual and structural factors are associated with homelessness.[394] Individual factors include early life trauma, mental illness, alcohol and other drug use and problem gambling.[124, 394] Structural factors include poverty, lack of low-cost housing and loss of public housing tenancy, and lack of housing options post release from prison and discharge from psychiatric hospital-based care.[124, 394]

In addition, people who are homeless are less likely to be linked to general practitioners or to receive healthcare than the general population.[398, 399] Conversely, homeless people are more likely to present to hospital emergency departments with advanced chronic disease compared to the general population.[394, 398, 401] Interventions that have been shown to be successful at engaging homeless people in care include tailored primary healthcare programmes and integrated case management and housing support.[402] Similarly, integrated HCV services are needed to enhance HCV testing and treatment in this population. Although high HCV prevalence among people who are homeless has been reported,[394] HCV treatment uptake and outcomes are limited.

The aim of this study is to describe the cascade of HCV care among people attending a service for homeless people and participating in the LiveRLife homelessness study in Sydney, Australia. The specific objectives are to describe the HCV RNA prevalence, liver disease burden, linkage to care and HCV DAA treatment uptake and outcomes among the LiveRLife homelessness cohort; and examine factors associated with HCV DAA treatment uptake.

4.3 Methods

4.3.1 Study design and participants

LiveRLife Homelessness is an observational cohort study evaluating an intervention integrating a liver health promotion campaign and non-invasive liver fibrosis assessment on linkage to care and HCV treatment uptake among people who are homeless. Participants were enrolled over four days in February 2016 and four days in November/December 2016 from a homelessness service located in inner-city Sydney.

Inclusion criteria were age ≥18 years and written informed consent. Current pregnancy was the only exclusion criterion. All participants provided written informed consent before study procedures commenced. The study protocol and amendments were approved by the Human Research Ethics Committee at St. Vincent's Hospital, Sydney.

4.3.2 Study site

The Ozanam Learning Centre (OLC) is a St Vincent de Paul community centre located in an inner-city suburb of Sydney. The OLC provides services to people who are homeless, at risk of homelessness or those who require social inclusion opportunities. Services include onsite education, living-skills and recreational activities. The OLC is adjoined by the Matthew Talbot Hostel which provides immediate support and temporary accommodation for people who are homeless or at risk of homelessness. Although the hostel caters for men ≥21 years of age, the OLC provides activities for men and women 18 years and older free-of-charge. The capacity of the hostel is 98 beds, but more than 35,000 men per year access services at the facility. Services include

a nurse-led primary healthcare clinic, the provision of meals, clothing, specialised case management, and legal and housing support. The daily nurse-led clinic, supported twice-weekly by a general practitioner who prescribes DAA therapy for HCV infection, includes specialised services such as psychiatric, diabetes, hepatitis C, optometry, and podiatry clinics.

4.3.3 Study procedures

Prior to the LiveRLife campaign days, recruitment posters were displayed at the study site and OLC 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 at OLC during the eight LiveRLife campaign days.

At enrolment, participants received an educational resource package (including LiveRLife campaign coffee mug, and liver health promotion and education booklet) and a AUS$20 voucher for their time. Participants received the AUS$20 voucher at the completion of study assessment on the campaign day. Enrolment assessments included finger-stick 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, Paris, France), clinical nurse assessment (including standard of care assessment), and venepuncture blood samples for standard of care clinical testing (including HCV RNA testing) and storage for future HCV research. Participants were

not provided their Xpert® HCV test results, given that the Xpert® HCV Viral Load Assay was 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 finger-stick blood collection, participants completed a self-administered survey on tablet computers collecting demographic information, injection drug use history, other drug use history, drug injecting behaviour, health service utilisation, FibroScan® and alcohol consumption. 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.[403] 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.[403] According to a cultural definition of homelessness, indicators of housing instability in Australia are categorised into three types*: primary homelessness* include 'sleeping rough' (sleeping on the street/car, in a squat, or improvised dwelling); *secondary homelessness* include frequently moving from one temporary shelter/accommodation to another (i.e. staying with friends, relatives, homelessness services); *tertiary homelessness* include people living in boarding houses, hostels, caravan parks with no secure lease or private facilities.[404, 405] For the purposes of this study, participants were categorised 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.[405] 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.[405]

After the survey, participants received transient elastography assessment. Liver fibrosis stage was assessed using the FibroScan®, which uses transient elastography to measure liver stiffness. FibroScan® 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).[176] An extra-large probe was not available.

Liver disease assessment was followed by a clinical HCV assessment by a general practitioner or a nurse. This involved a standard health check and a review of medical history, FibroScan® result (written on a scorecard with liver disease stage infographic[406]), and in some cases blood tests (including HCV RNA testing) for routine 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 HCV test results and for clinical follow-up with a general practitioner or nurse, and to complete a follow-up self-administered survey. The survey collected demographics, injecting drug behaviour since enrolment, post campaign liver disease knowledge and HCV knowledge. Where possible, participants who tested HCV RNA detectable were contacted and scheduled for follow-up appointments. Participants were remunerated with a further AU$20 voucher at follow-up.

After the Australian Government funding of 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 by a general practitioner, as per clinical guidelines. For participants initiating DAA therapy, medical records were audited retrospectively, and data collected on a standardised data collection form. Treatment data collection included prescriber type, lifetime and current opioid substitution therapy (OST), lifetime injection drug use and injection drug use in the last 6 months, HIV infection status, HCV genotype, HCV treatment regimen, dosage and duration of treatment, date of HCV treatment initiation, treatment discontinuation, and sustained virological response 12 weeks post end of treatment (SVR12).

4.3.4 Study outcomes

The study endpoints include HCV infection (detectable HCV RNA), significant liver disease (stage >F2), linkage to care (defined as clinical follow-up attendance), HCV treatment uptake following initial assessment, and treatment outcome. HCV infection was determined by HCV RNA quantification using Abbott RealTime HCV Viral Load Assay performed on venepuncture samples. Where the Abbott RealTime assay was not performed, HCV RNA testing was completed using the Xpert® HCV Viral Load Fingerstick Assay, performed on finger-stick whole-blood samples. Participants with documented date of treatment initiation were considered as having received treatment. Successful treatment outcome was sustained virological response at 12 weeks (SVR12), defined as serum HCV RNA below the limit of detection at 12 weeks or greater following end of treatment.

4.3.5 Statistical analysis

Descriptive statistics, including means, frequencies and percentages were used to summarise the data. Factors hypothesised *a priori* to be associated with HCV treatment uptake were assessed, including age, sex, housing stability (unstable housing vs stable housing), recent injecting drug use (injecting in the previous month), OST, liver fibrosis stage, and alcohol consumption. Unadjusted analyses were performed using univariate logistic regression with odd ratios (OR) and associated 95% confidence intervals (CI). All P values are 2-sided; a level of 0.05 was considered statistically significant and. Statistical analyses were performed using the Stata v14.0 (College Station, TX, USA).

4.4 Results

4.4.1 Participant characteristics

During February (four days) and November/December (four days) 2016, 205 participants were enrolled and 202 completed study assessments (Figure 1). Mean age was 48 years, 82% (n=165) were male, and 8% (n=16) identified as Aboriginal or Torres Strait Islander (Table 1). Twenty-four participants were missing demographic survey due to loss of data during data transfer from tablet to computer and one stolen tablet. Fifty-eight percent (n=118) reported unstable housing, and 30% (n=60) ever being incarcerated in a prison or juvenile justice centre. Among participants reporting current unstable housing, 47% (n=55) reported staying in shelter/refuge, 42% (n=50) were street/homeless, 6% (n=7) staying temporarily with friends, and 6% (n=7) staying in other accommodation (including public housing and staying with parents). Overall, 39% (n=78) reported a history of injection drug use, of whom 63% (n=49) reported injecting drugs in the previous month, and 28% (n=22) reported currently receiving OST. Among participants reporting injecting drugs in the previous month, 57% (n=28) reported that methamphetamine was the last drug injected, followed by opioids (41%; n=20), and cocaine (2%; n=1). The predominant last drug injected among those never receiving OST/not currently on OST (n=35) was methamphetamine (63%; n=22), followed by opioids (34%; n=12), cocaine (4%, n=1). A high proportion (38%) of participants with high risk alcohol intake was observed.

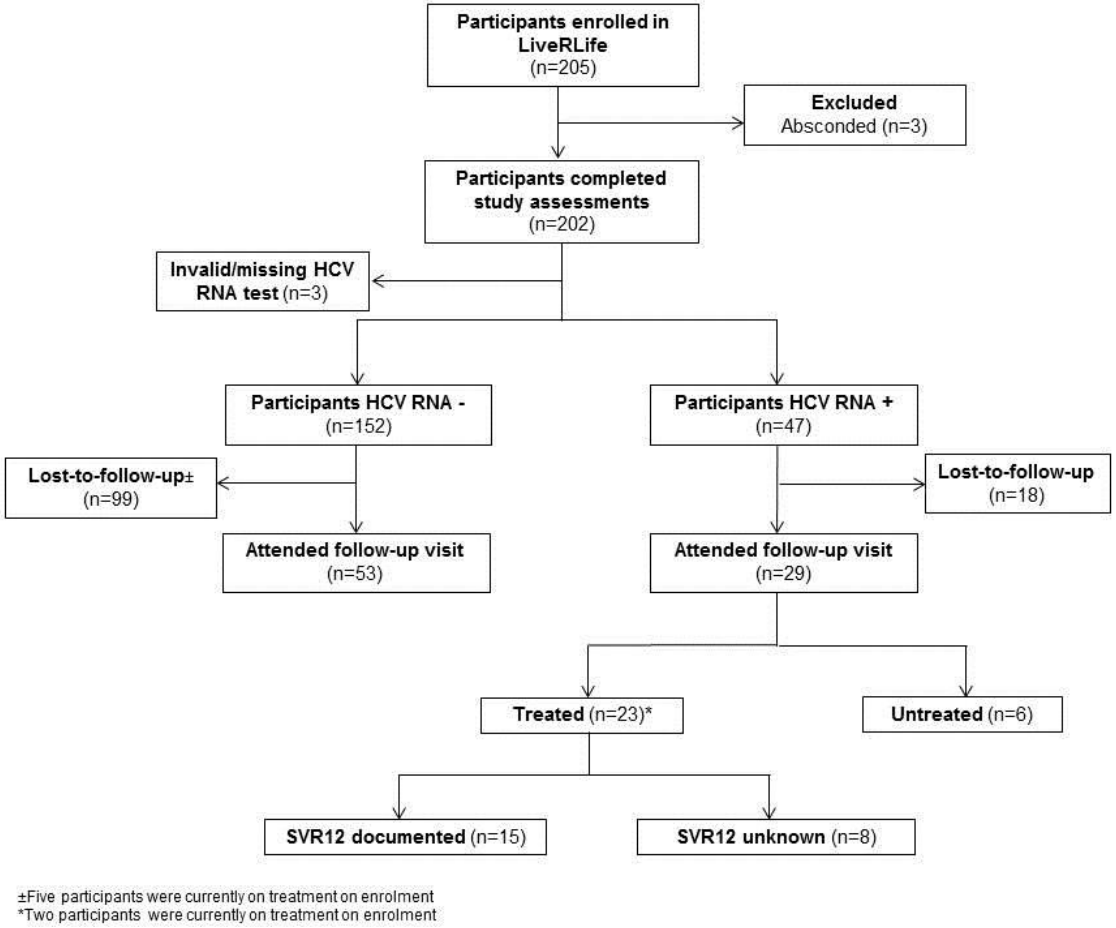

Figure 1: Participant disposition

Table 1: Participant characteristics enrolled in the LiveRLife homelessness study (n=202)[*]

Characteristic	HCV RNA negative (n=152), n (%)	HCV RNA positive (n=47), n (%)	Overall (n=202)
Age, mean (SD)	49 (12.5)	45 (9.0)	48 (12.1)
Age groups			
18 – 35	22 (14%)	6 (13%)	29 (14%)
36 – 45	47 (31%)	17 (36%)	65 (32%)
46 – 55	36 (24%)	20 (43%)	56 (28%)
≥ 56	47 (31%)	4 (9%)	52 (26%)
Sex[a]			
Male	126 (83%)	37 (79%)	165 (82%)
Female	8 (5%)	2 (4%)	11 (5%)
Transgender	1 (1%)	1 (2%)	2 (1%)
Aboriginal/Torres Strait Islander self-identification[a]			
Yes	10 (7%)	5 (11%)	16 (8%)
No	123 (81%)	35 (74%)	160 (79%)
Unknown	2 (1%)	-	2 (1%)
Completed high school or higher education[a]			
Yes	72 (47%)	27 (57%)	78 (39%)
No	63 (41%)	13 (28%)	100 (49%)
Main source of income[a]			
No income	8 (5%)	1 (2%)	9 (4%)
Full-time/part-time/casual	11 (7%)	2 (4%)	14 (7%)
Government assistance	111 (73%)	37 (79%)	150 (74%)
Other	5 (3%)	-	5 (2%)
Housing[a,b]			
Stable	47 (31%)	12 (26%)	60 (30%)
Unstable	88 (58%)	28 (60%)	118 (58%)
Incarceration[a]			
Ever (not in past 12 months)	41 (27%)	19 (40%)	60 (30%)
In past 12 months	11 (7%)	8 (17%)	20 (10%)
Never	83 (55%)	13 (28%)	98 (49%)
Injected drugs (ever)[a]			
No	92 (61%)	5 (11%)	100 (49%)
Yes	43 (28%)	35 (74%)	78 (39%)
Age at first injection, median (Range)[c]	22 (12 – 52)	21 (13 – 45)	21 (12 – 52)
Injected drugs in past 6 months[c]	24 (56%)	30 (86%)	54 (69%)
Frequency of injection in past 6 months[c]			
Daily or more	5 (12%)	10 (29%)	15 (19%)
<Daily	19 (44%)	20 (57%)	39 (50%)
None in past 6 months	19 (44%)	5 (14%)	24 (31%)

Injected drugs in past month[d]	21 (88%)	28 (93%)	49 (91%)
Frequency of injection in past month[d]			
Daily or more	5 (21%)	8 (27%)	13 (24%)
<Daily	16 (67%)	20 (67%)	36 (67%)
None in past month	3 (13%)	2 (7%)	5 (9%)
High risk alcohol consumption (AUDIT-C) [a,e]			
High risk male/female	61 (40%)	14 (30%)	77 (38%)
Low risk male/female	34 (22%)	9 (19%)	43 (21%)
Never drinks	39 (26%)	16 (34%)	56 (28%)
Opioid substitution treatment [a]			
Current treatment	10 (7%)	12 (26%)	22 (11%)
Previous treatment, not current	6 (4%)	8 (17%)	14 (7%)
Never	119 (78%)	20 (43%)	142 (70%)
HCV RNA test result			
Positive	-	-	47 (24%)
Negative	-	-	152 (75%)
Invalid result/missing	-	-	3 (1%)
FibroScan® Liver disease staging[f]			
F0/F1 – No/mild fibrosis	111 (73%)	25 (53%)	137 (68%)
F2 – Moderate fibrosis	16 (11%)	13 (28%)	29 (14%)
F3 – Severe fibrosis	7 (5%)	2 (4%)	10 (5%)
F4 – Cirrhosis	7 (5%)	5 (11%)	12 (6%)
Invalid	10 (7%)	2 (4%)	12 (6%)
Missing/Not performed	1 (<1%)	-	2 (1%)

Note: All percentages are column percentages and some may not equal to 100% due to rounding; [*]HCV RNA test result invalid/missing (n=3); [a]Participants missing demographic survey (n=24) due to loss of data during data transfer from tablet to computer and one stolen tablet; [b]Stable housing: living in owned house/flat, rental house/flat or parent's house; Unstable housing: staying temporarily with friends, shelter/refuge, street/homeless; [c]Among participants with a history of injecting drug use (n=78); [d]Among participants who injected in the previous 6 months (n=54); [e]Transgender excluded from the AUDIT-C (n=2); [f]Missing due to unavailable XL-probe needed for this participant (n=1)

4.4.2 HCV RNA prevalence and HCV risk factors

Overall, 23% (n=47) had detectable HCV RNA consistent with active HCV infection. Among HCV RNA detectable participants, 62% (n=29) self-reported as having 'hepatitis C', 23% (n=11) self-reported as not having/or did not know if they had 'hepatitis C', and 15% (n=7) were missing this part of the survey. Associations between history of injection drug use and history of incarceration and HCV RNA status are presented in Supplementary Tables 1 and 2. Detectable HCV RNA prevalence among participants with either injecting or incarceration history was 35% (37/105), compared to 4% (3/73) among participants with neither injecting nor incarceration history. Among HCV RNA detectable participants with an available baseline characteristics (ie survey missing n=7), 85% (35/40) reported ever injecting drugs, of whom 70% (n=28) reported injecting in the previous month (Figure 2).

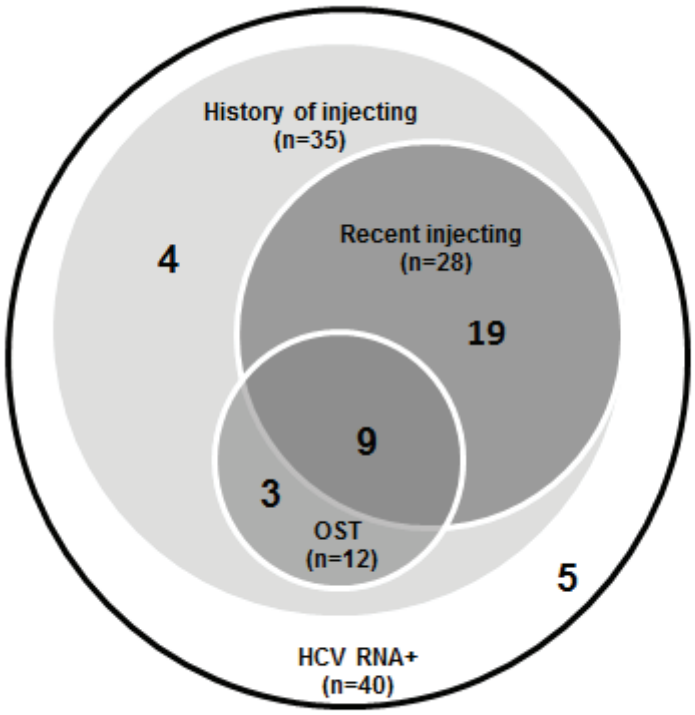

Figure 2: Injecting drug use and current opioid substitution treatment among participants with detectable HCV RNA (n=40*)

4.4.3 Liver disease assessment and HCV treatment uptake and outcomes

With the exception of one participant, all participants enrolled in the study received a liver disease assessment by transient elastography. Median liver stiffness score was 5.8kPa (Range: 2.8–45). The majority (68%) had no/mild fibrosis (F0/F1), 14% moderate fibrosis (F2), 5% severe fibrosis (F3) and 6% had cirrhosis (F4) (Table 1). Overall, 6% of participants (n=12) had an invalid liver stiffness score. Notably, a higher proportion (73%) of participants with undetectable HCV RNA had no/mild fibrosis (F1) compared to the proportion (53%) of no/mild fibrosis in the detectable HCV RNA group. Whereas, a higher proportion (43%) of participants with detectable HCV RNA had significant fibrosis (F2 – F4) in comparison to the proportion (21%) of significant fibrosis among the undetectable HCV RNA group. Among participants with no/low-risk alcohol consumption (n=99), 67% (n=66) had no/mild fibrosis, 23% (n=23) had significant fibrosis, and 10% (n=10) had invalid/missing results. Whereas, among participants with high-risk alcohol consumption (n=77), 75% (n=58) had no/mild fibrosis, 21% (n=16) had significant fibrosis, 4% (n=3) had invalid/missing results.

Among participants with detectable HCV RNA, 62% (n=29) attended a clinical follow-up visit and 49% (n=23) commenced DAA therapy, while 18 (38%) were lost to follow-up (Figure 3). Sixteen participants were prescribed DAA therapy by the general practitioner at the homeless clinic, and five by a specialist following referral to a tertiary hospital. Two participants self-reported being on HCV treatment at enrolment, however, treatment regimen and outcomes were not documented. Among those treated with sofosbuvir/ledipasvir for genotype 1a (n=12), three were treated for 8 weeks, while nine were treated for 12 weeks. One participant was treated with sofosbuvir/velpatasvir

(Australian Government funded in August 2017 for all genotypes) for genotype 1a for 12 weeks. Of participants treated with sofosbuvir/daclatasvir for genotype 3 (n=7), six were treated for 12 weeks and one for 24 weeks. One participant was treated with sofosbuvir/daclatasvir for genotype 2 for 12 weeks. Among the treated participants, two self-reported previous HCV treatment (Supplementary Table 3). Among participants attending clinical follow-up with no subsequent HCV treatment (n=6), reasons were death unrelated to liver disease (n=1), transfer of care to a tertiary heath service provider (n=1), and unknown (n=4).

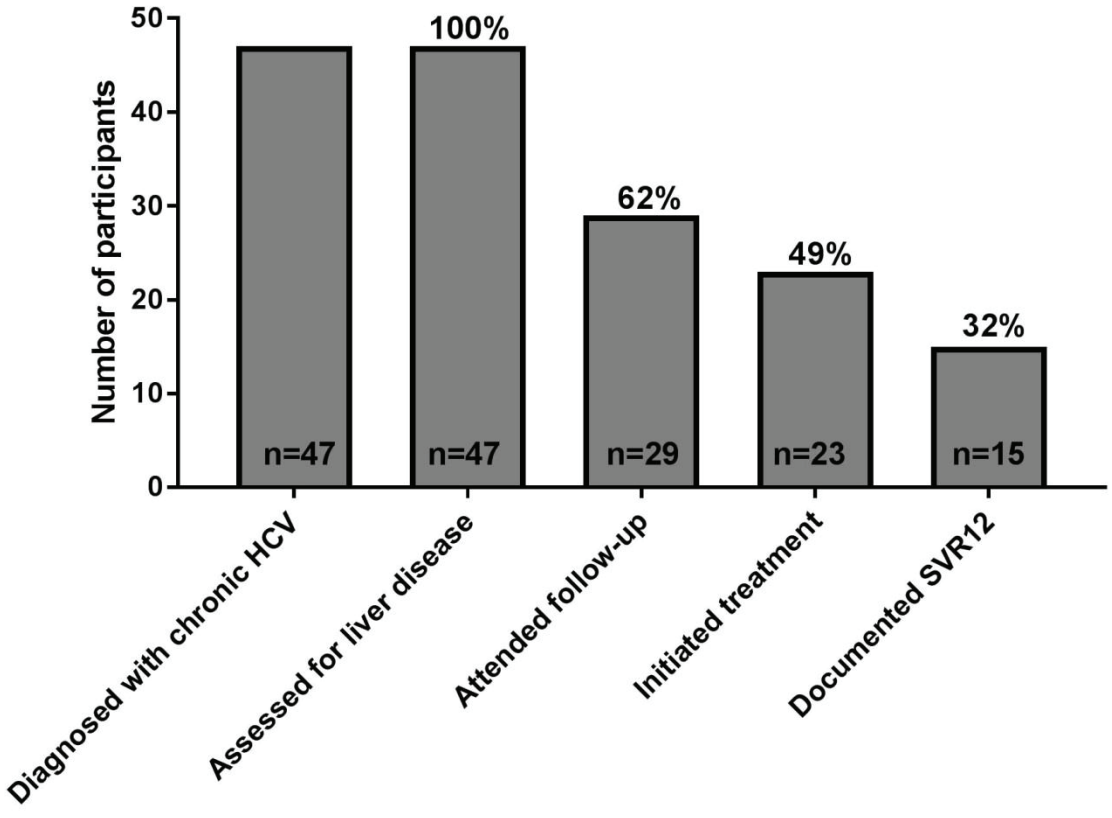

Figure 3: Cascade of care among participants with HCV infection in the LiveRLife homelessness study (n=47)

HCV=Hepatitis C virus; SVR12=Sustained virological response at 12 weeks post treatment

Overall, 65% (n=15) of those initiating DAA therapy achieved SVR12, while the remainder had no available treatment outcome. There were no participants with documented virological failure. Among participants receiving weekly DAA therapy dispensing from the study site, 80% (8/10) achieved SVR12.

Among the 27 participants with HCV infection enrolled in February 2016 (just prior to Australian Government funding of DAA therapy), nine (33%) initiated DAA therapy over the following five-month period, with only one participant having delayed initiation in November 2017 (Figure 4). Although a higher proportion (70%; 14/20) of participants initiated DAA therapy from the second round of screening in November/December 2016, initiation generally occurred over a longer eight-month period, with one participant initiating a year later (median time to initiation=98 days; Range 20–641). There was no association between time to clinical follow-up and treatment uptake.

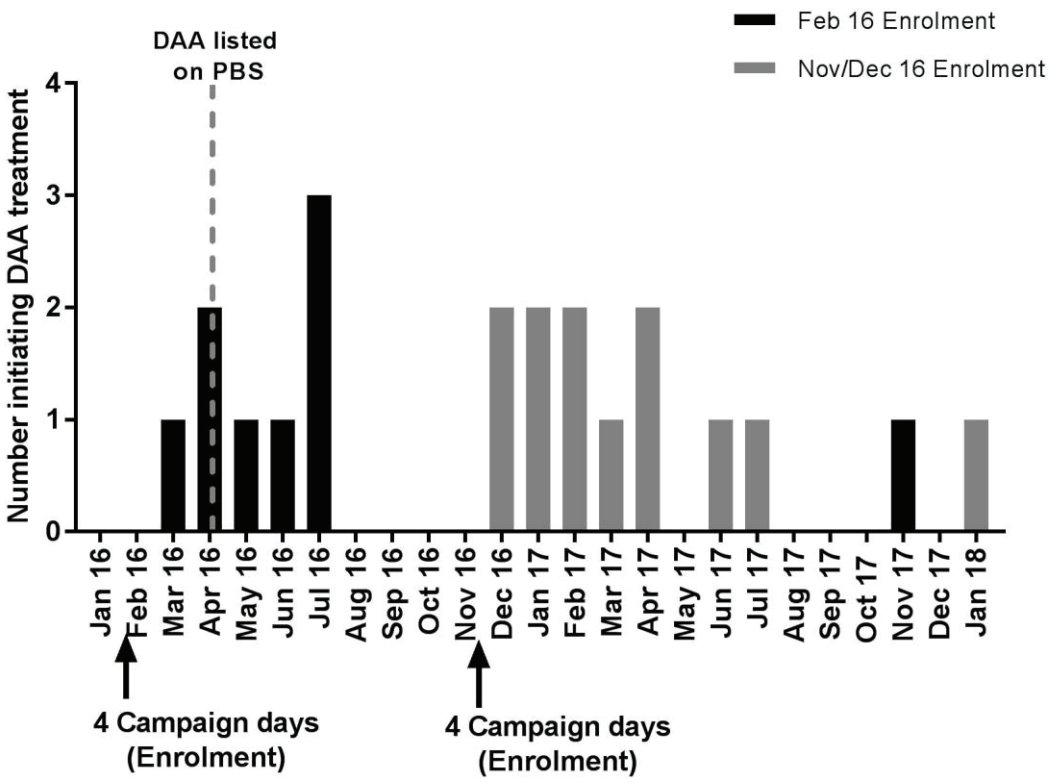

Figure 4: Treatment uptake among participants with HCV infection in the LiveRLife homelessness study (n=47[§])

PBS=Pharmaceutical Benefits Scheme; [§]Two participants were excluded due to being currently on treatment at enrolment and treatment date was not reported

In unadjusted logistic regression analyses, HCV treatment uptake among people with HCV infection was not associated with age, sex, housing stability, injecting drug use, OST or liver disease stage (Table 2). Of concern, only 33% (5/15) of participants with significant liver fibrosis initiated DAA therapy compared to 61% of those with no/mild liver fibrosis.

Table 2. Unadjusted logistic regression model assessing factors associated with HCV treatment uptake among HCV RNA detectable participants in the LiveRLife homelessness study (n=40[a])

	Treatment uptake, n (%[b])	Unadjusted model	
		OR (95% CI)	*P*
Age			
18 – 35 years	1 (17%)	1.00	
36 – 50 years	14 (61%)	7.78 (0.78, 77.93)	0.081
≥51 years	4 (36%)	2.85 (0.24, 33.90)	0.406
Sex			
Male	18 (47%)	1.00	
Female	1 (50%)	1.11 (0.06, 19.10)	0.942
Housing			
Stable	6 (50%)	1.00	
Unstable	13 (46%)	0.87 (0.22, 3.35)	0.836
History of injecting drug use			
No history of injecting	3 (60%)	1.00	
Yes, but not in previous month	4 (57%)	0.89 (0.09, 9.16)	0.921
Injecting in previous month	12 (43%)	0.50 (0.07, 3.48)	0.484
OST			
Never	9 (45%)	1.00	
Yes, previously received	2 (25%)	0.41 (0.07, 2.53)	0.335
Yes, currently receiving	8 (66%)	2.44 (0.55, 10.83)	0.239
High risk alcohol consumption (AUDIT-C)[c]			
Never	6 (38%)	1.00	
Low risk male/female	4 (44%)	1.33 (0.25, 7.01)	0.734
High risk male/female	9 (64%)	3.00 (0.68, 13.31)	0.148
FibroScan® Liver disease stage[d]			
No/mild fibrosis (F0/F1)	14 (61%)	1.00	
Moderate/severe fibrosis (F2/F3)	4 (33%)	0.32 (0.07, 1.39)	0.129
Cirrhosis (F4)	1 (33%)	0.32 (0.03, 4.10)	0.382

[a]Missing demographic survey (n=7) due to loss of data during data transfer from tablet to computer and one stolen tablet; [b]Row percentages; [c]Transgender excluded from the AUDIT-C (n=1); [d]Two participants excluded due to invalid/missing fibroScan results

4.5 Discussion

Findings indicate that an active HCV screening and liver disease assessment model of care with a committed clinical service including a general practitioner DAA prescriber encouraged and facilitated linkage to care among people attending a homelessness service. However, HCV treatment uptake and documented cure remained suboptimal in this highly marginalised population. This study underscores the need for innovative and holistic HCV screening and linkage to care strategies to optimise the HCV care cascade among people who are homeless.

Comparable to previous studies[122, 407, 408] HCV RNA prevalence among the study population was high (23%), however, the majority of participants with HCV infection reported a history of injection drug use. Consistent with previous research, there was a strong relationship between reported HCV risk factors (history of injecting drug use or incarceration) and HCV RNA prevalence.[408] In fact, the majority (n=25, 63%) of those with HCV infection had a history of injecting and incarceration. Only a small number (n=3, 8%) of participants had neither a history of injecting or incarceration. The high proportion with HCV infection and a history of injecting (88%) indicates that participants were willing to report potentially highly stigmatised risk behaviour. There is a likely several reasons for this, including previous positive encounters with the service, and comfort and trust in which that participants may have felt towards the study site staff and peer workers. Further data, however, is required to evaluate whether this apparent high level of risk behaviour reporting is present among homeless populations in other Australian and international settings, particularly given the proximity of the homelessness service to a historical street-based drug market area. Given the high HCV

prevalence among our study population and other homeless populations (with various distributions of key risk factors), our data supports a broad HCV screening strategy of all within homelessness settings.

People who are homeless face a number of complex barriers to accessing primary healthcare services.[132] Homeless people who inject drugs are more likely to engage in unsafe injecting practices, including injecting in public where prevalence of sharing of injecting equipment is high.[135, 405, 409] Further, homeless people who inject drugs may face barriers accessing harm reduction services including needle and syringe programs and OST.[132, 136, 405, 410] Incarcerated people who inject drugs are disproportionately affected by HCV infection and in most settings lack access to harm reduction services.[121] Previous qualitative research among homeless people who inject drugs reported that participants felt that the impact of homelessness on their drug use behaviour made HCV acquisition inevitable.[137] In some instances, homeless people who inject drugs may not be aware of the services that are available, or may have been barred from accessing services due to aggressive behaviour towards others.[132] Previous research on HIV testing among people who are homeless found that regular encounters with health services was associated with increased uptake of HIV testing.[411]

Data on linkage to care and treatment outcomes among people who are homeless in the interferon-free DAA era are beginning to emerge. Our findings are consistent with previous studies showing that people who are homeless are less likely to be linked to HCV care and more likely to be lost to follow-up.[412] However, high HCV treatment willingness among people who are homeless has been documented.[299] Although

homeless people who inject drugs are concerned about HCV exposure,[413] concerns regarding liver disease seem less important.[137] In one study, homeless people who injected drugs expressed fear of disclosing a positive HCV diagnosis to others and of being stigmatised by health/hostel providers, family and friends which may further perpetuate not seeking treatment.[413]

HCV treatment uptake and documented cure was suboptimal in the current study and lower than DAA therapy uptake of 61% among a population of PWID in Vancouver, Canada.[412] Notably, in this study by Alimohammadi et al, a significant proportion of those not initiating treatment were homeless.[412] Although treatment uptake in the current study was higher than that (32%) among a sample of PWID in Australia in a study by Butler et al.,[414] unstable housing was found to be significantly associated with no treatment uptake.[414] The higher uptake among the current cohort may also be attributable to this model of care integrating a liver health promotion campaign and non-invasive liver fibrosis in a homelessness setting. Unlike the high SVR rates reported among PWID[220, 415] and non-PWID in clinical trials, our finding was consistent with real-world studies which have found lower documented SVR12 rates.[222, 224, 416] However, virological failure has been uncommon, with loss to follow-up driving poorer treatment outcomes in SVR12 intention-to-treat analyses.[224] Previous research found that a history of homelessness in the prior year was associated with not achieving SVR.[222, 416]

We also observed a higher proportion of treatment uptake among people currently receiving OST (66%) compared to those never receiving or not currently receiving OST

(39%). This result is consistent with the finding from the study by Butler et al., showing that current OST is significantly associated with DAA treatment uptake.[414] People on OST are likely easier-to-engage population and more willing to receive HCV therapy.[414, 417] However, further efforts are needed to improve access to OST services by homeless people who inject drugs. People who are homeless face difficulties accessing services due to the high health and social needs, as well as competing priorities. These competing priorities include finding food, shelter and a place to wash on a daily basis.[132] Other barriers include anxiety over presenting to health services and of being stigmatised by service providers, cost of transportation and prescription medications, lack of patient identification, and the burden of appointments including taking time-off work to attend clinic visits.[136, 410] In addition, previous research among a sample of people currently injecting drug in Australia showed that a third was not eligible for OST because of not being opioid dependent (i.e. people who use methamphetamine).[418] In the current study, among participants who injected drugs in the previous month and never received/not currently receiving OST, the majority (63%) reported methamphetamine as the last drug injected. Further studies are required to examine whether OST is associated with treatment uptake and improved outcomes among PWID in homelessness settings.

Treatment uptake among people with significant fibrosis was low. In some cases, participants with cirrhosis may have been referred to a specialist for care. High alcohol consumption and drug use, and other competing factors and co-morbidities may have contributed to not initiating treatment. In addition, poor liver disease knowledge despite liver disease staging assessment and subsequent discussion of the result with the clinical

team may have been a factor for not engaging in care. Poor liver disease and HCV knowledge among PWID has been previously reported.[177]

This study has some limitations. The small sample size limited statistical power to evaluate predictors of treatment uptake. Participants were recruited from a service for homeless people and may not have included a significant proportion of the very hard to reach population who 'sleep rough' or experiencing primary homelessness; thus this sample may not be representative of the broader population of people who are homeless. The hostel catered only for men; therefore women who are homeless were under-represented in this cohort, and further research in mixed or female-only homelessness services is required. Due to the uncontrolled study design, and on 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. The potential for social desirability bias may be present in this study, but likely minimised by the use of self-administered surveys on computer tablets.[392, 393]

The development of DAA therapy has generated considerable optimism and informed the setting of HCV elimination targets. To achieve HCV elimination, however, strategies to enhance HCV testing, linkage to care and treatment for highly marginalised populations need to be developed, in the knowledge and context, of multiple unmet needs such as stable housing, OST (in the case of homeless people who inject drugs), and mental health services. Innovative strategies require evaluation in this population, including an HCV 'test and treat' model of care, incorporating point of care HCV RNA testing and same-day DAA initiation designed to minimise loss to follow-up and

optimise treatment uptake. Further partnerships between homelessness services, HCV clinical services, and government and community organisation are required to develop specific HCV strategies for this highly marginalised population.

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Declaration of interests

GD is a consultant/advisor and has received research grants from AbbVie, Gilead and Merck. MM has received speaker payments from AbbVie. JG is a consultant/advisor and has received research grants from AbbVie, Cepheid, Gilead Sciences and Merck/MSD.

4.6 Supplementary material

Supplementary Table 1: History of injecting drug use and history of incarceration among participants enrolled in the LiveRLife homelessness study (n=178)

	History of injecting drug use	
History of incarceration	**No**	**Yes**
No	73 (74%)	25 (26%)
Yes	27 (34%)	53 (66%)

Supplementary Table 2: History of injecting drug use and History of incarceration among HCV RNA detectable Participants (n=40)

	History of injecting drug use	
History of incarceration	**No**	**Yes**
No	3 (23%)	10 (77%)
Yes	2 (7%)	25 (93%)

Supplementary Table 3. Treatment outcomes stratified by previous HCV treatment (n=23)*

	Previous HCV treatment		
	Treatment naïve (n=11)	**Treatment experienced (n=2)**	**Unknown/ missing (n=10)**
Liver disease stage			
F0/F1	8	2	6
F2	3	-	2
F3	-	-	-
F4	-	-	2
Genotype			
1a	6	1	6
2	1	-	-
3	4	1	2
Unknown	-	-	2
DAA regimen & duration			
Sofosbuvir/ledipasvir (8 weeks)	1	-	2
Sofosbuvir/ledipasvir (12 weeks)	4	1	4
Sofosbuvir/velpatasvir (12 weeks)	1	-	-
Sofosbuvir/daclatasvir (12 weeks)	5	1	1
Sofosbuvir/daclatasvir (24 weeks)	-	-	1
Documented SVR12			
Yes	9	-	6
Unknown	2	2	4

*Based on survey self-report

Chapter 5: 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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Declaration

I certify that this submission was a direct result of my research towards this PhD and that reproduction in this thesis does not breach copyright regulations.

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5.1 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 an observational cohort study between 2014 and 2018 provided finger-stick whole-blood samples for dried blood spot and Xpert HCV Viral Load, and venepuncture samples. Participants received 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 pre-DAA era to 38% in 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. Innovative models of care that address the social and structural determinants of access to care are required to further enhance treatment uptake.

Key words: HCV, linkage to care, DAA, cascade of care, treatment uptake

5.2 Background

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.[3] 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,[244, 263, 419] and HCV treatment uptake among PWID persist.[3, 235, 237] Further, data on the burden of HCV-related liver disease among PWID in community-based settings is sparse.[420-422] 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.[3] Around 30% of these deaths are attributed to long term HCV-related sequelae (cirrhosis and hepatocellular carcinoma).[3] 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, 142]

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.[277, 287, 290, 423] 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: 1) 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; 2) examine factors independently associated with significant liver fibrosis; and 3) examine HCV treatment uptake in the pre-DAA and DAA eras, and identify factors independently associated with DAA treatment uptake.

5.3 Methods

5.3.1 Study design and participants

LiveRLife is an observational cohort study evaluating an intervention integrating a liver health promotion campaign and non-invasive liver fibrosis assessment on linkage to care and HCV treatment uptake among people with a history of injection drug use. The development of the health promotion resource materials have been described in detail elsewhere.[177]

Participants were enrolled between 12 August 2014 and 22 February 2018 from 16 sites in Australia covering three states/jurisdictions 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). The detailed study protocol is provided in the supplementary material.

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, received a 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 finger-stick 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.

5.3.2 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 AUS$20 shopping voucher for their time. Enrolment assessments included finger-stick 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, Paris, France), and clinical nurse assessment (including standard of care assessment). Participants also provided venepuncture blood samples 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 finger-stick blood collection, participants completed a self-administered survey on tablet computers collecting demographic information, drug use history, health service utilisation, 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 categorised 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.[405] 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.[405] 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.[403] 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.[424, 425]

After the survey, participants received 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).[176] 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[406]), 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 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 subsidised 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 standardised 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.

5.3.3 Study outcomes

The study endpoints include 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 Xpert® HCV Viral Load Fingerstick Assay, performed on finger-stick whole-blood samples.[372, 381] Prior to the availability of the Xpert® HCV Viral Load Fingerstick Assay in 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 finger-stick whole-blood samples.[426]

5.3.4 Statistical analysis

Descriptive statistics, including means, frequencies and percentages were used to summarise the data. Factors hypothesised *a priori* to be associated with significant liver disease (F2-F4) were evaluated including age, sex, Aboriginal/Torres Strait Islander identity, recent injection drug use (injecting in the previous month), body mass index (BMI), alcohol consumption and HCV RNA status at baseline. Factors hypothesised *a priori* to be associated with HCV DAA treatment uptake were assessed, including age, sex, Aboriginal/Torres Strait Islander identity, housing stability (unstable housing vs stable housing), recent injection drug use, OST, liver fibrosis stage, and alcohol consumption. Unadjusted analyses were performed using univariate logistic regression with odd ratios (OR) and associated 95% confidence intervals (CI). All P values are 2-

sided; a level of 0.05 was considered statistically significant and statistical analyses were performed using the Stata v14.0 (College Station, TX, USA).

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.

5.4 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 summarised in Supplementary Table 1.

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) at baseline. 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 percent (n=281) screened positive for high-risk alcohol consumption using the AUDIT-C tool.

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 months)	391 (47%)	186 (47%)	176 (46%)
In past 12 months	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 months[c]	605 (72%)	268 (68%)	285 (75%)
Frequency of injection in past 6 months[c]			
None in past 6 months	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%)
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 months; [g]Transgender excluded from the AUDIT-C calculations as studies validated cut-off in males and females (n=8); [h]Participants missing demographic survey in total cohort (n=19); [i]Invalid result due to Xpert® device processing error (n=45) and missing (n=18); [j]Prior to February 2016, previous or current HCV treatment was an exclusion criteria

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 5.9kPa (IQR 4.7 – 7.7). The majority (68%) had no or mild fibrosis (F0/F1), 12% moderate fibrosis (F2), 6% severe fibrosis (F3), 8% 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%) ($p<0.001$) (Table 2).

In adjusted analysis (Table 2), older age [(36 – 50 years group: aOR, 1.91; 95% CI, 1.19 – 3.080), (≥ 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.

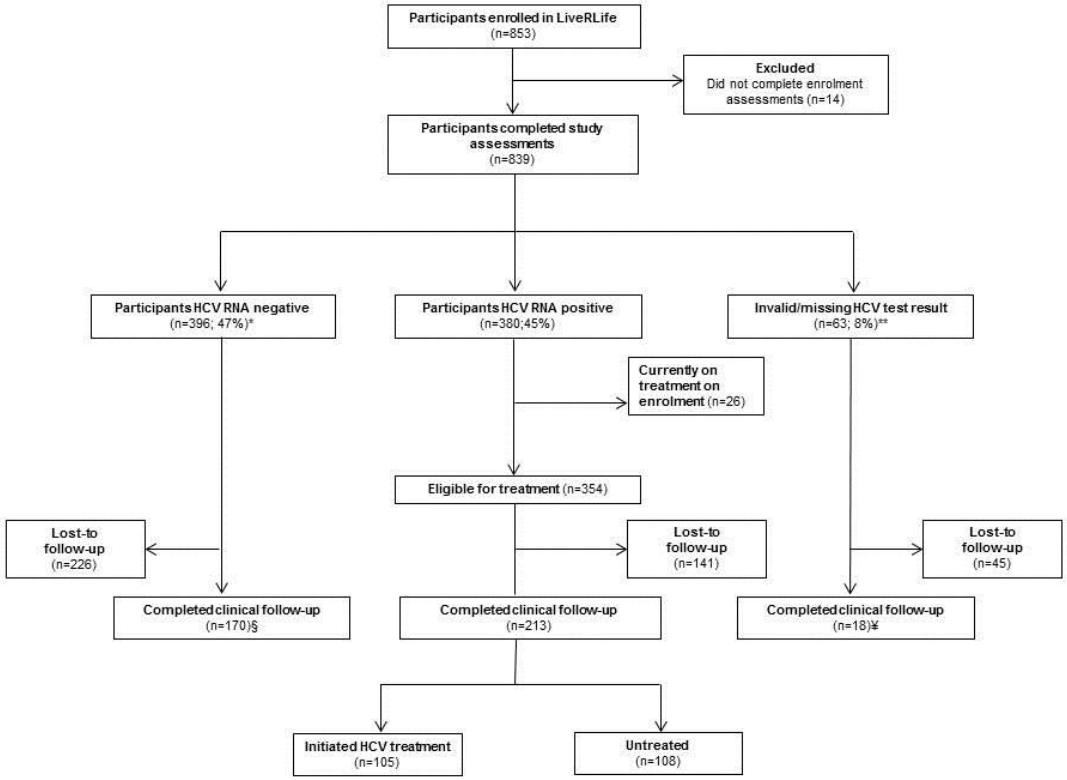

Figure 1. Clinical assessment and treatment uptake among the LiveRLife cohort (n=839)

Note: clinical follow-up includes per-protocol follow-up & 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)

Table 2. Unadjusted and adjusted analyses of factors associated with significant liver fibrosis (F2 – F4) among enrolled participants (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 years	30 (16%)	1.00		1.00	
36 – 50 years	116 (29%)	2.07 (1.32, 3.2)	**0.001**	1.91 (1.19, 3.08)	**0.007**
≥51 years	76 (38%)	3.10 (1.91, 5.02)	**<0.001**	3.17 (1.87, 5.34)	**<0.001**
Sex[c]					
Male	156 (29%)	1.00		1.00	
Female	61 (25%)	0.80 (0.57, 1.13)	0.208	0.86 (0.59, 1.25)	0.421
Aboriginal/Torres Strait Islander[c]					
No	172 (29%)	1.00		1.00	
Yes	45 (26%)	0.85 (0.58, 1.24)	0.394	1.00 (0.66, 1.51)	0.992
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)	0.304	0.81 (0.57, 1.15)	0.231
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)	0.459	0.97 (0.62, 1.49)	0.874
High risk male/female	61 (23%)	0.66 (0.46, 0.96)	**0.029**	0.71 (0.48, 1.05)	0.087
Body Mass Index (Kg/m^2)					
<30	143 (25%)	1.00		1.00	
≥30	58 (41%)	2.13 (1.45, 3.14)	**<0.001**	2.51 (1.66, 3.81)	**<0.001**
Missing	21 (28%)	1.15 (0.67, 1.97)	0.608	1.49 (0.83,2.68)	0.184
HCV RNA results					
Negative	71 (19%)	1.00		1.00	
Positive	137 (38%)	2.58 (1.84, 3.60)	**<0.001**	2.79 (1.95, 3.99)	**<0.001**
Missing/Invalid result	14 (24%)	1.31 (0.68, 2.52)	0.418	1.64 (0.82, 3.28)	0.161

[a]Participants missing/invalid FibroScan score (n=49); [b] Participants missing demographic survey and transgender excluded from AUDIT-C survey (n=26); [c]Participants missing demographic survey (n=18); [d]Transgender excluded from Audit-C as studies validated cut-off in males and females (n=8)

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 (Supplementary Table 2). 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 (Supplementary Table 3).

Among 839 participants who competed 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) (Supplementary Table 4).

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 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).

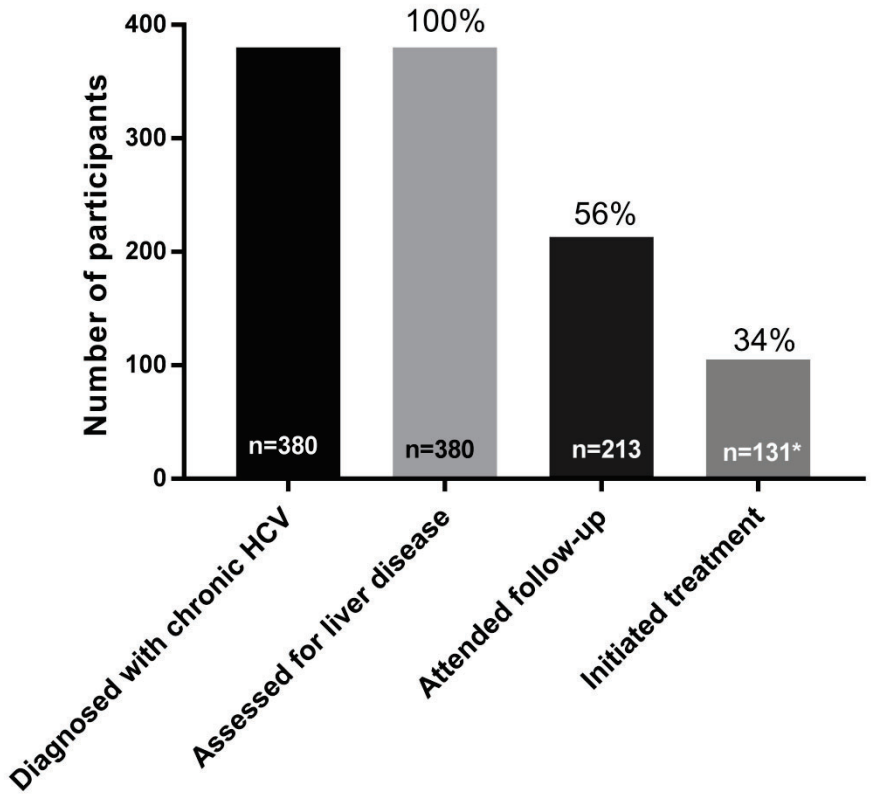

Figure 2. Cascade of HCV care among participants with HCV infection in the LiveRLife study

*Includes already on treatment at enrolment (n=26)

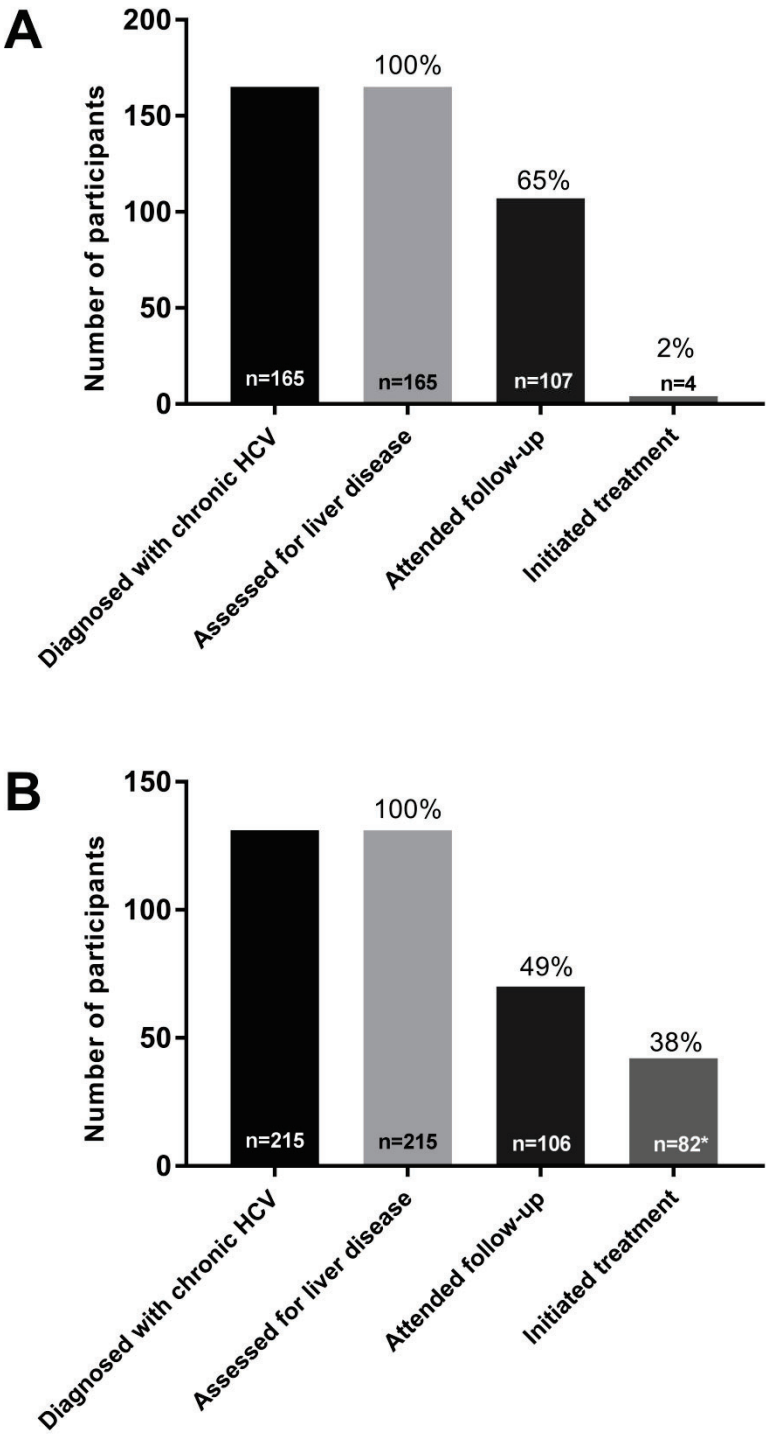

Figure 3. Pre- and post-universal DAA access cascade of HCV care among participants with HCV infection with 12 months of follow-up time to treatment uptake

A: Among participants enrolled prior to the availability of subsidised DAA treatment in March 2016 (i.e. pre-DAA era); B: Among participants enrolled after the availability of subsidised DAA treatment in March 2016 (i.e. DAA era); *Includes already on treatment at enrolment (n=26)

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 treatment are summarised in Supplementary Table 5. 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) were associated with HCV treatment uptake (Supplementary Table 6).

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 years	15 (22%)	1.00		1.00	
36 – 50 years	55 (28%)	1.39 (0.72, 2.67)	0.325	2.03 (0.92, 4.49)	0.082
≥51 years	32 (36%)	2.02 (0.98, 4.14)	**0.056**	2.88 (1.18, 7.04)	**0.020**
Sex[d]					
Male	77 (31%)	1.00		1.00	
Female	22 (23%)	0.67 (0.39, 1.16)	0.150	0.63 (0.33, 1.21)	0.168
Aboriginal/Torres Strait Islander[d]					
No	86 (31%)	1.00		1.00	
Yes	13 (21%)	0.59 (0.30, 1.14)	0.114	0.74 (0.34, 1.59)	0.435
Housing[d]					
Stable	68 (30%)	1.00		1.00	
Unstable	31 (27%)	0.87 (0.53, 1.43)	0.580	1.38 (0.74, 2.56)	0.312
Completed high school or higher education[d]					
No	67 (28%)	1.00		1.00	
Yes	32 (32%)	1.21 (0.73, 2.01)	0.457	1.02 (0.55, 1.91)	0.951
Incarceration[d]					
Never	34 (35%)	1.00		1.00	
Yes	65 (26%)	0.65 (0.39, 1.08)	0.096	0.72 (0.39, 1.34)	0.305
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)	0.077	0.69 (0.37, 1.29)	0.248
Current OST[d]					
No	24 (28%)	1.00		1.00	
Yes	75 (29%)	1.04 (0.60, 1.79)	0.883	0.83 (0.40, 1.71)	0.614
Alcohol consumption (AUDIT-C)[e]					
Never	45 (29%)	1.00		1.00	

Low risk male/female	16 (26%)	0.85 (0.44, 1.66)	0.633	0.62 (0.28, 1.36)	0.235
High risk male/female	38 (31%)	1.11 (0.66, 1.85)	0.703	1.32 (0.70, 2.49)	0.386
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)	0.453	1.09 (0.60, 1.96)	0.781
Missing/invalid result	4 (24%)	0.80 (0.25, 2.54)	0.700	0.86 (0.23, 3.20)	0.819
Clinical follow-up attendance					
None	28 (17%)	1.00		1.00	
Nurse follow-up	42 (35%)	2.71 (1.56, 4.71)	**<0.001**	3.19 (1.61, 6.32)	**0.001**
Physician follow-up	27 (59%)	7.16 (3.51, 14.60)	**<0.001**	11.83 (4.89, 28.59)	**<0.001**
Both nurse/physician follow-up	5 (31%)	2.29 (0.74, 7.10)	0.152	3.19 (0.89, 11.47)	0.076

[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 (studies validated cut-off in males and females) (treatment uptake n=99)

5.5 Discussion

Among a highly marginalised 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 non-invasive liver disease assessment initiative identified 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 characterise liver disease burden, including among those with and without HCV infection.

In evaluation of linkage to care, a suboptimal proportion of participants (45%) returned for clinical assessment 2 – 12 weeks following baseline assessment. 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.[237] In a national surveillance study of PWID

attending needle and syringe programs, 41% of the current PWID population had received DAA treatment.[427]

Barriers to HCV care, including individual, provider and structural factors,[214, 280] continue in the DAA era.[282] 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 side-effects and adverse treatment outcomes remain.[277, 281, 282, 297] Even in settings where HCV testing uptake is high, poor knowledge among PWID about the effectiveness of DAA treatment has been documented.[282, 428] 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.[211, 282] Further, many PWID report persistent feelings of being stigmatised by health providers and being undeserving of treatment (particularly due to high DAA cost) and perceived lack of referral and treatment.[282] 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 characterisation 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[141, 145, 429] and obesity.[151] PWID are generally exposed to HCV early in their injecting careers,[120] 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.[145, 429] Our findings are comparable in terms of prevalence of significant fibrosis among community-based PWID HCV populations in Australia[222, 430] and the United States[431], but lower than those reported in PWID in India[432] and Portugal.[433] Half of the Indian cohort with chronic HCV had severe fibrosis and a third had cirrhosis.[432] 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).[432] Similarly, in the Portuguese sample with chronic HCV, a third had cirrhosis, and HIV coinfection was common (16%) and associated with more advanced liver disease.[433] 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 -uninfected populations is an important finding. Ageing PWID populations are driving accelerating liver disease burden through high HCV prevalence,[10, 85, 89] but may also be at risk of progressive liver disease through chronic conditions such as type-2 diabetes and fatty liver disease. Further characterisations 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 optimise the cascade of HCV of care among PWID are lacking.[379] The LiveRLife screening strategy may be effective in enhancing HCV testing and liver disease staging, however, the drop-off in the HCV care cascade, 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, 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]

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. 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 is also potentially subject to social desirability bias however this was minimised by the use of self-administered surveys on computer tablets.[393]

The LiveRLife study has demonstrated a marked increase in HCV treatment uptake in the DAA era and characterised 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.[277] Further innovation, in relation to both screening strategies and HCV therapeutic interventions are required to advance HCV elimination efforts among PWID.

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Declaration of interests

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5.6 Supplementary material

Supplementary Table 1. Participant enrolment, HCV infection prevalence and treatment uptake by site

Sites (n=16)	Location (State)	Year of enrolment	Screened n (%)	HCV RNA prevalence n (%)	Treatment uptake n (%)**	Treatment uptake within 12 months of screening n (%)**
Drug and alcohol clinics (n=12)						
Newcastle Pharmacotherapy Service	NSW	2014	74 (9%)	53 (72%)	16 (30%)	3 (6%)
Coffs Harbour Drug and Alcohol Service	NSW	2014	58 (7%)	34 (59%)	17 (50%)	1 (3%)
Campbelltown Drug Health Service	NSW	2016	35 (4%)	18 (51%)	6 (33%)	6 (33%)
Alcohol Tobacco & Other Drugs Services	QLD	2016	21 (3%)	7 (33%)	6 (86%)	6 (86%)
Rankin Court Treatment Centre	NSW	2016	40 (5%)	24 (60%)	15 (63%)	15 (63%)
Biala Alcohol & Drug Service	QLD	2016	50 (6%)	26 (52%)	8 (31%)	8 (31%)
Drug and Alcohol Services South Australia	SA	2016	33 (4%)	19 (58%)	10 (53%)	10 (53%)
Bayside Alcohol and Drug Service	QLD	2017	44 (5%)	17 (39%)	9 (53%)	9 (53%)
Gateway clinic Nepean Hospital	NSW	2017	52 (6%)	20 (38%)	4 (20%)	4 (20%)
Royal Prince Alfred Hospital OST clinic	NSW	2018	49 (6%)	13 (27%)	3 (23%)	3 (23%)
Fleet Street Opioid Treatment Services	NSW	2018	58 (7%)	18 (31%)	6 (33%)	6 (33%
Blacktown OST clinic	NSW	2018	58 (7%)	14 (24%)	6 (43%)	6 (43%)
Needle syringe program (n=1)						
Youthlink	QLD	2016	41 (5%)	9 (22%)	6 (67%)	6 (67%)
Medically supervised injecting centre (n=1)	NSW	2014, 2017	126 (15%)	60 (48%)	8 (13%)	3 (5%)
Community health clinic (n=1)						
Kirketon Road Centre	NSW	2014	65 (8%)	46 (71%)	11 (24%)	0 (0%)
Aboriginal medical service (n=1)						
Orange Aboriginal medical Service	NSW	2017	35 (4%)	2 (6%)	0 (0%)	0 (0%)

Total	839 (101%)*	380	131	86

*Percentage more than 100% due to rounding; **Includes already on treatment at enrolment (n=26)

Supplementary Table 2. Unadjusted and adjusted analyses of factors associated with significant liver fibrosis (F2 – F4) among participants with detectable HCV RNA (n=361)[a]

	Significant liver fibrosis (F2 – F4; n=137), n (%)	Unadjusted Model		Adjusted Model[b]	
		OR (95% CI)	*P*	aOR (95% CI)	*P*
Age					
18 – 35 years	19 (26%)	1.00		1.00	
36 – 50 years	78 (39%)	1.83 (1.01, 3.32)	**0.046**	1.89 (1.00, 3.54)	0.049
≥51 years	40 (45%)	2.32 (1.19, 4.53)	**0.014**	2.43 (1.19, 4.97)	**0.015**
Sex[c]					
Male	98 (38%)	1.00		1.00	
Female	36 (37%)	0.93 (0.57, 1.51)	0.769	0.87 (0.52, 1.45)	0.593
Aboriginal/Torres Strait Islander[c]					
No	107 (37%)	1.00		1.00	
Yes	27 (40%)	1.13 (0.66, 1.95)	0.661	1.20 (0.68, 2.14)	0.527
Recent injecting drug use[c]					
Not in previous month	45 (41%)	1.00		1.00	
Injecting in previous month	89 (37%)	0.83 (0.53, 1.32)	0.443	0.85 (0.53, 1.37)	0.505
Alcohol consumption (AUDIT-C) [c,d]					
Never	69 (44%)	1.00		1.00	
Low risk male/female	24 (34%)	0.67 (0.37, 1.20)	0.173	0.72 (0.40, 1.33)	0.296
High risk male/female	39 (32%)	0.60 (0.37, 0.98)	0.042	0.70 (0.42, 1.16)	0.164
Body Mass Index (Kg/m^2)					
<30	93 (35%)	1.00		1.00	
≥30	30 (49%)	1.83 (1.04, 3.21)	**0.035**	1.89 (1.06, 3.39)	**0.031**
Missing	14 (45%)	1.56 (0.74, 3.30)	0.247	1.94 (0.87, 4.32)	0.107

[a]Participants missing/invalid FibroScan score (n=19); [b]Participants missing demographic survey and transgender excluded from AUDIT-C (n=12); [c]Participants missing demographic survey (n=8; denominator=353); [d]Transgender excluded from AUDIT-C (n=4)

Supplementary Table 3. Unadjusted and adjusted analyses of factors associated with significant liver fibrosis (F2 – F4) among participants with undetectable HCV RNA (n=370)[a]

	Significant liver fibrosis (F2 – F4; n=71), n (%)	Unadjusted Model		Adjusted Model[b]	
		OR (95% CI)	*P*	aOR (95% CI)	*P*
Age					
18 – 35 years	8 (9%)	1.00		1.00	
36 – 50 years	31 (17%)	2.20 (0.97, 5.00)	0.060	2.22 (0.94, 5.24)	0.068
≥51 years	32 (32%)	5.01 (2.17, 11.60)	**<0.001**	5.65 (2.31, 13.82)	**<0.001**
Sex[c]					
Male	45 (20%)	1.00		1.00	
Female	24 (18%)	0.75 (0.40, 1.40)	0.367	0.97 (0.53, 1.76)	0.919
Aboriginal/Torres Strait Islander[c]					
No	54 (20%)	1.00		1.00	
Yes	15 (16%)	0.75 (0.40, 1.40)	0.367	0.96 (0.48, 1.90)	0.896
Recent injecting drug use[c]					
Not in previous month	30 (23%)	1.00		1.00	
Injecting in previous month	39 (17%)	0.71 (0.42, 1.21)	0.205	0.72 (0.40, 1.28)	0.265
Risk of alcohol consumption (AUDIT-C) [c,d]					
Never	32 (20%)	1.00		1.00	
Low risk male/female	20 (24%)	1.30 (0.69, 2.45)	0.418	1.54 (0.78, 3.04)	0.214
High risk male/female	16 (14%)	0.68 (0.35, 1.30)	0.240	0.71 (0.35, 1.42)	0.331
Body Mass Index (Kg/m^2)					
<30	41 (16%)	1.00		1.00	
≥30	24 (36%)	3.01 (1.65, 5.48)	**<0.001**	3.68 (1.91, 7.07)	**<0.001**
Missing	6 (15%)	0.92 (0.37, 2.34)	0.867	0.94 (0.33, 2.67)	0.908

[a]Participants missing/invalid FibroScan score (n=26); [b]Participants missing demographic survey and transgender excluded from AUDIT-C (n=); [c]Participants missing demographic survey (n=9; denominator=); [d]Transgender excluded from AUDIT-C (n=2)

Supplementary Table 4. Outcome of nurse or physician clinical assessments on follow-up (n=378)

	Assessed by nurse (n=249); n (%)	Assessed by physician (n=129); n (%)
Recommended for further HCV assessment	181 (73%)	117 (91%)
Recommended to modify alcohol intake	70 (28%)	37 (29%)
Referred for further assessment and treatment of alcohol use disorder	1 (<1%)	3 (2%)
Recommended to modify cannabis use	53 (21%)	26 (20%)
Recommended to reduce weight/referred to dietician	36 (14%)	15 (12%)

Note: participants may have received multiple recommendations

Supplementary Table 5. Genotype, DAA treatment regimen and duration among participants initiating DAA treatment (n=102)

DAA regimen and duration	Genotype 1a (n=38)	Genotype 1b (n=10)	Genotype 2 (n=4)	Genotype 3 (n=45)	Genotype unavailable (n=5)
Sofosbuvir/ledipasvir					
8 weeks	8	1	-	-	-
12 weeks	20	7	-	-	1
Sofosbuvir/daclatasvir					
12 weeks	2	-	1	24	-
16 weeks	-	-	-	1	-
24 weeks*	-	-	-	8	-
Paritaprevir/ritonavir/ombitasvir/dasabuvir					
12 weeks	2	-	-	1	-
Sofosbuvir/velpatasvir					
12 weeks	4	-	-	6	2
Grazoprevir/elbasvir					
8 weeks	-	1	-	-	-
12 weeks	1	-	-	-	-
Sofosbuvir/velpatasvir					
12 weeks	-	-	3	-	-
Data unavailable	1	1	-	5	2

*One participant was treated with sofosbuvir/daclatasvir + ribavirin for 24 weeks

Supplementary Table 6. Unadjusted and adjusted analyses of factors associated with DAA treatment uptake among participants with HCV infection and have injected drugs in the previous six months (n=262)

	Treatment uptake (n=71**), n (%)	Unadjusted model		Adjusted model*§	
		OR (95% CI)	*P*	aOR (95% CI)	*P*
Age					
18 – 35 years	12 (23%)	1.00		1.00	
36 – 50 years	38 (25%)	1.12 (0.53, 2.36)	0.763	1.34 (0.56, 3.23)	0.513
≥51 years	21 (36%)	1.84 (0.78, 4.25)	0.152	2.12 (0.76, 5.88)	0.150
Sex					
Male	56 (29%)	1.00		1.00	
Female	15 (21%)	0.66 (0.35, 1.27)	0.214	0.59 (0.27, 1.26)	0.172
Aboriginal/Torres Strait Islander					
No	62 (29%)	1.00		1.00	
Yes	9 (19%)	0.57 (0.26, 1.24)	0.154	0.66 (0.28, 1.60)	0.362
Housing					
Stable	45 (27%)	1.00		1.00	
Unstable	26 (27%)	0.95 (0.54, 1.68)	0.873	1.40 (0.70, 2.79)	0.338
Completed high school or higher education					
No	48 (26%)	1.00		1.00	
Yes	23 (30%)	1.22 (0.67, 2.19)	0.515	1.16 (0.57, 2.38)	0.681
Incarceration					
Never	22 (33%)	1.00		1.00	
Yes	49 (25%)	0.69 (0.38, 1.26)	0.222	0.67 (0.33, 1.37)	0.270
Current OST					
No	22 (29%)	1.00		1.00	
Yes	49 (26%)	0.90 (0.50, 1.63)	0.729	0.81 (0.37, 1.76)	0.589
Alcohol consumption (AUDIT-C) [a]					
Never	32 (28%)	1.00		1.00	
Low risk male/female	11 (23%)	0.77 (0.35, 1.70)	0.524	0.61 (0.24, 1.55)	0.299
High risk male/female	28 (29%)	1.01 (0.56, 1.84)	0.968	1.12 (0.54, 2.34)	0.759
FibroScan® Liver disease stage					

No/mild fibrosis (F0/F1)	45 (28%)	1.00		1.00	
Significant liver fibrosis (F2 – F4)	24 (27%)	0.95 (0.53, 1.70)	0.872	1.02 (0.52, 2.01)	0.958
Missing/invalid result	2 (22%)	0.75 (0.15, 3.74)	0.725	0.72 (0.12, 4.41)	0.725
Clinical follow-up attendance					
None	20 (16%)	1.00		1.00	
Nurse follow-up	28 (30%)	2.21 (1.15, 4.23)	0.017	2.32 (1.09, 4.91)	0.028
Physician follow-up	19 (56%)	6.59 (2.87, 15.09)	<0.001	7.78 (2.95, 20.47)	<0.001
Both nurse/physician follow-up	4 (40%)	3.47 (0.90, 13.41)	0.072	3.21 (0.67, 15.40)	0.145

*Denominator = 258; **Participants already on treatment at enrolment excluded (n=26); [§]Random effects logistic regression model employed to take into account heterogeneity of treatment uptake across sites; [a]Denominator = 258 due to exclusion of transgender as studies validated cut-off in males and females (treatment uptake n=71)

Chapter 6: Thesis discussion

The overarching aim of the research presented in this thesis was to investigate the feasibility and outcomes of strategies to increase HCV testing, linkage to care and treatment uptake in high-risk populations (PWID and people who are homeless) during a period of transition in the clinical management of chronic HCV infection from interferon-based therapy to DAA treatment. There were four specific objectives, which included describing the outcomes along the HCV care cascade among PWID and people who are homeless. In this chapter, the key findings of the research are summarised with respect to the four objectives and related hypotheses. The implications of the findings, directions for future research and thesis strengths and limitations are also discussed.

6.1 Key findings

Objective 1: To systematically evaluate the effectiveness of interventions to enhance HCV testing, linkage to care, and treatment uptake among PWID

Objective 1 is addressed in Chapter 2.

A systematic review of the literature was undertaken to evaluate the effectiveness of interventions to improve the care cascade for HCV infection among PWID. Bibliographic databases of literature were searched for interventional, comparator studies published before 20 July 2016. Studies evaluating the effectiveness of

interventions aimed at improving the engagement of the study population in HCV testing, linkage to care or treatment uptake were included in the analysis. Risk of bias in both randomised and non-randomised studies was assessed, and RR and corresponding 95% CIs were generated for each study outcome included in the analysis.

Fourteen studies met the inclusion criteria and were analysed. Interventions which improved HCV testing included on-site testing with pre-test counselling and education; and DBS testing implemented in drug and alcohol clinics and prisons. Interventions which enhanced linkage to care included facilitated referral for HCV assessment and scheduling of specialist appointments for clients. Interventions which enhanced HCV treatment uptake included integrated HCV care, drug use and psychiatric services delivered by a multidisciplinary team with case management services, with or without non-invasive liver disease assessment. Interpretation of these evaluations, however, was limited due to the high risk of bias present in these studies, particularly in non-randomised studies. Most studies were small in sample size with high risk of bias due to confounding. There were no studies identified in the context of DAA therapy and none in LMIC. This review underscores a paucity of rigorous comparative studies evaluating interventions to improve the HCV care cascade in this priority population.

Objective 2: To assess the acceptability and preferences of point of care finger-stick whole-blood and venepuncture HCV RNA testing among PWID in Australia

Objective 2 is addressed in Chapter 3.

Acceptability and preferences for HCV RNA testing methods were assessed among PWID participating across 13 sites in the LiveRLife study. Participants completed a questionnaire about the acceptability and preferences for HCV RNA testing methods, time to HCV test results and the reasons for their preferences.

Among 565 participants enrolled in the LiveRLife study between 27 June 2016 and 22 February 2018, 65% reported a preference for finger-stick testing over venepuncture (35%). A greater proportion of females preferred finger-stick testing compared to males (74% vs. 61%, p=0.002). Among those who preferred finger-stick testing (n=366), 61% preferred finger-stick testing with results in 60 minutes, 8% preferred results in 120 minutes, and 31% preferred results in two weeks. Among participants who preferred venepuncture testing (n=199), 37%, 13%, and 50% preferred testing with results in 60 minutes, 120 minutes, and two weeks, respectively. The reason for preferring finger-stick testing over venepuncture in 62% of participants was that it was quick, followed by venous access difficulties (21%). In adjusted analyses, among people injecting drugs in the previous month, females were twice as likely to prefer finger-stick over venepuncture compared to males (aOR 1.92; 95% CI 1.11, 3.30; p=0.019), and Aboriginal and/or Torres Strait Islanders were less likely to prefer finger-stick over venepuncture compared to non-Aboriginal participants (aOR 0.57; 95% CI 0.34, 0.9; p=value 0.033). The high acceptability of finger-stick testing warrants further

investigation of simplified HCV testing algorithms facilitating single visit HCV diagnosis and potential same day initiation of DAA therapy.

Objective 3: To assess HCV RNA prevalence, liver disease burden, linkage to care and treatment uptake and outcomes among people attending homelessness service in Sydney, Australia

Objective 3 is addressed in Chapter 4.

Outcomes along the HCV care cascade among people attending a homelessness service in Sydney participating in the LiverRLife study were evaluated. Participants provided finger-stick whole-blood samples for Xpert® HCV Viral Load assay and venepuncture samples for HCV testing. Participants completed self-administered socio-demographic and drug use survey, and received transient elastography for liver disease staging. Treatment uptake and outcomes data were retrospectively collected.

Among the 202 participants enrolled in the LiveRLife homelessness sub-study, the prevalence of active HCV infection was high (23%). Among those with liver disease assessment (n=201), 6% had cirrhosis (11% in those with active HCV infection). Active HCV infection was prevalent among participants with either injecting or incarceration history (35%; 37/105), compared to a prevalence of 4% (3/73) among participants

without these risk factors. Among participants with detectable HCV RNA, 62% (n=29) attended a clinical follow-up visit and 49% (n=23) commenced DAA therapy, while 18 (38%) were lost to follow-up. Among participants initiating treatment, 65% had a documented SVR12, and the remainder did not have a documented treatment outcome. There were no documented cases of virological failure. HCV treatment uptake in the DAA era among this highly marginalised population was encouraging.

Objective 4: To a) describe the HCV care cascade 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) identify factors independently associated with significant liver fibrosis; c) examine HCV treatment uptake in the pre-DAA and DAA eras, and determine factors independently associated with DAA treatment uptake.

Objective 4 is addressed in Chapter 5.

The LiveRLife study is an observational cohort study evaluating an intervention integrating a liver health promotion campaign and non-invasive liver fibrosis assessment with linkage to care and treatment among people with a history of injection drug use. Participants were recruited from 16 sites in Australia between 12 August 2014 and 22 February 2018. At enrolment, participants provided finger-stick whole-blood sample for Xpert® Viral Load assay and venepuncture samples for HCV RNA testing.

Participants completed self-administered socio-demographic and drug use survey, and received transient elastography for liver fibrosis assessment. Clinical follow-up and treatment uptake data were retrospectively collected.

Among the 839 participants enrolled in the study, 45% (n=380) had detectable HCV RNA, consistent with active infection. All participants were assessed for liver fibrosis and 8% had cirrhosis. As expected, significant liver fibrosis (F2 – F4) was more common in participants with HCV infection (38%) compared to those without (19%) ($p<0.001$). Among participants with active HCV infection, 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. HCV treatment uptake increased considerably from 2% in the interferon era to 38% in the DAA era.

6.2 Implications of thesis findings

The advent of highly effective (>95% cure rates), all-oral, short duration, well-tolerated DAA therapy has provided an unprecedented opportunity and galvanised efforts to reverse the burden of HCV infection worldwide. PWID are a key population in endeavours to eliminate HCV infection as a public health threat by 2030. Elimination efforts fundamentally rely on increased HCV testing and diagnosis, linkage to care and treatment uptake rates. To this end, findings from this thesis highlight ongoing and

critical gaps in the HCV care cascade among PWID and people who are homeless in the DAA era.

Despite the optimism generated with the introduction of DAA therapies, findings from Chapter 2 highlight the paucity of well-designed comparative studies (including RCTs) evaluating interventions to enhance the HCV care cascade among clearly-specified populations of PWID. In addition, as evident from results in Chapter 3, the acceptability and preferences for interventions of PWID are crucial to engaging individuals in the HCV care cascade. Finally, as demonstrated in Chapters 4 and 5, HCV treatment uptake among marginalised high-risk populations has dramatically increased in the DAA era; however, significant gaps in diagnosis, linkage to care and treatment uptake persist. Collectively, evidence generated by the studies in this thesis highlights an urgent need for novel and acceptable interventions that address the social and structural challenges in engaging and retaining marginalised populations along the HCV care cascade. Moreover, these interventions should be aimed at engaging marginalised individuals into a simplified 'test and treat' HCV care cascade in order to optimise outcomes at both the clinical- and population-levels.

Evidence derived from Chapter 2 indicated successful interventions targeted at improving HCV testing, linkage to care and treatment uptake and outcomes in the interferon era included the integration and co-location of HCV care within primary healthcare services tailored to PWID, such as OST clinics and community-based mental health services. While other effective interventions have been described in the literature

including peer-led outreach testing and linkage to care, rapid HCV antibody testing in mobile clinics and low-threshold, interpretations of their impact were limited due their non-comparator, uncontrolled study design.

In the DAA era, the integration and co-location of services within OST clinics and community-based drug user health services will continue to be an important strategy and requires further scale-up. Further, emerging studies describing DAA treatment outcomes evaluating the integration of HCV testing and treatment services within services for homeless people with dedicated multidisciplinary teams and frequent monitoring demonstrate improved treatment adherence and SVR.[434, 435] Features of these models of care include weekly calls from care coordinators, follow-up appointments during treatment and SVR12.

Furthermore, expansion of HCV services could include effective outreach models of care that engage 'harder to reach' populations (including non-opioid dependent PWID) that do not access traditional services. Recent qualitative research by Coupland et al., suggests that community-based outreach could be an effective strategy in engaging and retaining people diagnosed with HCV infection in the HCV care cascade.[277] Findings from this study identified key factors facilitating acceptability of this model of care included privacy and discretion and establishing rapport and trust with non-judgemental care providers, especially important in engaging PWID who have not been tested for HCV before.[277] The requirement of more than one-off sessions of post-test counselling was vital for improving knowledge about HCV viral clearance and treatment response,

HCV-related care and treatment.[277] Preference for salient information delivered in a tailored/individualised fashion was an important finding.[277] Associations between poor knowledge and drop-offs along the care cascade have been well-documented in the literature.[136, 266, 410] Community-based outreach models may be particularly impactful among new initiates to injection drug use and those at higher risk of HCV transmission.[277]

Rigorous evaluations of interventions in the DAA era are beginning to emerge. The HepCATT was a non-randomised, comparative pilot study, evaluating the impact of a complex, multi-faceted intervention in three specialist addiction clinics in England on the rate of engagement of HCV-infected PWID with an appropriate treatment pathway and on rates of HCV testing and referral for specialist assessment.[436] The intervention comprised placement of a half-time facilitator undertaking various activities including training of key workers, direct interaction with clients, introduction of DBS testing and streamlining and support for specialist assessment appointments. The study demonstrated that engagement with HCV therapy increased by 31 percent at the intervention sites but decreased at the control sites. In addition, testing, referral and treatment rates in the intervention sites showed increases, with estimated ORs of 3.9, 16 and 21-fold, respectively. In light of restrictions of DAA treatment to people with significant fibrosis, 55 of 89 of the engaged but not treated PWID were classified as 'treatment-ready'. Loss of individuals at each stage of the HCV care cascade was observed, with 65% (159/246) attending a clinic appointment on referral, and 38% (54/143) of the engaged patients treated. The most common reasons for not attending a clinic appointment were being unwilling (n=23), followed by social/life-style mental

issues (n=19). These findings confirm the well-described multiple barriers that PWID continue to experience at the individual, structural and policy levels.

An important barrier to HCV testing and linkage to care among marginalised populations is the complicated HCV diagnostic pathway. Multiple studies have demonstrated the drop-out of individuals between HCV antibody and confirmatory HCV RNA testing and linkage to care.[244, 262, 263] Key factors include the burden of multiple visits to medical practitioners and phlebotomists, length of time to receipt of results (up to 2 weeks for HCV RNA), travelling to off-site phlebotomists, venous access difficulties, and poor knowledge among PWID and medical providers regarding the difference between HCV antibody testing and confirmatory tests of active HCV infection. Point of care HCV RNA testing using finger-stick whole-blood collection providing rapid HCV RNA result has great potential to simplify the care cascade and facilitate same day DAA treatment initiation ie 'test and treat'. The only CE marked assay with high sensitivity and specificity is the Xpert HCV VL Fingerstick assay which provides HCV RNA test result in less than one hour.[381] As demonstrated in Chapter 3, this method of blood collection and time to results was acceptable and preferred to venepuncture among PWID, especially among women. Although Aboriginal and/or Torres Strait islander people were less likely to prefer finger-stick testing than non-Indigenous people, this finding was inconsistent with previous glycaemic index point of care monitoring studies in Aboriginal Community Controlled Health Services. Further quantitative and qualitative evaluations are required to assess feasibility and acceptability of simplified HCV models of care among Aboriginal and/or Torres Strait Islander Australians.

Findings presented in Chapters 4 and 5 indicated that enhanced screening (through the LiveRLife project) and unrestricted, subsidised access to DAA therapies have substantially increased HCV treatment uptake among marginalised populations in Australia. These results broadly mirror treatment uptake in the overall Australian HCV population pre- and post-DAA access.[88, 235, 263] Although Australia observed a dramatic treatment uptake in the first few months following PBS subsidy of DAA therapy, uptake has since declined (Figure 1). A total of 66,550 people initiated treatment between March 2016 and September 2018, representing treatment uptake of approximately 30% of the chronic HV population in 2015 (~ 68,193). Australia is an enviable position because of its policy of unrestricted access to DAA therapy, and is considered 'on-track' for HCV elimination. Modelling studies have suggested that around 14,000 people need to be treated each year in order for Australia to stay on track to eliminate HCV.[167] The findings of this study highlight the need for continuing and renewed efforts to screen high-risk populations, in particular 'harder to reach' groups such as people who are homeless or in prison.

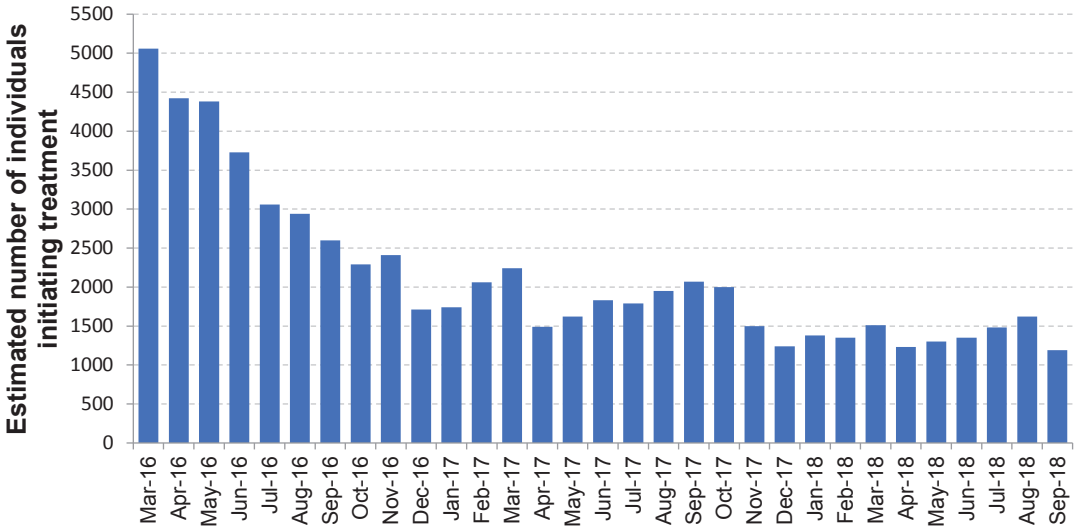

Figure 1: Monthly number of individuals initiating DAA treatment in Australia

Australia is considered an international leader in the HCV response, and although suboptimal, results from this thesis are encouraging in relation to treatment uptake among marginalised populations. DAA therapy uptake among PWID in Canada[437] and USA[272] has been more limited. Low treatment uptake among PWID[272] and the general population[438] (~10%) in the US is most likely driven by healthcare payer restrictions, including liver disease stage-based, and in some jurisdictions, drug/alcohol use. [439] Similarly, in Canada treatment uptake (~16%) is low among PWID, although those with HIV co-infection, on antiretroviral therapy, and with advanced liver disease were more likely to be prescribed DAA treatment.[437] Consistent with other studies, older people and those linked to HCV care (attending clinical follow-up) were more likely to initiate treatment.[300, 437]

Findings from the characterisation of liver disease burden among community-based PWID (Chapter 5) provided important additions to the literature. This research provided strong evidence for the association of older age and significant fibrosis among PWID, reflective of the 'ageing cohort' effect, and HCV infection as a key driver of significant fibrosis. Older age and obesity were also associated with significant fibrosis in both infected and uninfected participants, further highlighting the need for holistic strategies that address other co-morbidities, as well as unmet needs and competing priorities among PWID.

6.3 Directions for future research

The advent of HCV DAA therapy has provided the foundation and impetus for HCV elimination, but evidence-based holistic models of care that address the structural and social barriers to care among highly marginalised populations are needed to achieve elimination goals. Moreover, new evidence needs to be generated in the context of unrestricted access to DAA therapy. Findings from this thesis suggest several directions for future research in efforts to improve the quality of life of people with HCV and achieve HCV elimination by 2030.

First, as described in Chapter 1, PWID are a highly heterogeneous population in relation to recency and frequency of drug injection, opioid dependency and OST, and injection risk behaviours. Further, incarceration and homelessness are commonly experienced by PWID, adding a layer of complexity to public health intervention design and

implementation. Given the limitations in the data in the literature on the natural history of injection drug use, transitions of PWID between homelessness and incarceration, and severe stigma associated with injection drug use, definitions and size estimates of PWID populations have been limited and sub-optimally applied in HCV studies. Further, there is a critical gap in estimates of active HCV infection in PWID populations in many settings due to the lack of surveillance data (including reliance on antibody-based data) among PWID within countries. As such, further research is needed to better estimate population size and to better define and characterise sub-populations of PWID. This will require the implementation of robust surveillance systems and the creation of enabling environments which engage 'hard to reach' populations without stigma and discrimination.

Second, future research needs to evaluate the impact of simplified models of care on engaging PWID in the HCV care cascade, including single-visit 'test and treat' strategies which provide a rapid HCV RNA test allowing for same day diagnosis and DAA treatment initiation. This model of care holds great promise particularly among 'harder to engage' PWID groups, people who are incarcerated and people who are homeless. In addition, such models of care should allow expansion of testing and treatment in decentralised settings such as OST clinics, community health centres, prisons, NSPs and mobile outreach services. Currently, the only CE marked commercially available point of care HCV RNA assay with high sensitivity and specificity is the Xpert® HCV VL Fingerstick which utilises a finger-stick whole-blood sample and delivers a result in under an hour. As evident from findings in Chapter 3,

finger-stick whole-blood collection for HCV RNA testing and the receipt of same day results is acceptable among PWID.

Australia is in an ideal position to evaluate simplified models of care given features of the national HCV strategy including unrestricted and subsidised access to DAA treatment, broad prescriber type (e.g., general practitioners and approved nurse practitioners) and existing infrastructure for the provision of OST and NSP services. The removal of mandatory requirement for pre-treatment HCV genotype is likely in 2019, and will further simplify the management of HCV infection and facilitate same day treatment initiation. Genotype testing may remain important for monitoring patient outcomes, including reinfection, and for surveillance. The LiveRLife study has informed the design of a number of studies evaluating simplified models of care. The TEMPO (NCT03492112) study is a non-randomised controlled study which will evaluate the impact of finger-stick HCV testing/diagnosis and same day initiation of sofosbuvir/velpatasvir or glecaprevir/pibrentasvir, and peer-based support on diagnosis, linkage to care and treatment uptake among PWID attending NSPs. NSPs provide a unique opportunity to engage 'harder to reach' populations, particularly those who do not access OST services and who are not opioid-dependent. Additionally, the AMPLIFY study is an innovative cluster randomised controlled trial of the same model of care recruiting people with recent injecting drug use or in receipt of OST attending drug and alcohol clinics. The primary endpoint will be the proportion of HCV RNA positive PWID initiating treatment by 12 weeks after enrolment.

Third, further research and the development of rapid, reliable and accurate HCV RNA diagnostic assays which provide test results in shorter timeframes are needed to scale-up screening, and potentially facilitate 'test and treat' interventions. The prices of diagnostics will also need to be lowered, particularly for LMIC where the majority of the world's HCV burden lies. In fact, in some LMIC, the prices of HCV diagnostics now exceed the prices of DAAs.[260] Further, fast track quality assurance efforts and WHO prequalification in countries will be required to facilitate scale-up in a timely-manner.

Another novel intervention which requires further evaluation is offering self-testing to PWID. HIV self-testing was first reported in the early 2000s among health workers in Sub-Saharan Africa, primarily due to concerns about confidentiality and privacy.[370] Self-testing is 'a process in which an individual, who wants to know his or her status collects a specimen, performs a test and interprets the result themselves in private'.[370] The other utility of self-testing is the opportunity to self-collect a specimen (e.g. finger-stick on DBS) which is then sent to a laboratory for testing. A reactive self-test requires a confirmatory diagnostic test and counselling. The advantage of a home self-testing strategy is that it provides the opportunity to test discreetly and conveniently, thereby increasing testing uptake among people who do not access traditional services and those who are hard to reach or reside in remote settings. PWID are particularly concerned about confidentiality, stigma and discrimination and self-testing provides a novel avenue to expand HCV testing services and linkage to care to 'hard to reach' populations who not access services, and those who may have never been tested before.[440-442]

Although the available literature on the acceptability and effectiveness of HIV self-testing is favourable,[443] knowledge of the effectiveness of this intervention and its potential acceptability among PWID testing for HCV is limited, and future feasibility evaluations are needed. Results from an acceptability study among PWID in the United Kingdom demonstrated advantages and disadvantages related to remote HCV self-testing.[442] The study indicated that choice, control and privacy were perceived of as advantages of remote self-testing. Further evaluation of simple, accurate HCV self-testing diagnostic interventions (using oral fluids or DBS) for first time tester or for monitoring reinfection among PWID are needed in Australia and in other countries.

There is some evidence from studies in the HIV and HBV fields of the effectiveness for incentives in encouraging the uptake of interventions in various populations including PWID. For example, a randomised controlled trial by Topp et al., investigated the effectiveness of financial incentives in increasing completion of an accelerated 3-dose HBV vaccination schedule among PWID.[444] In an ITT analysis, the study demonstrated that participants receiving cash incentives were significantly more likely to receive all three doses. Behavioural economic models of conditional cash transfers integrated into simplified models of care could potentially be effective in improving HCV treatment uptake among marginalised populations, including PWID.

Finally, while models of care to enhance the care cascade among prisoners are outside the scope of this thesis, it is worthy of mention given the relationship between injection

drug use, incarceration and homelessness. Further work is needed to scale-up HCV cascade of care interventions in people who are incarcerated and people who are homeless. It is estimated that around 30% of prisoners are chronically infected with HCV, and almost half of all prisoners report lifetime injection drug use.[445] At this point in time there is limited data on DAA treatment uptake among prisoners in Australia. The STOP-C (Surveillance and Treatment of Prisoners with Hepatitis C) project (NCT02064049) is currently evaluating the feasibility and impact of a rapid scale-up of DAA therapy as a treatment as prevention strategy, enrolling prisoners from four prisons within NSW. Results of this study will be crucial in informing future HCV care cascade research in this vulnerable population.

6.4 Thesis limitations and strengths

There are a number of strengths to the research presented in this thesis. First, the findings contribute new important knowledge on the effectiveness of interventions, outcomes along the HCV care cascade pre- and post-DAA era, and the acceptability of novel HCV diagnostics among a cohort of PWID. The description of the HCV care cascade in people who are homeless in the DAA era is particularly novel; a population that is highly marginalised and has received little attention to date. Second, the LiveRLife project (Chapters 3 and 5) recruited a large sample (n=565 and n=853, respectively) of people with histories of injection drug use from a variety of drug user health services across 16 sites from three states in Australia (NSW, QLD, and SA). Third, the large sample size provided the statistical power to evaluate factors associated with preference of finger-stick testing, significant liver fibrosis, and DAA treatment

uptake among PWID. Further, the sample size allowed for robust full models by including the important predictors. Characterisation of liver disease in community-based PWID with and without HCV infection provides important new data. Fourth, PWID and people who are homeless populations were clearly-defined and allowed for the characterisations of community-based cohorts (OST, incarceration histories) which adds significant knowledge to the literature and informs future research. Finally, participant surveys were self-administered on computer tablets which likely minimised social desirability bias.

Chapter 2 provided a comprehensive systematic review of the literature globally of interventions and identified significant gaps in strategies to enhance the care cascade in PWID. Although pooled estimates were not possible, RRs were generated for outcomes and were utilised to inform future research directions. However, due to the small number of studies retrieved and the heterogeneous nature of interventions in the systematic review, pooled estimates were unlikely to be informative and therefore not generated. Almost half of all studies were non-randomised and had high risk of bias, limiting the interpretation of the effectiveness of interventions. Also, many comparator groups were 'standard of care' or historical arms, which arguably would yield statistically significant differences but with wide CIs.

In both Chapters 3, 4, and 5, participants were recruited from services that were largely tailored towards PWID (e.g. OST clinics, homelessness service) and are likely engaged in care or motivated. Therefore, our samples may not be generalisable to the broader

population of PWID in Australia or in other countries or those less engaged or further socially excluded. In addition, some participants may have been aware of their HCV diagnosis and were expecting to initiating treatment with the launch of Australian Government subsidy of DAAs. The small sample size in Chapter 4 limited the ability to perform evaluation of factors associated with treatment uptake. Nonetheless, descriptive statistics documenting the prevalence of treatment uptake by various characteristics were informative. The LiveRLife study was designed prior to the roll-out of unrestricted and subsidised access to DAA therapies and was focused on diagnosis and linkage to care. In addition, given the non-comparator and uncontrolled design, the specific impact of this intervention could not be evaluated.

6.5 Conclusion

The introduction of DAA therapy has transformed the clinical management of HCV infection and given impetus to the WHO goal of eliminating HCV infection as a public health threat by 2030. Although DAA therapy has provided the tools to achieve this, HCV elimination is contingent on substantially increasing the number of people tested, diagnosed, linked to care and treated. Improving the HCV care cascade among marginalised high-risk populations of PWID and people who are homeless is paramount in these efforts. This thesis calls for the development of evidence-based, acceptable and novel interventions that address the social, structural and policy-related barriers to care in order to enhance the HCV care cascade among marginalised populations. The future direction of such interventions should include simplified, affordable and reliable 'test and treat' models of care in a variety of settings, including custodial settings, services

for homeless people and community-based outreach. The success of these interventions hinges on providing effective drug user health services, including OST and NSP, at sufficient coverage and in all settings, without stigma and discrimination. Finally, this thesis calls for renewed and united support from all stakeholders, including policy-makers, community organisations, healthcare professionals and academics in efforts to make HCV elimination a reality.

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