Elimination of hepatitis C virus among people who inject drugs in Australia

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A thesis in fulfilment of the requirements for the degree of

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The Kirby Institute

Faculty of Medicine

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Thesis Title

Elimination of hepatitis C virus among people who inject drugs in Australia

Thesis Abstract

Background: Hepatitis C virus (HCV) is a global public health threat contributing to morbidity and mortality worldwide—particularly among people who inject drugs (PWID). **Aims:** The aim of this research was to assess progress towards HCV elimination among PWID during the direct-acting antiviral therapy (DAA) era. Specific aims included assessing (1) current HCV prevalence among PWID and associated factors (2), treatment uptake among PWID and associated factors, and (3) inpatient hospitalisation as a setting to enhance DAA uptake. **Methods:** In Chapter Two, current HCV and treatment uptake are analysed among PWID attending drug treatment and needle and syringe programs throughout Australia in an observational cohort (the ETHOS Engage Study). Factors associated with current HCV infection and HCV treatment uptake were assessed using logistic regression. In Chapter Three, DAA uptake data from a population-based linkage study covering all people in New South Wales with HCV notification were analysed using logistic regression. In Chapter Four, survival analysis was used to assess population-level DAA uptake by history and characteristics of hospitalisation. In Chapter Five, the change in HCV viremia and treatment uptake among PWID between two recruitment waves was assessed in the ETHOS Engage Study. Logistic regression was used to assess the factors associated with current HCV infection and treatment uptake in the second recruitment wave. **Key Findings:** HCV viraemic prevalence has declined considerably following high DAA uptake among PWID populations in recent years. Despite this success, there remain populations requiring enhanced support. Indicators of higher marginalisation—including homelessness, frequent injection drug use, and frequent hospitalisation—were associated with lower treatment uptake. Among PWID who were hospitalised, treatment uptake was lower among those who had been hospitalised for drug use, injection-related infectious diseases, and mental health disorders. Current HCV infection was associated with markers of higher marginalisation. Between the two ETHOS Engage recruitment waves, we observed a decline in HCV viremia and an increase in treatment; however, gaps remain. **Conclusion:** Public health action is needed to enhance HCV care among marginalised groups of PWID. Innovative and novel interventions—including the utilisation of inpatient hospitalisation—are needed to enhance care. Contribution from multidisciplinary stakeholders is necessary to ensure HCV elimination is equitably reached across all PWID.

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Publication Details #1

Full Title:	Progress towards elimination of hepatitis C infection among people who inject drugs in Australia: The ETHOS Engage Study
Authors:	Heather Valerio, Maryam Alavi, David Silk, Carla Treloar, Marianne Martinello, Andrew Milat, Adrian Dunlop, Jo Holden, Charles Henderson, Janaki Amin, Phillip Read, Philippa Marks, Louisa Degenhardt, Jeremy Hayllar, David Reid, Carla Gorton, Thao Lam, Gregory J Dore, Jason Grebely
Journal or Book Name:	Clinical Infectious Diseases
Volume/Page Numbers:	73/e69-78
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Status:	published
The Candidate's Contribution to the Work:	Data collection, data analysis, interpretation of results, writing manuscript, corresponding author to the journal
Location of the work in the thesis and/or how the work is incorporated in the thesis:	This publication is included in the thesis as Chapter Two.

Publication Details #2

Full Title:	High hepatitis C treatment uptake among people with recent drug dependence in New South Wales, Australia
Authors:	Heather Valerio, Maryam Alavi, Matthew Law, Shane Tillakeratne, Janaki Amin, Naveed Z Janjua, Mel Krajden, Jacob George, Gail V Matthews, Behzad Hajarizadeh, Louisa Degenhardt, Jason Grebely, Gregory J Dore
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Publication Details #3

Full Title:	Opportunities to enhance linkage to hepatitis C care among hospitalised people with recent drug dependence in New South Wales, Australia: A population-based linkage study
Authors:	Heather Valerio, Maryam Alavi, Matthew Law, Hamish McManus, Shane Tillakeratne, Sahar Bajis, Marianne Martinello, Gail V Matthews, Janaki Amin, Naveed Z Janjua, Mel Krajden, Jacob George, Louisa Degenhardt, Jason Grebely, Gregory J Dore
Journal or Book Name:	Clinical Infectious Disease
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The Candidate's Contribution to the Work:	Data analysis, interpretation of results, writing manuscript, corresponding author to the journal
Location of the work in the thesis and/or how the work is incorporated in the thesis:	This publication is included in the thesis as Chapter Four.

Candidate's Declaration

I confirm that where I have used a publication in lieu of a chapter, the listed publication(s) above meet(s) the requirements to be included in the thesis. I also declare that I have complied with the Thesis Examination Procedure.

Acknowledgements

My PhD experience was a challenging, joyful, fantastic experience, and this would not have been possible without an army of people who have supported me.

I would first like to acknowledge my PhD supervisors Gregory Dore, Jason Grebely and Maryam Alavi. Greg, thank you for sharing your wisdom and expertise. Your track record of fighting injustice in health, persistence in lifting voices that go unheard, and approach to health inequity changed and shaped me in countless ways. Jason, thank you for your support and faith. I have learned so much from the energy, passion, and gratitude you have shared with me. Maryam jan, who has been my beacon guiding me through the murky waters of academia and beyond, your presence on this journey has meant so much to me. I am so lucky to have walked this path with you, my mentor and friend. Your determination to improve the lives of others continually reminds me of why we do what we do.

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Abbreviations:

aOR	adjusted odds ratio
APDC	Admitted Patient Data Collection
AUD	alcohol use disorder
AUDIT-C	Alcohol Use Disorders Identification Test - Consumption
BOCSAR	Bureau of Crime Statistics and Research
CI	confidence interval
DAA	direct-acting antiviral
DC	decompensated cirrhosis
ETHOS	Enhancing Treatment of Hepatitis C in Opioid Substitution settings
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
kPa	Kilopascale
MSM	men who have sex with men
NCIMS	Notifiable Conditions Information Management System
NSP	needle and syringe program
NSW	New South Wales
OAT	opioid agonist therapy
OR	odds ratio
PBS	pharmaceutical benefits scheme
PCR	polymerase chain reaction
PWID	people who inject drugs
PY	person-years
SVR	sustained viral response
UI	uncertainty interval
WHO	World Health Organization

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List of Publications and Conferences

Publications

A list of peer-reviewed publications (including those under review, in press, and published) related to this thesis are below in chronological order:

2021

- Valerio H, Alavi M, Silk D, Treloar C, Martinello M, Milat A, Dunlop A, Holden J, Henderson C, Amin J, Read P, Marks P, Degenhardt L, Hayllar J, Reid D, Gorton C, Lam T, Dore GJ, Grebely J. Progress towards elimination of hepatitis C infection among people who inject drugs in Australia: The ETHOS Engage Study. *Clinical Infectious Diseases* **2021**; 73 (1):e69-e78. (Chapter 2)

- Valerio H, Alavi M, Law M, Tillakeratne S, Amin J, Janjua N, Krajden M, George J, Matthews GV, Hajarizadeh B, Degenhardt L, Grebely J, Dore GJ. High Hepatitis C treatment uptake among people with recent drug dependence in New South Wales, Australia. *Journal of Hepatology* **2021**; 74(2), 293-302. (Chapter 3)

- Valerio H, Alavi M, Law M, McManus H, Tillakeratne S, Bajis S, Martinello M, Amin J, Janjua N, Krajden M, George J, Matthews GV, Hajarizadeh B, Degenhardt L, Grebely J, Dore GJ. Opportunities to enhance linkage to hepatitis C care among hospitalised people with recent drug dependence in New South Wales, Australia: A population-based linkage study. *Clinical Infectious Diseases* **2021;** doi: 10.1093/cid/ciab526. (Chapter 4)

Conference presentations

A list of conference presentations (including both in person and virtual oral and poster presentations) related to this thesis are below in chronological order:

2019

- Valerio H, Alavi M, Silk D, Treloar C, Milat A, Dunlop A, Holden J Henderson C, Read P, Degenhardt L, Dore GJ, Grebely J. Uptake of testing, linkage to care, and treatment for hepatitis C infection among people who inject drugs in Australia: The ETHOS Engage study.
    - Oral Presentation: European Association for the Study of the Liver International Liver Congress, Vienna, Austria, 10-14 April 2019.
    - Poster Presentation: The Canadian Liver Meeting, Montreal, Canada, 25-26 May 2019
    - Poster: Australasian Viral Hepatitis Elimination Conference, Sydney, Australia, 5-6 August
    - Oral Presentation: The International Network of Hepatitis in Substance Users, Montreal, Canada, 11-13 September

2020

- Valerio H, Alavi M, Matthews GV, Law M, McManus H, Amin J, Janjua N, Krajden M, Tillakeratne S, Gleeson V, George J, Degenhardt L, Grebely J, Dore GJ. Opportunities to enhance linkage to hepatitis C care among people hospitalized for injection drug use-related complications: A population-based study.

- Poster: European Association for the Study of the Liver International Liver Congress, virtual conference, 23-26 June

2021

- Valerio H, Alavi M, Silk D, et al. Progress towards elimination of hepatitis C infection among people who inject drugs in Australia: The ETHOS Engage Study.
  - Oral Presentation: Network of Alcohol and Other Drugs Agencies: Enhancing Connections, Sydney, Australia, 22-23 April
- Valerio H, Alavi M, Law M, McManus H, Tillakeratne S, Bajis S, Martinello M, Matthews GV, Amin J, Janjua N, Krajden M, George J, Degenhardt L, Grebely J, Dore GJ. Opportunities to enhance linkage to hepatitis C care among people hospitalized for injection drug use-related complications: A population-based study.
  - Oral Presentation: Australasian Viral Hepatitis Conference, Sydney, Australia 30 May-1 June.
- Valerio H, Alavi M, Conway A, Silk D, Treloar C, Martinello M, Milat A, Dunlop A, Murray C, Henderson C, Amin J, Read P, Marks P, Degenhardt L, Hayllar J, Reid D, Gorton C, Lam T, Montebello M, Wade A, Dore GJ, Grebely J. Declining prevalence of current HCV infection and increased treatment uptake among people who inject drugs: The ETHOS Engage study.
  - Oral Presentation: International Network of Health and Hepatitis among Substance Users Conference, virtual conference, 13-15 October 2021
  - Poster: Australasian Professional Society on Alcohol and Other Drugs Conference, virtual conference, 7-10 November 2021

Thesis Abstract

Background: Hepatitis C virus (HCV) is a global public health threat contributing to morbidity and mortality worldwide—particularly among people who inject drugs (PWID).

Aims: The aim of this research was to assess progress towards HCV elimination among PWID during the direct-acting antiviral therapy (DAA) era. Specific aims included assessing (1) current HCV prevalence among PWID and associated factors (2), treatment uptake among PWID and associated factors, and (3) inpatient hospitalisation as a setting to enhance DAA uptake.

Methods: In Chapter Two, current HCV and treatment uptake are analysed among PWID attending drug treatment and needle and syringe programs throughout Australia in an observational cohort (the ETHOS Engage Study). Factors associated with current HCV infection and HCV treatment uptake were assessed using logistic regression. In Chapter Three, DAA uptake data from a population-based linkage study covering all people in New South Wales with HCV notification were analysed using logistic regression. In Chapter Four, survival analysis was used to assess population-level DAA uptake by history and characteristics of hospitalisation. In Chapter Five, the change in HCV viremia and treatment uptake among PWID between two recruitment waves was assessed in the ETHOS Engage Study. Logistic regression was used to assess the factors associated with current HCV infection and treatment uptake in the second recruitment wave.

Key Findings: HCV viraemic prevalence has declined considerably following high DAA uptake among PWID populations in recent years. Despite this success, there remain populations requiring enhanced support. Indicators of higher marginalisation—

including homelessness, frequent injection drug use, and frequent hospitalisation—were associated with lower treatment uptake. Among PWID who were hospitalised, treatment uptake was lower among those who had been hospitalised for drug use, injection-related infectious diseases, and mental health disorders. Current HCV infection was associated with markers of higher marginalisation. Between the two ETHOS Engage recruitment waves, we observed a decline in HCV viremia and an increase in treatment; however, gaps remain.

Conclusion: Public health action is needed to enhance HCV care among marginalised groups of PWID. Innovative and novel interventions—including the utilisation of inpatient hospitalisation—are needed to enhance care. Contribution from multidisciplinary stakeholders is necessary to ensure HCV elimination is equitably reached across all PWID.

Chapter 1: Chapter introduction

This chapter provides an overarching review of the published, peer-reviewed, literature concerning hepatitis C virus (HCV). In doing this, Chapter One provides a brief overview of the remarkable progress that has been made in the field of HCV from its discovery to the present. To achieve this, Chapter One is laid out as follows: first, an abridged description of the natural history of HCV infection will be discussed, followed by the global and Australian epidemiology of HCV infection, review of the evolution of HCV therapy, and cascade of HCV care. The rationale for, and the impetus towards HCV elimination will be reviewed. For each theme, Chapter One will present a broad view and subsequently narrow its focus onto the population at most risk of HCV infection in Australia, people who inject drugs (PWID). The barriers and facilitators to HCV elimination will be reviewed. Finally, this chapter will culminate with the justification, objectives, and aims of this thesis.

1.1 Natural history of HCV

The hepatitis C virus was first described as a unique blood-borne virus and causative agent of liver disease in 1989 [1]. HCV is a single-stranded ribonucleic acid (RNA) virus and belongs to the flavivirdae family. Throughout the 1970s and 1980s, incidence of what was known as “non-A, non-B viral hepatitis” was increasing and its effect on liver morbidity was clear [2, 3]. Despite hope that the molecular characterisation of HCV would lead to quick development of a vaccine for primary prevention of the virus, due to its genetic diversity—including seven major genotypes and more than 60 subtypes [4]—coupled with a high frequency of mutation, vaccine development for HCV remains challenging [5, 6] and reinfection after viral clearance is possible, given ongoing risk behaviour [7, 8]. As such, prevention of HCV disease burden has relied

greatly on understanding the natural history and epidemiology of infection to ensure that those at most risk of infection have access to a broad range of strategies to minimise risk of virus acquisition and transmission. These strategies include harm reduction, ensuring high availability of testing and diagnosis, and for those infected, initiation onto antiviral treatment with minimal to no barriers to care.

1.1.1 HCV morbidity

Although case definitions are not uniform across all diagnoses, acute HCV infection is generally defined by detection of the virus in the blood, which initially occurs 2-14 days after exposure, an escalation in alanine aminotransferase and aspartate aminotransferase (serum liver enzymes), and the development and detection of HCV antibodies in the blood 20-150 days after initial exposure [9]. As acute HCV infection is often asymptomatic (70-85% experience no symptoms), the epidemiology of acute HCV has been difficult to accurately describe [9, 10].

During the acute phase of HCV infection, a person can potentially clear the virus with no therapeutic intervention, a process known as spontaneous or natural clearance. The factors associated with spontaneous clearance include female sex, among other genetic markers [10, 11]. Recent population-level evidence from British Colombia, Canada has estimated that 28% of the total population with acute HCV will spontaneously clear and the remaining 72% will develop chronic HCV [12]. Although not well elucidated, a small proportion of those with chronic HCV infection go on to spontaneously clear infection (0.19-0.39 per 100 person years [PY]) [13, 14].

1.2 Epidemiology of HCV infection:

1.2.1 Global HCV epidemiology

Historical antibody prevalence data are likely an underestimate, due to a range of factors including: (1) underdiagnosis of acute HCV infection in most settings due to asymptomatic nature (2) the exclusion of high risk groups from surveillance studies and seroprevalence surveys used to generate estimates (e.g. the exclusion of incarcerated people from the National Health and Nutrition Examination Survey in the United States), and (3) publication bias (exclusion of non-peer-reviewed, non-published literature in generation of estimates) [15]. Nevertheless, in 2005 it was estimated that 2.8% (uncertainty interval [UI]:2.6%-3.1%) of the global population had been exposed to HCV [15]; however, the seroprevalence (HCV antibody) estimates and trends in prevalence varied considerably across region (as defined by close epidemiological homogeneity) [16]. The highest prevalence was reported in the Central and East Asia regions, with >3.5% of the population affected [15].

Quantification of the global HCV viraemic population was undertaken in 2015 to provide more precise and up-to-date estimates of HCV prevalence by pooling literature, country expert interviews, and employing mathematical modelling methodologies [17]. This study, led by the Polaris Observatory, estimated that 1.0% (UI: 0.8%-1.1%) of the global population—equating to 71.1 (UI: 62.5-79.4) million people—were infected with HCV (viraemic) in 2015, with country-level prevalence estimates varying from 0.1-6.3% [17]. The country with the highest prevalence in terms of the proportion of the population affected was Egypt, and the country with the highest total number of people with HCV viremia was India [17]. Regional HCV viraemic prevalence varied from 0.5-3.6%, with the highest estimated prevalence reported for Central Asia [17].

The most recent HCV prevalence estimate, by the WHO and Polaris Observatory, estimated that in 2019 there were a total of 58 (UI:46-76) million people living with HCV viraemia in the world, equivalent to 0.75% of the global population [18]. HCV viraemic prevalence was highest in the European Region (12 million; UI:10-14 million) and the Eastern Mediterranean Region (12 million; UI:10-13 million) [18].

Incidence of HCV is difficult to accurately measure as the initial stages of HCV infection are often asymptomatic and the resources to measure incidence are insufficient. Measuring national-level incidence would be enhanced by annual population-level age-specific seroprevalence surveys; however, this methodology is expensive and unfeasible in most settings. National-level data on HCV incidence are non-existent for most countries. Estimates of HCV incidence are usually made on the basis of extrapolating smaller studies to the population level, mathematical modelling, and using new diagnoses in younger PWID as a proxy indicator for newly acquired infection. With this in mind, the global incidence estimate of HCV in 2015 was 23.7 per 100,000 population, varying between WHO regions from 6.0 (Western Pacific) to 62.5 (Eastern Mediterranean) per 100,000 population [19]. Furthermore, of the 58 million infections in 2019, 1.5 million were newly acquired, equating to 21.4 per 100,000 population [18].

1.2.2 HCV epidemiology in Australia

HCV became a notifiable infection in Australia in the early 1990s. Between 1990 and 2000, incidence of HCV escalated in Australia [20, 21], with approximately 160,000 HCV notifications made during this period [20]. Prevalence continued to grow, and in 2012, an estimated 230,000 people (equating to 1% of the Australian population) had HCV viraemic infection [22]. This prevalence estimate has since been adjusted

downwards with a 2015 estimate of 188,690 [23]. OF these, an estimated 22% (n=33,200) received treatment during 2016. Following this rapid uptake of direct-acting antiviral (DAA) therapy in 2016, the estimate of HCV viraemic prevalence declined to 117,810 by the end of 2020 [23] .

Incidence of HCV in Australia appears to be declining, consistent with decreases in prevalence. Between 1999 and 2006, notification rates declined by nearly 50% among young adults (surrogate marker for newly acquired infection) [24]. Additionally, between 2015 and 2018, notifications of new HCV infection fell 8% from 10,353 to 9,493 [25]. Encouragingly, incidence of HCV is projected to continually decrease under different treatment scenarios, including decreasing and plateauing treatment uptake [26].

1.3 Disease outcomes and mortality

Often considered “the silent epidemic”, chronic HCV infection is internationally regarded as a major public health burden given its sequalae includes the development of cirrhosis, and further progression to decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC) [10]. Chronic HCV infection causes limited liver damage within the first decade of initial infection [10]; however, untreated chronic HCV can develop into liver fibrosis, and duration of HCV infection is associated with accelerated liver disease progression [10, 27]. Indeed, although the physiological effects of HCV progress slowly in the first decade after infection, for those who remain untreated, ageing carries exponential risk of escalating liver disease in the following decades of infection [10]. Twenty years after initial infection, an estimated 7-24% of people will develop cirrhosis, and 41% will develop cirrhosis within 30 years [28, 29]. Development of

cirrhosis is accelerated by co-infection with hepatitis B virus (HBV) and HIV as well as alcohol consumption [10, 28].

Decompensated cirrhosis is defined by a severe deterioration of liver function resulting in end-stage liver failure [30]. Among patients with HCV-related cirrhosis, 3-12% will develop DC with each year [31, 32], and in the absence of liver transplant, research has shown the cumulative annual mortality risk of patients living with DC to be 70% within five years of initial diagnosis [33]. Additionally, patients with cirrhosis have a 3.5% annual progression rate to HCC, the most common type of liver cancer, and the third leading cause of cancer deaths in 2020, internationally [34, 35].

1.3.1 Burden of disease

Due to its asymptomatic nature, slow liver disease progression, and ageing cohort, the burden of HCV infection has been projected to increase over time; including growing incidence of severe liver morbidity (cirrhosis, DC, and HCC) resulting in liver transplantation and/or liver-related mortality, both globally and in Australia [21, 36].

Globally, between 1990 and 2013 mortality due to viral hepatitis rose from 0.89 million (UI:0.86-0.94) to 1.45 million (UI:1.38-1.54) deaths, equating to an increase of 10.6 million years of life lost over that period [37]. Hepatitis B virus (HBV) and HCV accounted for 96% of global viral hepatitis mortality, and of those deaths, HCV accounted for 48% (UI:46-50) [38]. The majority of mortality due to HCV was attributable to cirrhosis, DC, and/or HCC, and the rising trend in mortality was observed in all settings regardless of income [37]. Since 2000, there has been a 22% increase in deaths related to viral hepatitis, resulting in 400,000 deaths HCV-related deaths globally in 2015 [19]. In Australia, the number of people receiving liver transplantation due to HCV-related liver morbidity increased between 1997-2006 [24] and the disease burden

due to HCV trended upwards [39]. Although encouragingly, in the DAA era HCV-related deaths have decreased, from 3.6 to 2.5 per 1,000 population over the period 2015-2018 [40].

1.4 Routes of transmission: Identifying populations at most risk

HCV is an infectious blood-borne virus that is transmitted to and from humans parenterally through blood-to-blood contact [10]. The primary routes of transmission include modifiable risk behaviours in which blood may be exchanged with another person. This includes the use of inadequately screened blood products for dialysis, transfusion, or transplant [41, 42], sharing equipment used for injecting drugs [43, 44], nosocomial injuries [41, 45], high-risk sexual behaviours, particularly among men who have sex with men [46], the reuse of unsterilised medical, piercing, or tattooing equipment [45, 47], and mother-to-child vertical transmission [48].

In most settings internationally, the screening of donated blood, blood products, and organs for transplant began in the early 1990s when HCV antibody detection became available. Although it is difficult to estimate the exact contribution of blood transfusions to HCV prevalence, transfusion of unscreened blood products may have accounted for 5-15% of early HCV infections in Australia [20].

The majority of HCV infections in high income countries occurred among younger individuals between the 1970s and 1990s due to the increase in injection drug use [8, 21, 49]. Recent data have emerged which suggest the incidence of HCV infection due to injecting drug use is increasing in low and middle-income settings [50]; however, these estimates are based on a small number of data sources from a small number countries and thus remain somewhat uncertain. Nevertheless, PWID are globally regarded as one of the most at-risk populations for HCV infection. Globally, it is estimated that 52% of

people who inject drugs had ever been exposed to HCV (HCV antibody positive) [50] and 40% of incident HCV infections occurring between 2018 and 2030 will be attributable to injecting drugs [51]. PWID, therefore, are the priority population for HCV-related treatment and care in Australia and many other settings.

1.4.1 Prevention

Prevention and control of HCV infection hinges on a large proportion of PWID having access to high coverage of harm reduction for primary prevention of infection and transmission [52, 53]. Harm reduction includes undisrupted access to sterile equipment for injecting drugs via needle and syringe programs (NSP) and medicalised addiction management via opioid agonist treatment (OAT). Multiple studies have provided evidence of the association of NSP and OAT on reduced HCV infection risk [53, 54]; however, in a recent systematic review, only four countries which make up a relatively small proportion of the global population of PWID (Australia, Austria, Netherlands, and Norway) were found to have both high coverage of NSP (greater than 200 needle-syringes per PWID) and OAT (greater than 40 OAT clients per 100 PWID) [55]. Globally, coverage of harm reduction is low, with only an estimated 33 needle-syringes per PWID per year available in 2015 and 16 per 100 PWID estimated to be receiving OAT [55].

1.5 Estimating the population of PWID

As PWID are a key population at risk of HCV infection, the collection of data to identify and characterise the epidemiology of injection drug use is critical. PWID are far from a homogeneous group. Among both historical and active PWID, there is a wide range of sub-populations resulting from the complex intersectionality of injecting drug use with biological, demographic, and behavioural factors. These factors include, but

are not limited to age, sex, gender identity, sexual identity, ethnicity, housing status, incarceration history, sex work, participation in harm reduction (needle and syringe programs [NSP] and/or opioid agonist therapy [OAT]), alcohol consumption, frequency of injection, main drug of choice, and polysubstance use. To ensure equitable healthcare access and utilisation, it is important to understand the epidemiology of injection drug use and the epidemiology of HCV among all sub-populations of PWID.

1.5.1 Epidemiology of injection drug use

The prevalence of injecting drug use and injection equipment sharing is relatively well categorised in high-income countries such as the United States, the United Kingdom, and Australia; however, there are only a small proportion of countries with population-level prevalence estimates of injecting drug use [50]. A systematic review estimated that 15.6 million people (95% uncertainty interval [UI] 10.2-23.7 million) had injected drugs in 2015, equating to 0.33% of the global population of people 15-64 years [50]. Of these, 10.5 (UI: 6.8-15.0) had injected drugs daily or more [56]Globally, the largest populations of PWID were in Southeast Asia (4.0 million, UI:3.0-5.0 million), followed by Eastern Europe and North America with 3.0 million (UI: 1.7-5.0 million) and 2.6 million (UI: 2.6-4.4 million) PWID, respectively [50]. It is estimated that 20% of PWID are women, 28% are <25 years of age, 22% are unstably housed or have experienced recent homelessness, 58% have a history of incarceration, and 26% had recently used a needle or syringe after another person [50].

1.5.2 Global HCV epidemiology among PWID

A global review published by Degenhardt and colleagues pooled data to derive global, regional, and country-level estimates of HCV antibody prevalence among PWID [50]. According to these results, 52% (UI:42%-62%) of PWID globally have been exposed to

HCV and are HCV antibody positive, and this varied by region and ranged from 22%-65% [50], with the highest prevalence observed in Eastern Europe.

A subsequent global review by Grebely et al. estimated that 6.1 million (UI: 3.4-9.2) people who have recently injected drugs (last 12 months) are living with chronic HCV infection [57]. Globally, among all people living with chronic HCV infection, 8.5% (UI:4.6-13.1) were estimated to have recent injection drug use. The authors of this review note considerable variation between countries, with 0.5-73% of people infected with HCV viraemia who have recently injected drugs. Notably, when summed, the number of people with recent injecting drug use from Russia, the United States, China, and Brazil combined to account for 51% of viraemic HCV infection in the global population of people who have recently injected drugs [57]. The estimated prevalence of HCV viraemic infection and corresponding number of people with recent injecting drug use living with HCV viraemic infection are shown in Figures 1 and 2.

While global incidence of HCV among PWID is hard to measure, a systematic review and meta-analysis estimated the incidence of HCV among non-incarcerated PWID in nine European countries to be 26/100 person years (PY) [58]. Indeed, incidence is highest among PWID compared to other HCV-related risk factors [51]. When injection drug use was removed from a mathematical model predicting new global HCV infections between 2018 and 2030, an estimated 43% of infections were averted [51].

1.5.3 Epidemiology of injection drug use in Australia

There are an estimated 68,000-118,000 PWID aged 15-64 years in Australia, equating to 4-8 per 1,000 Australians [59]. By combining two systematic reviews, Grebely et al. estimated that 37,500 (UI:27,500-48,500) people in Australia had recently injected drugs (previous 12 months) [57]. Australian PWID are an ageing cohort. Based on data

obtained from the Australian Needle and Syringe Program National Data Reports (1995-2020)—a seroprevalence survey of PWID recruited from a national network of NSP sites across Australia [60, 61]— median age of participants increased from 27/29 years (observed between 1995-2001) to 43 years (observed in 2020), with a paired reduction in the proportion of participants under 25 years from 25% (1995-2001) to 5% (2020) [61, 62]. Likewise, the median time since first injection had increased from 7 years in 1998 to 22 years in 2020 [61, 62].

In 2020, 22% of respondents to the Australian Needle and Syringe Program Survey identified as Aboriginal Australian or Torres Strait Islander [61]. Of all survey respondents (n=1,324), 33% were women, the median age was 42 to 43 years, 13% had been incarcerated in the previous 12 months, 50% reported injecting daily or more, 47% reported last injecting methamphetamine, 23% had reported reuse of a peer's injecting equipment in the last month, and 26% were currently engaged in OAT (53% among those who last injected opioids) [61].

1.5.4 Epidemiology of HCV among PWID in Australia

The Australian Needle and Syringe Program Survey reported a significant decrease in HCV antibody prevalence among PWID in Australia between 2016 (51%) and 2020 (39%) [61]. Among respondents to the 2020 survey, 16% had current HCV infection, a marked reduction from 57% in 2015 [61, 63].

Cohort studies have been useful in estimating the incidence of HCV among PWID in Australia [64-66]. Data from these studies suggests the incidence of HCV among PWID in Australia decreased from approximately 31 per 100 PY [65, 66] to less than 17 per 100 PY [64] between 1999 and 2010. Among PWID in Australia, incidence was estimated to be higher in females than in males, with rates of 20 and 14 per 100 PY,

respectively [67]. However, likely due to the higher proportion of women who spontaneously clear compared to men [11], the observed prevalence of current HCV infection among PWID in 2020 was higher among males (17%) than females (15%) [61].

1.6 HCV testing and diagnosis

Patients at risk of HCV exposure require testing, yet there is no one-size-fits-all HCV diagnostic strategy for all settings. The optimal screening and diagnosis strategy for each country varies in line with the patient profile and epidemic of each setting [68, 69]. The high proportion of people living with HCV estimated to have been diagnosed in Australia (81%) without universal screening [23], suggesting a transmission risk-based screening strategy fits best [70].

The traditional testing paradigm to work up an affected individual is often costly, complex, and multicomponent: (1) first, a serological assay is used to test and diagnose presence of HCV antibodies, (2) if detected, nucleic acid testing is required for confirmation of viraemic infection, and (3) if HCV RNA are detected, there are further considerations made to assess for treatment, including liver disease staging and genotyping [68, 69]. Traditionally, all diagnostic stages require separate venous whole blood collection by a phlebotomist, often within a pathology setting. Blood is tested at a central laboratory, and results can take multiple weeks to return to the patient [71, 72]. Depending on the preferred liver disease assessment, a separate venous whole blood collection may be necessary [68, 69].

1.7 The evolution of HCV treatment

HCV is curable through treatment. A sustained viral response (SVR)—equivalent to HCV cure—is defined as unquantifiable HCV RNA 12 weeks post-treatment

completion. Early data on achieving SVR has evidenced its association with improved quality of life [73], reduced hepatic and non-hepatic morbidity [74, 75], reduction in hepatic mortality [75, 76], and increased survival [77]. In addition, SVR has been shown to be associated with a reduction in mental health morbidity and improved health-related behaviours [74]. Despite this, many PWID were historically precluded from HCV treatment.

Initial therapeutic development for HCV was challenging, resulting in the utilisation of genetically engineered interferon to augment immune response and curtail viral replication. In the two decades following the discovery of HCV, the standard treatment necessitated interferon injection. For nearly the first decade following its discovery, HCV was treated with interferon alfa injection alone for 24 or 48 weeks and resulted in SVR for 15%-20% of those who completed treatment, varying by genotype [78]. Although the 1998 approval of ribavirin combined with interferon, and the 2003 approval of pegylated interferon improved the proportion of patients achieving SVR to 31%-38% [78] and 44-56% [79], respectively, severe adverse events, and drug-drug contraindications associated with interferon-based therapy precluded many from qualifying for treatment [80].

The adverse effect profile—including influenza-like symptoms, haematologic symptoms, psychiatric symptoms (including depression, acute psychosis, suicidal ideation, and personality change), fatigue, insomnia, alopecia, and gastrointestinal issues, among others [81]—meant interferon treatment was not recommended for many groups of patients: those with psychiatric comorbidities or other medical comorbidities such as HIV coinfection, diabetes, anaemia, epilepsy, and autoimmune disease [78]. Despite evidence that interferon-based treatment outcomes among PWID were acceptable when compared to the general population [80], the high risk of side effects

and prevalence of contraindicating psychological and medical comorbidities, resulted in treatment uptake remaining extremely low [82, 83].

In 2011, greater understanding of the HCV life cycle led to the development and approval of a class of pharmacotherapy which works directly on HCV to inhibit its viral protease and thus viral replication. This class of pharmacotherapy, known as direct-acting antiviral (DAA) therapy, proved beneficial in improving the proportion of patients achieving SVR; however, these early generation DAA therapies (boceprevir and telaprevir) required simultaneous use of pegylated interferon and ribavirin [84]. These early generation DAA therapies in combination with pegylated interferon and ribavirin were more highly efficacious (66% and 75% for those HCV genotype 1 patients treated with boceprevir and telaprevir, respectively) [85]; however, given the necessity to administer early generation DAA therapy concurrently with pegylated interferon and ribavirin, adverse events persisted.

Recent major therapeutic developments have revolutionised the HCV treatment landscape, evolving from interferon -based and containing treatment regimens to the era of interferon -free DAA therapy. The development of interferon-free DAA (DAA hereafter) therapy for the treatment of HCV is considered one of the greatest medical breakthroughs of recent decades. The Food and Drug Administration in the United States approved the first DAA regimen to treat HCV (sofosbuvir plus ribavirin) in late 2013 [86], with multiple regimens from multiple manufacturers, including the use of generic medication in low and middle income settings [87], following thereafter. Clinical trials of DAA therapy demonstrated their high efficaciousness, with >90% of people cured within 8-24 weeks of treatment [88], including HCV genotype 3 [89]. As such, these medicines generated considerable optimism in HCV research and care, particularly with the most recent advent of pan-genotypic [90]DAA therapy.

Evidence from a systematic review of clinical trials and real world (observational) evidence has demonstrated that DAA therapy is highly effective among those with injection drug use and among those who were receiving OAT [91]. Furthermore, high adherence to DAA therapy has been reported among PWID currently receiving OAT and among those who recently injected drugs [91, 92]. While the rate of HCV reinfection following DAA therapy is higher among people who had recent injection drug use, this was relatively low and should not preclude PWID from treatment [7].

Modelling studies projected the potential impact of DAA therapy on HCV incidence, prevalence, and liver-related mortality by prioritising key populations for treatment initiation [93, 94]. These studies have demonstrated that enhancing DAA therapy uptake among key populations—including those with advanced liver fibrosis—has the potential to profoundly reduce severe HCV-related liver morbidity and mortality [93, 95]. Despite early concern [96], there is no evidence that DAA therapy is associated with increased incidence of HCC [97, 98]. In fact, the impact of high DAA therapy uptake has been evidenced from recently published population-based studies which report reductions in hospitalisations relating to decompensated cirrhosis [99, 100], plateauing of HCC diagnoses [99], and reduction in HCV-related liver mortality [99, 101].

In addition to curbing HCV-related mortality, modelling has shown that increasing the proportion of PWID who receive DAA therapy will potentially impact population-level prevalence and in turn reduce incidence and transmission [94]. Such modelling work has demonstrated the benefit of DAA therapy by a mechanism better known as treatment as prevention [94]. It is important to acknowledge that beyond the population-level benefits of viral clearance, PWID who have cleared their HCV through DAA therapy have reported additional individual-level benefits, including increased feelings of “normality” and psychological wellbeing [102]. Thus, DAA therapy is highly

effective, tolerable, and associated with population-level and individual-level benefits, particularly among PWID.

Although there was early evidence of the potential benefit of unrestricted DAA therapy [94, 103, 104], due to its initial high cost, many settings internationally were required to prioritise treatment to particular populations or restrict treatment based on drug and alcohol use, liver disease stage, and prescriber-type [38, 105]. Australia is one of few nations which quickly negotiated broad access to government-subsidised DAA therapy for all adults who are infected with chronic HCV, placing no restrictions on prescriber-type, concurrent drug and alcohol use, or previous successful HCV therapy [106]. Australia's innovative approach to secure an unlimited supply of DAA therapy, under a single annual payment cap, made all infected adults eligible for therapy from March 2016. Understanding the factors which contribute toward treatment uptake in a setting of unrestricted DAA therapy is critical as these restrictions begin to ease in more international settings [107].

1.8 Towards HCV elimination

The remarkable evolution of HCV therapy made the concept of HCV elimination plausible. Due to the growing concern in HCV-related mortality worldwide, in 2016, the World Health Organization (WHO) Global Health Sector Strategy called for the elimination of HCV as a public health threat by 2030, with support from all 194 WHO Member States [19, 108]. This elimination is measured by two key indicators: (1) 90% reduction in HCV incidence, and (2) 65% reduction in HCV-related liver mortality [108]. Achieving these targets has the potential to avert 1.5 million liver-related deaths as a result of HCV by 2030 [109]. As the HCV epidemic curve and disease trajectory varies significantly between and within nations, these targets may not be feasible for all

countries. As such, the WHO has recently established elimination targets in terms of absolute numbers with objective to (1) reduce annual HCV incidence to ≤5 per 100,000 population and ≤2 per 100,000 population of PWID and (2) reduce annual HCV-related mortality to ≤2 per 100,000 population [18].

High coverage of HCV prevention and DAA treatment are key to realise these targets. Between 2015 and 2030, prevention-level targets will need to be met in order to achieve elimination, including: (1) increasing coverage of harm reduction from 27 to >300 sterile needle and syringes per person who is actively injecting drugs per year, (2) increasing the proportion of adequately screened donated blood and blood products from 89% to 100%, and (3) and ensuring safety of 100% of healthcare related injections [18]. Additional service-related targets include increasing the proportion of those living with chronic HCV who are diagnosed from 20% to 90% and increasing treatment initiations of those diagnosed from 7% to 80% [18].

1.9 The HCV cascade of care

The "cascade of care" was first conceptualised as a tool to measure the extent to which people living with HIV were engaged with harm reduction, testing, and diagnosis, antiretroviral therapy, and ongoing follow-up [110]. This framework has since been adapted to evaluate the public health response to HCV by measuring the extent to which those who are living with HCV are engaged with essential clinical services including: HCV antibody testing, HCV RNA testing, linkage to clinical care, initiation onto HCV treatment, and SVR assessment [63].

1.9.1 Global cascade of HCV care

Multiple studies have shown that the pre-DAA era cascade of HCV care was poor [12, 111]. Many countries do not have sufficient published data on the cascade of HCV care

in the DAA era [112]; however, as indicated above, it is estimated that a small population, around 20%, of the globally infected population have been diagnosed, of which 7% have received treatment as of 2015 [19].

Engagement with the HCV cascade of care varies considerably between settings and populations of affected people [112]. The importance of funded government support in its role to improve the HCV cascade care should not be underestimated. In fact, countries with the highest treatment uptake include those with nationally funded HCV screening, testing, and elimination programs, including Iceland (95%), Egypt (92%), and Georgia (79%) [112].

1.9.2 Australian cascade of HCV care

Diagnosis of chronic HCV in Australia is high, with an estimated 75-80% diagnosed [82]. Considering the low treatment uptake in the interferon treatment era—relating to 1-2% of individuals with HCV initiated onto therapy annually [113]—and the number of patients "warehoused" waiting for DAA therapy to be licensed, it was expected that there would be an initial influx of treatment initiates, and understanding this would decrease over time [95]. Indeed, from the initial listing of DAA therapy on the pharmaceutical benefits scheme (PBS) in March 2016, there was a remarkable surge of Australian adults living with HCV who initiated treatment, with 16% of the chronic HCV population initiating treatment in the first ten months of unrestricted access [113]. Although this initial uptake has declined, 49% of the chronic HCV population had initiated treatment by the end of 2020 [114].

1.9.3 Australian cascade of HCV care among PWID

In Australia, engagement in the cascade of HCV care among PWID in the pre-DAA era was suboptimal. In 2015, Australian PWID were estimated at 93,000, of whom 89%

(n=83,039) had ever been screened for HCV antibodies. Of the 93,000 PWID in Australia, an estimated 57% (n=53,111) were HCV antibody positive, 46% (n=24,540) of whom had received a confirmatory HCV RNA test for chronic infection [63]. Of all PWID, 45% (n=41,810) were estimated to have current or historical chronic HCV infection, of whom 47% had ever received a genotype test, 31% had ever been to a specialist, 8% had ever received HCV treatment (interferon-based) and 3% were cured [63].

Updated estimates using the same cohort indicate a consistent pattern of increased testing and treatment uptake in the DAA era among both PWID and the general Australian population living with HCV [115]. In 2018, it was estimated that 18,757 people who injected drugs on a regular basis in Australia were ever infected with HCV (HCV antibody positive), of whom 78% had received confirmatory HCV RNA testing, of whom 47% had initiated DAA therapy, 88% of whom had achieved SVR [115]. This high treatment uptake and SVR among PWID is encouraging, and it is estimated that PWID account for approximately 25% of all SVRs in Australia recorded between 2015 and 2019 [115].

1.10 Facilitators and barriers to HCV care among PWID

Enhancing the public health approach to HCV—and ultimately eliminating HCV as a public health threat—relies on funded, national governance which provides structure for the collection of robust surveillance data. These data are in turn used to monitor key indicators to evaluate progress toward elimination and highlight populations needing increased intervention and engagement. In addition to enhanced surveillance systems, national strategies for HCV testing and treatment have been shown to be important in expanding access to harm reduction and DAA treatment [112]. Despite this, a recent

audit reported that 62% of the respondent WHO Member States (N=135/194 Member States, accounting for 87% of the total infected HCV population) had a national viral hepatitis strategy, only half of which have dedicated funding [116].

Although paramount in achieving HCV elimination, modelling has shown that unrestricted access to DAA therapy on its own will not facilitate elimination efforts [117]. Indeed, it has been acknowledged by researchers and people living with HCV alike: The elimination of HCV as a public health threat necessitates the removal of barriers to care, in order to improve testing, retention in services, HCV treatment, and post-treatment monitoring among PWID [117, 118]. The public health sector will need to develop and implement strategies and policies to reduce barriers among those who may be difficult to engage in traditional standard of care, with interventions to remove barriers and facilitate the cascade of HCV care, specifically among marginalised populations. Those most marginalised people with HCV include PWID, people living with HIV, people who have been incarcerated, people who are homeless, among others. It is important to acknowledge that these are often overlapping, intersecting populations [119]. Understanding the barriers and facilitators to enhance DAA treatment among these populations of PWID is necessary to achieve HCV elimination targets.

Systematic barriers to HCV care persist, particularly among PWID [120]. Even if a healthcare system is set up to accept all for unrestricted DAA therapy for HCV, diligence is needed to ensure PWID are welcomed and unjudged. People who have been marginalised, including PWID, have historically faced many barriers to accessing adequate healthcare including encountering increased discrimination and stigmatisation from society and health providers in relation to their injection drug use [121]. Stigma is a particularly important social construct, perpetuated by institutions and individuals [122] and a known facilitator of morbidity [123]. PWID who reported experiencing

more stigma have been shown to be more likely to engage in high-risk injection drug use and have active HCV infection [124]. Recently, the Australian Government introduced a new public health indicator to monitor the stigma and discrimination encountered by people living with HCV and/or who have recently injected drugs [125]. Over half of participants reported experiencing discrimination and feeling stigmatised within a healthcare setting in the last year [125]. Stigma from the systematic level can be reduced through educating people who commonly interface with PWID, including those within the medical setting [126].

Furthermore, there are several notable barriers to HCV testing among PWID [68]. First, poor venous health among PWID is common, and anxiety regarding the difficulties in relation to blood collection via hard to access veins has been documented as a significant barrier to HCV testing in this population [71, 127]. Simplified HCV testing—including mechanisms for testing which use finger-stick blood or saliva have been shown to promote testing uptake [128, 129]. Furthermore, testing at the point-of-care—that is to say, testing within a setting that regularly interfaces with people who are at risk of HCV infection—has been shown to increase testing uptake in high-risk populations [128, 130]. In addition to dried-blood-spot testing, which still requires a laboratory-based assay, comprehensive testing mechanisms such as the Cepheid® Xpert HCV Viral Load Finger-stick can test for HCV viremia (HCV RNA) with only 100 μL of capillary whole blood with 100% sensitivity and 100% specificity [131] in one hour or less [132]. Such point-of-care testing has been shown to be acceptable among Australian PWID [133].

Current engagement with OAT is associated with improved engagement with HCV testing [134] and treatment [134, 135]. There is a growing body of evidence suggesting the importance of community clinics, such as those which provide OAT, in HCV

management and treatment. A recent systematic review has demonstrated the successes of integration of HCV care within drug treatment and services within high income countries [136]. Furthermore, results from a randomised control trial in Scotland provide evidence for the de-siloing of healthcare services to incorporate the entire cascade of care within services which interface with PWID [137]. In this study, PWID who were tested and offered HCV treatment within community pharmacy (in comparison to those who were referred to an offsite specialist, i.e. the traditional standard of care) were more likely to have received treatment and attained SVR [137].

Indeed, reducing attrition along the HCV cascade of care will involve the simplification of the traditional models of care, including reducing the number of visits required to diagnose HCV and initiate treatment [138]. Encouragingly, evidence of the successes of adopting such one-stop-shop models to test and treat HCV in low-and-middle-income settings is emerging [139]. The successes in using community drug treatment clinics to enhance HCV treatment may be testament to the trusting relationship between client and patient in these settings [140]. Such supportive environments have been shown to reduce stigma, engender trust, and facilitate uptake of HCV treatment and care [26, 141].

1.11 Is HCV elimination feasible in Australia?

Encouragingly, the fifth and current Australian National Hepatitis C Strategy has named PWID as a priority population for HCV care [70]. Along with this funded, national public health strategy, Australia's restructuring of the status-quo, including the abolishment of behavioural restrictions, and the utilisation of general practitioners to deliver DAA treatment, was one of few public health strategies internationally to greatly expand access to HCV therapy for PWID [106, 142]. Furthermore, through the

development of key public health initiatives, Australia secured funding for important facilitators to care and increased input from drug user and HCV community organisations and broadened HCV screening and treatment programs within community clinics, NSPs, and prisons [143].

Given this, a small undiagnosed population (19%) [63], the high effectiveness of DAA therapy, and high coverage of harm reduction [55], modelling has demonstrated that Australia is on track to achieve WHO elimination targets by 2030 [95, 144]; however, continuing this momentum may incur challenges, and the rate of HCV elimination across infected populations may not been equitable, particularly among PWID and those most marginalised [119].

1.12 Literature review summary

HCV is a global public health threat that contributes to excess morbidity and mortality and is endemic in population vulnerable to stigma, discrimination, and barriers to care: PWID. HCV treatment has historically had limited curative efficacy, was difficult to tolerate, and was contraindicated with many factors prevalent within populations of PWID. From its advent, DAA treatment has revolutionised HCV care. Although not a panacea, DAA treatment generated considerable optimism due to its potential to eliminate HCV through a treatment-as-prevention mechanism—i.e. high treatment uptake among the population at most risk of infection and transmission. Australia was one of few countries to remove drug and alcohol-based barriers to receiving treatment and is well-placed, globally, to demonstrate the feasibility of HCV elimination among PWID. Despite this, challenges remain in overcoming the barriers and identifying the facilitators to DAA treatment among PWID.

1.13 Thesis rationale

Epidemiological studies are needed to monitor and evaluate DAA treatment uptake among PWID to ensure the progress toward elimination is equitable and gain a fuller understanding of the barriers that persist in an unrestricted treatment era [145]. PWID are a diverse and heterologous population, and as such, the HCV treatment uptake and current HCV infection incurred by specific sub-populations needs to be better understood. Further research is needed to monitor and highlight the groups of affected PWID whose treatment uptake is inequitable and thus have higher rates of active infection. Enhanced understanding of the factors associated with DAA treatment uptake and current HCV infection are cornerstone in the pursuit of HCV elimination. In gathering this data, the public health approach to HCV elimination can expand beyond the current standard of care into non-traditional settings, calling upon a multidisciplinary workforce to make elimination targets a reality. These epidemiological data are crucial in the development and execution of such strategic, targeted public health interventions to facilitate elimination across all populations of PWID.

Herein, this thesis aims to:

Aim 1: To evaluate the prevalence of current HCV infection and treatment uptake among PWID attending drug treatment clinics and NSPs in Australia

Hypothesis: Factors relating to increased marginalisation (homelessness, recent incarceration, and injecting drug use frequency) will be associated with higher prevalence of current HCV infection and lower treatment uptake, while factors relating to increased engagement with health services (e.g. current receipt of OAT) will be associated with lower prevalence of current HCV prevalence and higher treatment uptake.

Aim 2: To evaluate HCV treatment uptake and associated factors in a population-level cohort in the DAA era in New South Wales, Australia

Hypothesis: People with evidence of drug dependence in the DAA era will have slightly lower, but comparable DAA treatment uptake compared to those with distant history and no history of drug dependence. Among those with evidence of recent drug dependence, factors which contribute to increased marginalisation (recent incarceration, history of alcohol use disorder) will be associated with less DAA treatment.

Aim 3: To evaluate the potential of inpatient hospitalisation to serve as a juncture for HCV care among a population-level cohort of DAA treatment-naïve people in New South Wales, Australia

Hypothesis: People with evidence of recent drug dependence will incur a higher incidence of hospitalisation than people with a distant history and no history of drug dependence. Among DAA treatment naïve people with evidence of recent drug

dependence, incidence of drug-related hospitalisation will be highest and this will serve as a potential setting for enhance DAA treatment.

Aim 4: To evaluate the change in HCV prevalence and treatment between 2018-2019 and 2019-2021 among PWID attending drug treatment clinics and NSPs in Australia

Hypothesis: The prevalence of current HCV infection will have reduced and the proportion of participants who have received treatment will have increased. Time will be significantly associated with both current HCV infection and HCV treatment. Other factors associated with HCV infection and HCV treatment will be similar to those found in Chapter Two (Aim 1).

Chapter 2: Progress towards elimination of hepatitis C infection among people who inject drugs in Australia: The ETHOS Engage Study

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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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2.1 Abstract

Background & Aims: Evaluating progress towards HCV elimination is critical. This study estimated prevalence of current HCV infection and HCV treatment uptake among people who inject drugs (PWID) in Australia. **Methods:** ETHOS Engage is an observational study of PWID attending drug treatment clinics and needle and syringe programs (NSP). Participants completed a questionnaire including self-reported treatment history and underwent point-of-care HCV RNA testing (Xpert® HCV Viral Load Fingerstick). **Results:** Between May 2018-September 2019, 1,443 participants were enrolled (64% injected drugs in the last month, 74% receiving opioid agonist therapy [OAT]). HCV infection status was uninfected (28%), spontaneous clearance (16%), treatment-induced clearance (32%), and current infection (24%). Current HCV was more likely among people who were homeless (adjusted odds ratio: 1.47; 95%CI: 1.00, 2.16), incarcerated in previous year (2.04; 1.38, 3.02), and those injecting drugs ≥daily (2.26; 1.43, 2.42). Among those with previous chronic or current HCV, 66% (n=520/788) reported HCV treatment. In adjusted analysis, HCV treatment was lower among females (0.68; 0.48, 0.95), participants who were homeless (0.59; 0.38, 0.96), and those injecting ≥daily (0.51; 0.31, 0.89). People aged ≥45 (1.46; 1.06, 2.01) and people receiving OAT (2.62; 1.52, 4.51) were more likely to report HCV treatment. **Conclusions:** Unrestricted DAA access in Australia has yielded high treatment uptake among PWID attending drug treatment and NSPs, with a marked decline in HCV prevalence. To achieve elimination, PWID with greater marginalisation may require additional support and tailored strategies to enhance treatment.

Keywords: hepatitis C virus, direct acting antivirals, people who inject drugs, hepatitis c virus elimination

2.2 Introduction

The World Health Organization (WHO)'s goal to eliminate hepatitis C virus (HCV) infection as a public health threat aims to reduce HCV incidence and related mortality by substantially increasing diagnosis and treatment [146]. Globally, an estimated 71 million people are infected with HCV, including an estimated 6.1 million who have recently injected drugs and a large population having injected drugs in the past [57, 146, 147]. Mathematical modelling has demonstrated the importance of rapid treatment initiation to reduce population-level HCV infection and prevent onward transmission among people who inject drugs (PWID) [94, 148]. Despite favourable treatment outcomes among PWID [91], system, societal, provider, and individual barriers persist and hinder optimal HCV care [120].

Since March 2016, adults infected with HCV have access to government reimbursed direct-acting antiviral (DAA) therapy with no drug, alcohol, or fibrosis stage restrictions [113]. This public health approach in the provision of unrestricted DAA therapy engendered one of the highest HCV treatment uptakes globally, with Australia named as one of few countries on track to achieve the WHO target of reducing new infections by 2030 [95, 144].

Although studies have explored DAA treatment among PWID, they are limited with respect to reimbursement restrictions, population size, single/homogenous settings, or insufficient virological data [91, 149-152]. This study evaluated progress towards HCV elimination among PWID in Australia among a large, national cohort of PWID recruited from drug treatment and needle and syringe programs (NSPs) during an unrestricted HCV treatment era. The primary aim of this study was to evaluate the proportion of

people with current HCV infection and associated factors. A secondary aim was to evaluate the proportion of people who had received HCV treatment and associated factors.

2.3 Patients and Methods

2.3.1 Data sources

ETHOS Engage is an observational cohort study. Participants were enrolled between 28 May 2018 and 06 September 2019 from 25 sites, including opioid agonist therapy (OAT) clinics (n=21) and NSPs (n=4); in New South Wales (n=17), Queensland (n=4), South Australia (n=2) and Western Australia (n=2).

Inclusion criteria were informed consent, age ≥18 years, history of injecting drug use, and either injection drug use in the previous 6 months or current OAT. Pregnant women were excluded given FibroScan® was contraindicated with at time of study protocol approval. The study protocol was approved by the Human Research Ethics Committees at St Vincent's Hospital, Sydney and the Aboriginal Health and Medical Research Council (HREC Ref: HREC/17/SVH/113).

2.3.2 Procedures

ETHOS Engage was advertised in the weeks preceding recruitment with posters, information cards distributed with injecting equipment, and word of mouth. Recruitment spanned two to five days at each site. Peer-support workers were on-site encouraging participation.

Participants provided 100 µl finger-stick capillary whole-blood sample to test for HCV RNA using the point-of-care Xpert HCV Viral Load Fingerstick assay (Cepheid, Sunnyvale, United States, lower limit of quantification 100 IU/mL; upper limit of quantification 10^8 log10 IU/mL) [131] and self-completed a computer tablet-based questionnaire collecting demographic, behavioural risk, previous HCV testing,

infection status, and treatment information. Fibrosis stage was assessed using transient elastography (FibroScan®, Echosens, Paris, France) and median stiffness (kPa) was discussed with appropriate clinical staff. Participation was compensated with a shopping voucher (AUD$30).

HCV RNA results were returned to clinics after quality assurance checks. Staff were encouraged to contact participants with current HCV infection to initiate treatment. Post-campaign treatment initiation and outcomes will be assessed in the three years proceeding campaign days.

2.3.3 Outcomes

The primary outcome was current HCV infection (HCV RNA detected with the Xpert HCV Viral Load Fingerstick assay). Previous work has demonstrated the high sensitivity (100%) and specificity (100%) of this assay in HCV RNA quantification [131, 153] and fingerstick testing acceptability among PWID [133].

The secondary outcome was self-reported history of HCV treatment among participants with either previous (self-reported history of HCV treatment) or current HCV infection (in participants who have been treatment eligible). Participants who were never infected (HCV RNA undetectable and self-reported as never having been diagnosed with HCV) and who had spontaneously cleared (HCV RNA undetectable, self-reported as having been diagnosed with HCV, and not having received HCV treatment) were also identified (Figure 1).

2.3.4 Statistical analysis

Logistic regression models were used to estimate the unadjusted and adjusted odds ratio (aOR) for: 1) factors associated with current HCV infection among the total cohort; and 2) factors associated with a history of HCV treatment among those with evidence of previous chronic or current HCV infection.

Demographic and behavioural factors hypothesised to be associated with current HCV infection and HCV treatment were determined *a priori*, comprising: (i) age at survey (stratified around median: <45, ≥45), (ii) gender, (iii) Indigenous ethnicity (Aboriginal and/or Torres Strait Islander), (iv) homelessness, (v) OAT status (never, past, within the last month/current), (vi) incarceration history (never, >1 year ago, within the last year), (vii) recency and frequency of injection drug use (> 1 year ago, within 1-12 months ago, within the last month <daily, and ≥daily), (viii) main drug injected in the last month (none, heroin, other opioids, methamphetamine, other) and (ix) hazardous alcohol consumption in the previous year, defined by the Alcohol Use Disorders Identification Test (AUDIT-C) [154].

All exposures were analysed in unadjusted analyses and considered for adjusted models if no collinearity was observed. Collinearity was assessed using variance-covariance matrices, with variables removed from adjusted models if ≥0.5 correlation was identified.

Each outcome was assessed for the overall eligible population, and subsequently restricted to participants with recent (last month) injecting drug use. In analyses restricted to participants with recent injecting drug use, injecting-related variables were

re-categorised as: recency and frequency of injecting (<daily, ≥daily); and main drug injected in the last month (heroin, other opioids, methamphetamine, other). In post-hoc analysis, predictors of HCV treatment were stratified by gender. Analyses were conducted using Stata 14.0 (StataCorp, College Station, TX, USA).

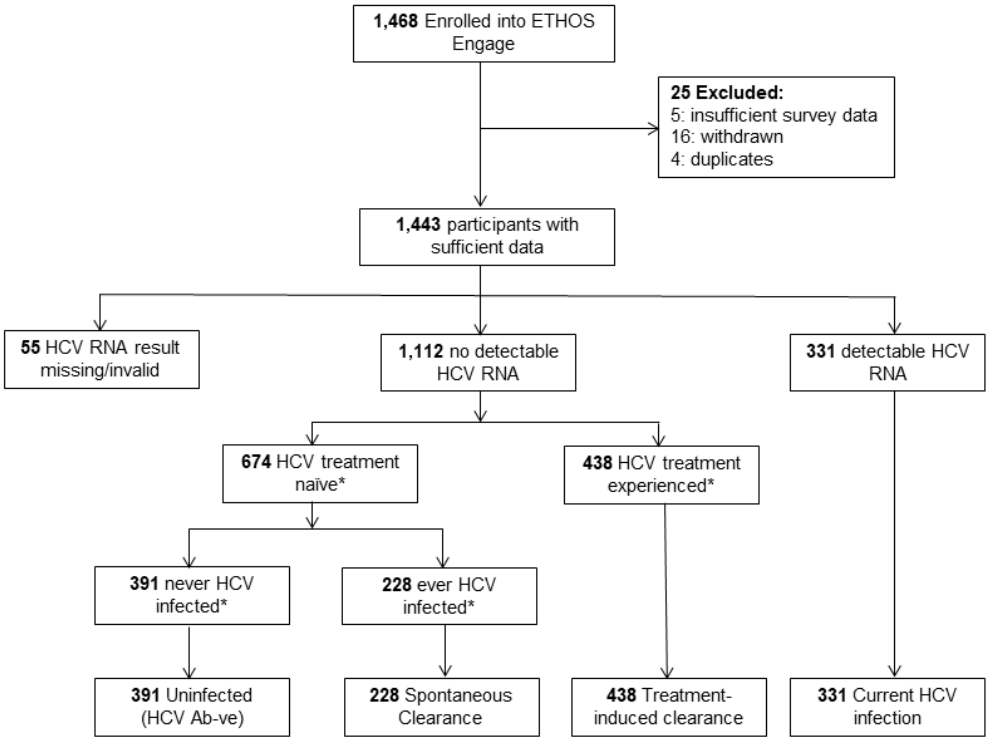
2.4 Results

2.4.1 Sample characteristics

Among 1,468 participants in ETHOS Engage, 5 (<1%) had insufficient questionnaire data, 16 (1%) withdrew participation, and 4 (<1%) duplicate enrolments were identified across sites, resulting in 1,443 participants (98%) eligible for analysis (Figure 1).

Median age was 43 (IQR: 37, 50), 65% (n=932) were male, 74% (n=1,070) were receiving OAT, and methamphetamine was the commonest main drug injected (31%, n=449). Nearly two-thirds (64%) of participants injected drugs in the last month, and 30% ≥daily, (Table 1). Characteristics stratified by recent injecting drug use, OAT status, and gender are presented in Supplementary Tables 1, 2, and 3.

Figure 1: ETHOS Engage participant flowchart, current HCV status (N=1,468)



*determined by self-report

Table 1: Characteristics of participants enrolled in ETHOS Engage (n=1,443)

Characteristic		Total (col%)
Total (N)		1,443
Age at survey	<45	791 (55%)
	≥45	652 (45%)
Gender	Male	932 (65%)
	Female	508 (35%)
	Transgender	3 (<1%)
Indigenous ethnicity	No	1,106 (77%)
	Yes	337 (23%)
Homeless	No	1,286 (89%)
	Yes	157 (11%)
OAT status	Never	205 (14%)
	Past	168 (12%)
	Current	1,070 (74%)
Incarceration history	Never	469 (32%)
	>1 year ago	715 (50%)
	Within last year	259 (18%)
Recency of injecting	>12 months	215 (15%)
	Within 1-12 months	307 (21%)
	Within last month, <daily	494 (34%)
	Within last month, ≥daily	427 (30%)
Main drug injected in last month	None	522 (36%)
	Heroin	312 (22%)
	Other opioids	132 (9%)
	Methamphetamine	449 (31%)
	Other	28 (2%)
Excessive alcohol consumption[†]	No	915 (64%)
	Yes	525 (36%)

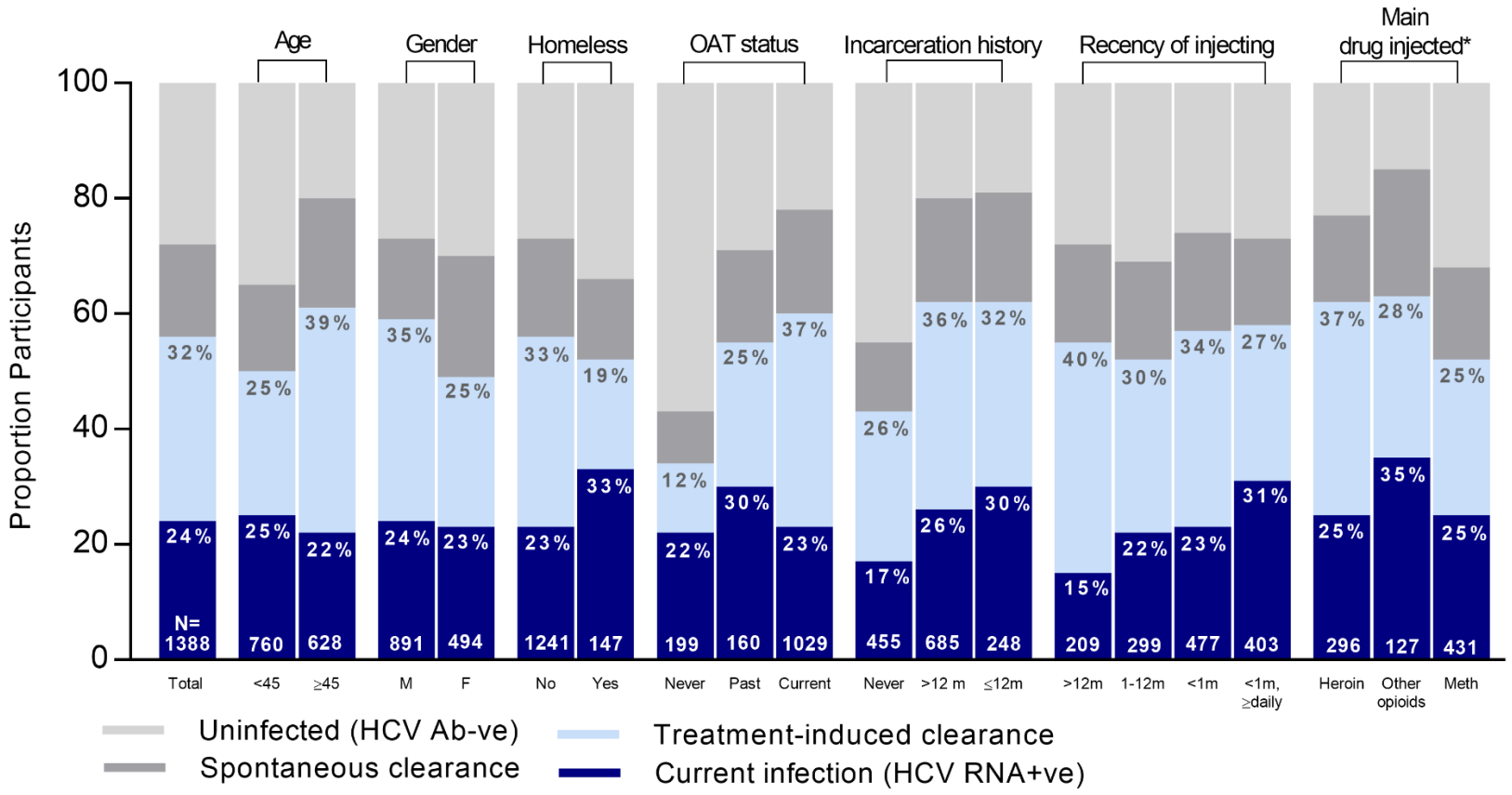
[†] Not reported for transgender participants

2.4.2 Factors associated with current HCV infection

Among all participants (n=1,443), 1,388 (96%) had valid Xpert Viral Load Fingerstick point-of-care results. Invalid results (n=55, 4%) included early withdrawal (n=16, 1%) and operator/machine error (n=39, 3%). Among those with valid results, 24% (n=331) were currently infected with HCV (HCV RNA detectable). The prevalence of current HCV infection stratified by characteristics is shown in Figure 2 and Table 2.

In adjusted analyses, factors associated with current HCV infection included homelessness (aOR: 1.47, 95%CI: 1.00, 2.16), incarceration history (vs. never, >1 year ago: aOR: 1.79, 95%CI: 1.30, 2.45; within the last year: aOR: 2.03, 95%CI: 1.38, 3.01), and ≥daily injecting drug use (aOR: 2.29, 95%CI: 1.45 – 3.62) (Table 3). In adjusted analyses among people with injecting drug use in the previous month, factors associated with current HCV infection were unchanged (Supplementary Table 4).

Figure 2: Current HCV prevalence among ETHOS Engage participants with known point-of-care HCV RNA result (n=1,388)



Abbreviations: M, male; F, female; OAT, opioid agonist therapy; m, month(s)
*Main drug injected in the last month. Data for participants injecting other drugs (n=24) not shown.

Table 2: Unadjusted and adjusted analysis of factors associated with current HCV infection all ETHOS Engage participants with available point-of-care HCV RNA results (n=1,388)

Characteristic		Total valid point-of-care result, n (col%)	Current HCV infection, n (row%)	OR (95% CI)	aOR (95% CI)
Total (N)		1,388	331 (24%)		
Age at enrolment	<45	760 (55%)	190 (25%)	-ref-	-ref-
	≥45	628 (45%)	141 (22%)	0.87 (0.68, 1.11)	0.92 (0.71, 1.20)
Gender	Male	891 (64%)	216 (24%)	-ref-	-ref-
	Female	494 (36%)	113 (23%)	0.93 (0.71, 1.20)	1.03 (0.78, 1.35)
	Transgender	3 (<1%)	2 (67%)	6.25 (0.56, 69.26)	omitted
Indigenous ethnicity	No	1064 (77%)	253 (24%)	-ref-	-ref-
	Yes	324 (23%)	78 (24%)	1.02 (0.76, 1.36)	0.93 (0.69, 1.26)
Homeless	No	1241 (89%)	282 (23%)	-ref-	-ref-
	Yes	147 (11%)	49 (33%)	1.70 (1.18, 2.45)	1.47 (1.00, 2.16)
OAT status	Never	199 (14%)	44 (22%)	-ref-	-ref-
	Past	160 (12%)	48 (30%)	1.51 (0.94, 2.43)	1.38 (0.85, 2.25)
	Current	1,029 (74%)	239 (23%)	1.07 (0.74, 1.53)	1.16 (0.78, 1.71)
Incarceration history	Never	455 (33%)	77 (17%)	-ref-	-ref-
	>1 year ago	685 (49%)	179 (26%)	1.74 (1.29, 2.34)	1.79 (1.30, 2.45)
	Within last year	248 (18%)	75 (30%)	2.13 (1.48, 3.07)	2.03 (1.38, 3.01)
Recency of injecting	>12 months	209 (15%)	31 (15%)	-ref-	-ref-
	Within 1-12 months	299 (22%)	67 (22%)	1.67 (1.04, 2.66)	1.54 (0.95, 2.49)
	Within last month, <daily	477 (34%)	109 (23%)	1.70 (1.10, 2.63)	1.54 (0.99, 2.41)
	Within last month, ≥daily	403 (29%)	124 (31%)	2.55 (1.65, 3.95)	2.29 (1.45, 3.62)
Main drug injected in last month	None	508 (37%)	98 (19%)	-ref-	
	Heroin	296 (21%)	75 (25%)	1.42 (1.01, 1.99)	
	Other opioids	127 (9%)	44 (35%)	2.21 (1.44, 3.29)	omitted

	Methamphetamine	431 (31%)	108 (25%)	1.40 (1.02, 1.90)	
	Other	26 (2%)	6 (23%)	1.25 (0.50, 3.20)	
Excessive alcohol consumption[†]	No	880 (64%)	197 (23%)	-ref-	-ref-
	Yes	505 (36%)	132 (26%)	1.25 (0.48, 3.20)	1.20 (0.92, 1.56)

Main drug injected in last month was not included in adjusted analyses due to collinearity with recency and frequency of injecting

[†] Not reported for transgender participants

2.4.3 Factors associated with HCV treatment

Overall, 55% (n=788) of participants had evidence of previous chronic (n=457) or current HCV infection (n=331). Among these (n=788, 55%; Table 3, Supplementary Figure 1), 66% (n=520) had self-reported ever initiating HCV treatment. (Table 2). The majority (85%) had initiated treatment in the DAA era (2016-2018) and 31% (n=162) reported receiving HCV treatment at a drug treatment clinic, 28% (n=148) from a hospital-based specialist clinic, 19% (n=100) from a general practitioner, 16% (n=85) in prison, 3% (n=14) within other community-based clinics, and 2% (n=9) within a NSP.

HCV treatment was lower in females (vs. males, 60% vs. 69%), those who were homeless (48% vs. 68%), those who never received OAT (vs. those currently receiving OAT, 42% vs. 70%), and those with ≥daily injecting drug use in the last month (vs. ≥1 year ago, 56% vs. 78%) (Table 3, Figure 3).

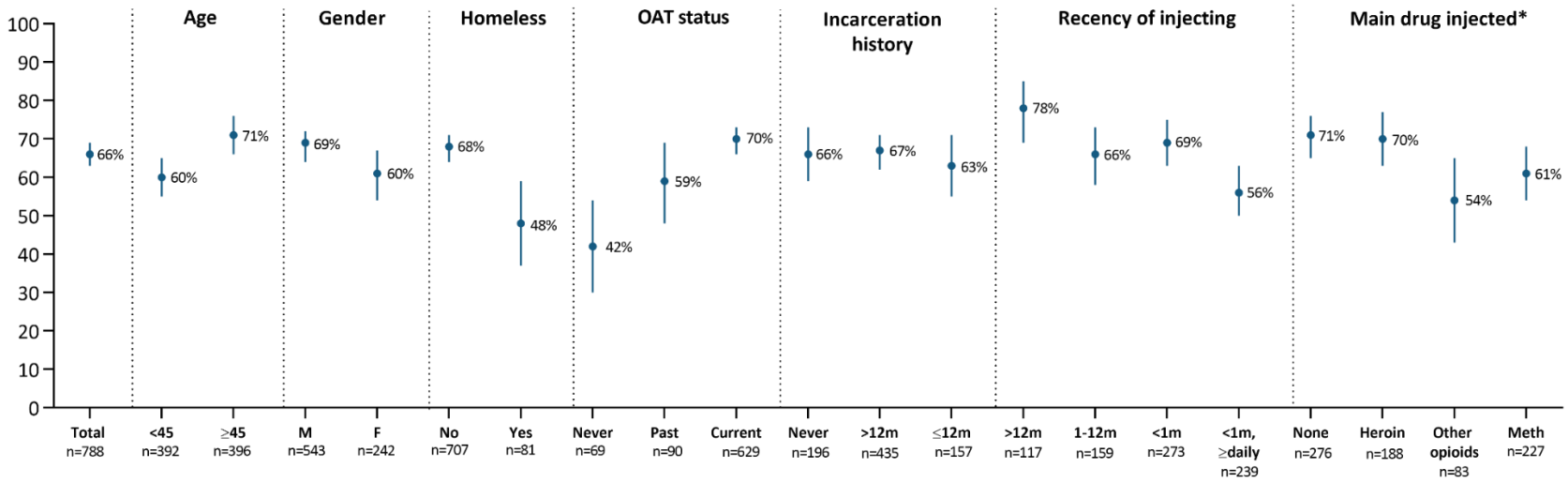
In adjusted analyses, HCV treatment was less likely among females (aOR: 0.68, 95% CI: 0.48, 0.96), people who were homeless (aOR: 0.59, 95% CI: 0.36, 0.96), and people with ≥daily injecting drug use (vs. no injecting in last year, aOR: 0.51, 95%CI: 0.30, 0.86). People aged ≥45 (vs. <45, aOR: 1.47, 95%CI: 1.07, 2.02) and people receiving OAT (aOR: 2.60, 95% CI: 1.51, 4.49) were more likely to receive HCV treatment (Table 3). In analyses restricted to people with recent injecting drug use (n=921), main drug injected in the last month was assessed in regression models. The factors associated with treatment were unchanged among this group (Supplementary Table 5).

To further investigate the association between gender and HCV treatment, stratified analyses were performed (Supplementary Table 3, 6). In adjusted analyses among males

with evidence of HCV infection (ever) (n=543/932, 58%), HCV treatment was less likely among those who were homeless (aOR: 0.49, 95%CI: 0.27, 0.8), and those with ≥daily injecting drug use (aOR: 0.49, 95%CI: 0.25, 0.95). HCV treatment was greater among males who had ever received OAT either in the past (aOR: 2.51, 95%CI: 1.13, 5.58) or currently (aOR: 2.86, 95%CI: 1.50, 5.49) (Supplementary Table 6). Age was not associated with HCV treatment (aOR: 1.14, 95% CI: 0.77, 1.70).

In adjusted analyses among females with evidence of HCV infection (ever) (n=242/508, 48%), the only factor independently associated with HCV treatment was age, with females aged ≥45 years more likely to have received treatment compared to those <45 years (aOR: 2.62, 95%CI: 1.47, 4.66) (Supplementary Table 6).

Figure 3: Self-reported historical HCV treatment among ETHOS Engage participants with evidence of previous or current HCV infection (n=788)



Abbreviations: M, male; F, female; OAT, opioid agonist therapy; m, month(s)
*Main drug injected in the last month. Data for participants injecting other drugs (n=24) not shown.

Table 3: Unadjusted and adjusted analysis of factors associated with self-reported historical HCV treatment among total ETHOS Engage participants who had evidence of previous or current HCV infection (n=788)

Characteristics		Previous or current HCV infection, n (row%)*	Treated, n (row%)	OR (95% CI)	aOR (95% CI)
Total (N)		788 (55%)	520 (66%)		
Age at enrolment	<45	395 (50%)	237 (60%)	-ref-	-ref-
	≥45	396 (61%)	283 (71%)	1.63 (1.22, 2.06)	1.47 (1.07, 2.02)
Gender	Male	543 (58%)	372 (69%)	-ref-	-ref-
	Female	242 (48%)	147 (61%)	0.71 (0.52, 0.98)	0.68 (0.48, 0.96)
	Transgender	3 (100%)	1 (33%)	0.23 (0.02, 2.55)	omitted
Indigenous ethnicity	No	613 (55%)	410 (67%)	-ref-	-ref-
	Yes	175 (52%)	110 (63%)	0.84 (0.59, 1.19)	0.87 (0.60, 1.26)
Homeless	No	707 (55%)	481 (68%)	-ref-	-ref-
	Yes	81 (52%)	39 (48%)	0.44 (0.27, 0.69)	0.59 (0.36, 0.96)
OAT status	Never	69 (34%)	29 (42%)	-ref-	-ref-
	Past	90 (54%)	53 (59%)	1.97 (1.04, 3.73)	1.88 (0.97, 3.63)
	Current	629 (59%)	438 (70%)	3.16 (1.90, 5.25)	2.60 (1.51, 4.49)
Incarceration history	Never	196 (42%)	130 (66%)	-ref-	-ref-
	>1 year ago	435 (61%)	291 (67%)	1.02 (0.72, 1.47)	0.91 (0.61, 1.34)
	Within last year	157 (61%)	99 (63%)	0.87 (0.56, 1.34)	0.85 (0.52, 1.39)
Recency of injecting	>12 months	117 (54%)	91 (78%)	-ref-	-ref-
	Within 1-12 months	159 (52%)	105 (66%)	0.56 (0.32, 0.96)	0.65 (0.37, 1.14)
	Within last month, <daily	273 (55%)	189 (69%)	0.64 (0.39, 1.07)	0.82 (0.48, 1.39)
	Within last month, ≥daily	239 (56%)	135 (56%)	0.37 (0.22, 0.61)	0.51 (0.30, 0.86)
Main drug injected in last month	None	276 (53%)	196 (71%)	-ref-	omitted
	Heroin	188 (60%)	132 (70%)	0.96 (0.64, 1.44)	
	Other opioids	83 (63%)	45 (54%)	0.48 (0.29, 0.80)	
	Methamphetamine	227 (51%)	139 (61%)	0.64 (0.44, 0.94)	
	Other	14 (50%)	8 (57%)	0.54 (0.18, 1.61)	
Excessive alcohol consumption[†]	No	495 (54%)	337 (68%)	-ref-	-ref-
	Yes	290 (55%)	182 (63%)	0.80 (0.59, 1.08)	0.85 (0.62, 1.16)

Main drug injected in last month was not included in adjusted analyses due to collinearity with recency and frequency of injecting* proportion of overall population (N=1,443); † Not reported for transgender participants

2.5 Discussion

In this national, well-characterised sample of PWID attending drug treatment clinics and NSPs in Australia, 24% were currently infected with HCV and 66% of people who had previous chronic or current HCV infection had ever received HCV treatment. Indicators of higher marginalisation were negatively associated with HCV treatment, and positively associated with current HCV infection. This study provides important insight into the impact of unrestricted DAA access and will inform policies and targeted strategies to further facilitate HCV elimination in Australia and globally.

Current HCV infection was higher (31%) in participants who reported ≥daily injecting drug use. Given the potential for HCV treatment to prevent onward transmission of infection [94, 103], treatment scale-up among people with frequent injecting drug use combined with harm reduction (OAT and NSP) will be critical for HCV elimination, particularly in countries where the majority of new infections occur among PWID. Enhanced support within low-threshold and targeted primary health settings, including individualised, tailored adherence support and peer-to-peer education and has been positively associated with treatment uptake and adherence among people with frequent injecting drug use [130, 155-158]. These strategies should be explored in the context of HCV treatment as prevention.

Treatment uptake was lower (56%) in those injecting ≥daily, consistent with previous studies [26, 152]. Despite an increased association with serious injection-related injury and blood borne virus infection, people who frequently inject drugs are more likely to experience barriers to healthcare access due to discrimination [159]. Such discrimination is associated with lower uptake of OAT and less access to a general

practitioner [160, 161], both associated with enhanced HCV knowledge and engagement[130, 162-164]. Overcoming these barriers may be possible through partnerships with peer-based organisations in primary health and harm reduction settings. Enhancing these partnerships may facilitate psychosocial support mechanisms, leading to improved healthcare-related communication between PWID and healthcare professionals, and greater treatment-related knowledge [158].

Participants who were homeless were more likely to have current HCV infection and less likely to report HCV treatment. These results are unsurprising given the strong associations between unstable housing and injection drug use [165] and the multiple barriers faced by people who are homeless in accessing healthcare: high prevalence of psychiatric comorbidities, competing priorities regarding day-to-day shelter and food security, increased stigmatisation, and lack of necessary identification for prescriptions [166, 167]. Interventions to address HCV in the context of these barriers are challenging. Previous work has indicated that housing complications were often cited as a common reason for missing appointments, despite being within models of care which integrate HCV therapy into specialised community medicine or within traditional low-threshold settings [168]. Higher marginalisation, such as experiencing homelessness, is associated with loss to follow-up and disengagement with HCV-related services [166, 167, 169]; however, treatment uptake among people who are homeless may be enhanced through one-stop-shop models which, utilise point-of-care testing, and offer immediate, same-day treatment initiation [155, 169] and policy interventions to improve housing stability [165]. Innovative, holistic strategies to engage people who are homeless with harm reduction and HCV care are required [166, 167].

Current OAT was associated with higher HCV treatment, consistent with published research [151, 152, 164, 166]. OAT engagement is associated with increased awareness of HCV therapy and its effectiveness [163]. Furthermore, OAT is associated with reductions across multiple health outcomes, including injecting risk behaviour [170], risk of HIV and HCV [171, 172], criminal activity [173], and all-cause and overdose [174] mortality. Ensuring high coverage and access to OAT is critical in achieving HCV elimination and improving health outcomes among PWID. Further, a significant proportion of PWID may not be opioid dependant, and efforts to increase HCV treatment among people who inject stimulants is warranted.

In line with previously published results, age was associated with HCV treatment [152]. Older PWID typically report less high-risk injection practices and increased uptake of health-related services, making this group generally easier to reach compared to younger PWID [175]. Surveillance suggests population-level ageing of PWID in Australia; however, in some settings there is a fast-growing population of younger PWID at risk of, or infected with, HCV and should therefore be considered a key population to engage in HCV care [130, 176]. While this study was insufficiently powered to analyse outcomes solely among younger PWID (<25, n=57), these results imply the importance of monitoring HCV and treatment initiation among this group.

The gender-specific differences in reported HCV treatment corroborate previous evidence, with females less likely to initiate treatment than males [177, 178]. Among women, the only independent factor associated with HCV treatment uptake was age, with older women more likely to have received treatment than younger women. Despite these results, gender was not associated with current HCV infection, related to the

higher likelihood of spontaneous clearance among females [179]. Previous work has highlighted increased marginalisation among women who inject drugs, and the higher vulnerability in this population that contributes to disengagement with healthcare [177]. The intersectionality of gender, age and other factors—such as ethnicity and receipt of OAT—is associated with treatment deferral [177, 178]. Gender-specific interventions which reduce vulnerabilities and marginalisation among women who inject drugs are key. Further research is necessary to understand the complexity of treatment deferral among younger women.

Considering the criminalisation of drug possession in Australia, the proportion of participants who had a history of incarceration (68%) was unsurprising. While not a factor associated with HCV treatment, incarceration was significantly associated with current HCV infection, highlighting prisons as key settings HCV prevention and treatment. Although injecting frequency attenuates following incarceration, among those who continue to inject, there is increased sharing of needles and syringes [180]. Increased coverage of harm reduction and novel person-centred strategies may be needed to ensure prevention, timely diagnosis, and initiation onto HCV therapy, both in prison and post-release [181, 182].

This study has limitations. Serological status was based on self-report and virology, potentially underestimating true HCV antibody prevalence; however, the inferred prevalence found here is similar to annual surveillance of PWID in Australia [130] and the utilisation of the Xpert Viral Load Finger-stick assay for HCV RNA has allowed characterisation of current HCV prevalence among vast majority of participants (>95%), differentiating these results from previous studies [151]. Furthermore,

participation in ETHOS Engage was voluntary, and recruitment was performed in healthcare settings, the majority of which operated primarily as, or in conjunction with OAT. The annual Australian NSP survey indicates nearly half of PWID last injected methamphetamine (48%) and ≥daily (51%). While it is encouraging that this study was able to engage a large population of PWID who were mainly injecting methamphetamine (31%) and injecting drugs ≥daily (30%), these results may be under-representative of the wider injecting population. This oversampling PWID engaged in OAT has potentially introduced selection bias, possibly overestimating HCV treatment and underestimating current infection compared to a wider population of PWID. Finally, questionnaire data rely on recall and self-report. Although self-report is considered a reliable source of data collection among people who use drugs, some may not have provided accurate answers [183]. While recall bias could not be systematically minimised, we aimed to reduce social-desirability bias by providing self-administered surveys and ensuring anonymity.

2.5.1 Conclusions and implications

In the context of HCV elimination, high treatment uptake across sub-populations was encouraging. These results highlight the successes of an unrestricted HCV treatment strategy in reaching marginalised populations of PWID and suggest progress towards achieving incidence-related HCV elimination targets. It is estimated that among the 93,500 people who have recently injected drugs in Australia, an estimated 37,500 are infected with HCV [50, 57]. As such, it will be critical to enhance efforts to engage with the most marginalised PWID sub-populations, including people who are homeless or incarcerated, to maintain this progress. To engage those who remain untreated and those who may require follow-up and retreatment, interventions which reduce barriers to

testing and treatment, including utilisation of dried blood spot and point-of-care technology and provision of financial incentives to initiate treatment within drug clinics should be further explored [128, 184, 185]. Additionally, the importance of a peer work force for the facilitation of HCV elimination should not be underestimated [157, 158].

Although largely indicative of a good news story on the path towards elimination of HCV among PWID, challenges remain. It is imperative that innovative strategies and holistic approaches to improve linkage to HCV-related care are adopted to further enhance engagement with people living with HCV who may delay treatment for competing priorities. There is an urgent need for increased efforts to address the gaps in care highlighted here to ensure HCV elimination is equitable across all PWID in Australia and globally.

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Harm Reduction Western Australia: Lyn Murphy

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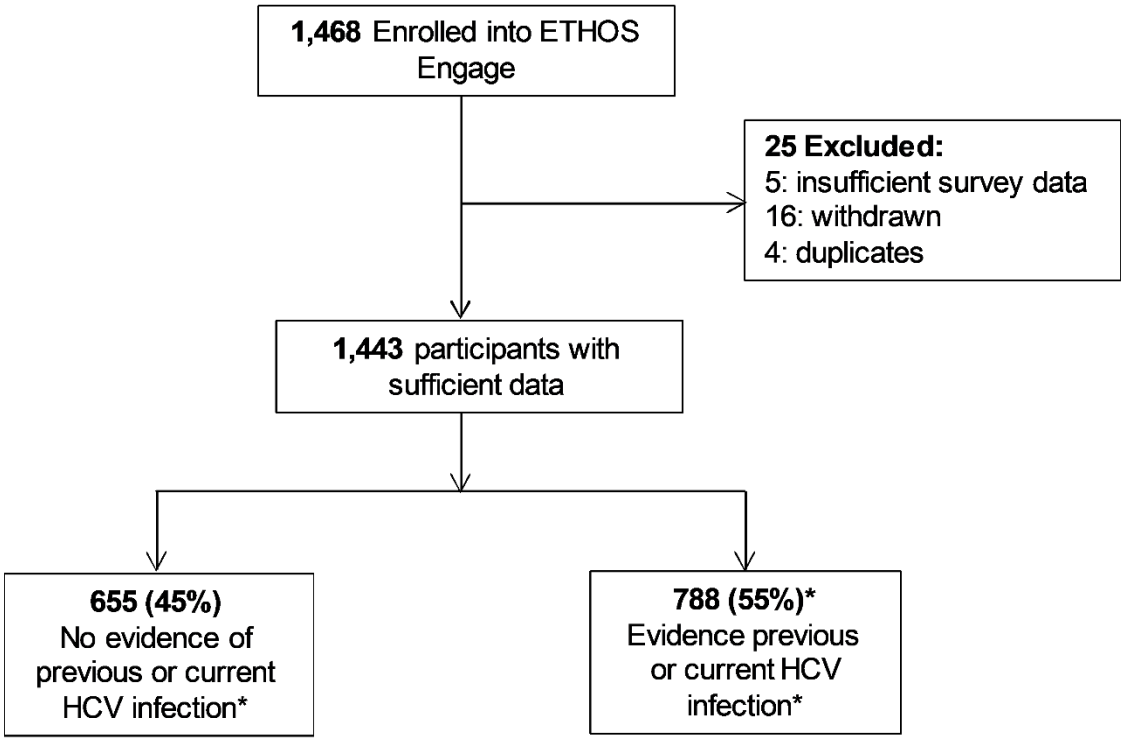
2.6 Supplementary Material

Supplementary Figure 1: Participant flowchart, ETHOS Engage (N=1,468)



Supplementary Table 1: Characteristics of participants enrolled in ETHOS Engage, stratified by recent injection drug use (N=1,443)

Characteristic		Total (col%)	Recent injection drug use, n (row%)
Total		1,443	921 (64%)
Age at enrolment	<45	791 (55%)	526 (67%)
	≥45	652 (45%)	395 (67%)
Gender	Male	732 (65%)	592 (64%)
	Female	508 (35%)	327 (64%)
	Transgender	3 (<1%)	2 (67%)
Indigenous ethnicity	No	1,106 (77%)	714 (65%)
	Yes	337 (23%)	207 (61%)
Homeless	No	1,286 (89%)	792 (62%)
	Yes	157 (11%)	129 (82%)
OAT Status	Never	205 (14%)	163 (80%)
	Past	168 (12%)	126 (75%)
	Current	1,070 (74%)	632 (59%)
Incarceration history	Never	469 (32%)	288 (61%)
	>1 year ago	715 (50%)	457 (64%)
	Within last year	259 (18%)	176 (67%)
Recency of injecting	>12 months	215 (15%)	NA
	Within 1-12 months	307 (21%)	NA
	Within last month, <daily	494 (34%)	494 (100%)
	Within last month, ≥daily	427 (30%)	427 (100%)
Main drug injected	None	522 (36%)	NA
	Heroin	312 (22%)	312 (100%)
	Other opioids	132 (9%)	132 (100%)
	Methamphetamine	449 (31%)	449 (100%)
	Other	28 (2%)	28 (100%)
Excessive alcohol consumption[†]	No	915 (64%)	562 (61%)
	Yes	525 (36%)	357 (68%)

[†] Not reported for transgender participants

Supplementary Table 2: Characteristics of ETHOS Engage participants stratified by OAT status (n=1,443)

Characteristic		Total (col%)	**OAT Status**, n (row%)		
			Never	Past	Current
Total		1,443	205 (14%)	167 (12%)	1070 (74%)
Age at enrolment	<45	791 (55%)	114 (14%)	85 (11%)	592 (75%)
	≥45	652 (45%)	91 (13%)	83 (12%)	478 (73%)
Gender	Male	932 (65%)	128 (14%)	115 (12%)	689 (74%)
	Female	508 (35%)	77 (15%)	53 (10%)	378 (74%)
	Transgender	3 (<1%)	0 (0%)	0 (0%)	3 (100%)
Indigenous ethnicity	No	1,106 (77%)	144 (13%)	133 (12%)	829 (75%)
	Yes	337 (23%)	61 (18%)	35 (10%)	241 (72%)
Homeless	No	1,286 (89%)	161 (13%)	139 (11%)	986 (77%)
	Yes	157 (11%)	44 (28%)	29 (18%)	84 (54%)
Incarceration history	Never	469 (32%)	101 (22%)	55 (12%)	313 (67%)
	>1 year ago	715 (50%)	85 (12%)	77 (11%)	553 (77%)
	Within last year	259 (18%)	19 (7%)	36 (14%)	204 (79%)
Recency of injecting	>12 months	215 (15%)	NA	NA	215 (100%)
	Within 1-12 months	307 (21%)	42 (14%)	42 (14%)	223 (73%)
	Within last month, <daily	494 (34%)	77 (16%)	50 (10%)	367 (74%)
	Within last month, ≥daily	427 (30%)	86 (20%)	76 (18%)	265 (62%)
Main drug injected in last month	None	522 (36%)	42 (8%)	42 (8%)	438 (84%)
	Heroin	312 (22%)	14 (4%)	26 (8%)	272 (87%)
	Other opioids	132 (9%)	18 (14%)	30 (23%)	84 (63%)
	Methamphetamine	449 (31%)	127 (28%)	67 (15%)	255 (57%)
	Other	28 (2%)	4 15%)	3 (11%)	21 (75%)
Excessive alcohol consumption†	No	915 (64%)	119 (13%)	95 (10%)	701 (77%)
	Yes	525 (36%)	86 (17%)	73 (14%)	366 (70%)

† Not reported for transgender participants

Supplementary Table 3: Characteristics of participants enrolled in ETHOS Engage, stratified by gender (N=1,140)*

Characteristic		Total (col%)	**Gender***, n (row%)	
			Male	Female
Total		1,140	932 (65%)	508 (35%)
Age at enrolment	<45	789 (55%)	485 (61%)	304 (38%)
	≥45	651 (45%)	446 (68%)	204 (31%)
Indigenous ethnicity	No	1,103 (77%)	741 (67%)	361 (33%)
	Yes	337 (23%)	190 (56%)	147 (44%)
Homeless	No	1,283 (89%)	832 (65%)	450 (35%)
	Yes	157 (11%)	99 (63%)	58 (37%)
OAT Status	Never	205 (14%)	128 (62%)	77 (38%)
	Past	168 (12%)	114 (68%)	53 (32%)
	Current	1,067 (74%)	689 (64%)	378 (35%)
Incarceration history	Never	467 (32%)	232 (50%)	234 (50%)
	>1 year ago	714 (50%)	499 (70%)	215 (30%)
	Within last year	259 (18%)	200 (77%)	59 (23%)
Recency of injecting	>12 months	215 (15%)	142 (66%)	73 (34%)
	Within 1-12 months	306 (21%)	197 (65%)	108 (35%)
	Within last month, <daily	493 (34%)	327 (66%)	166 (34%)
	Within last month, ≥daily	426 (30%)	265 (62%)	161 (37%)
Main drug injected in last month	None	521 (36%)	339 (65%)	181 (35%)
	Heroin	311 (22%)	195 (63%)	116 (37%)
	Other opioids	131 (9%)	86 65%)	45 34%)
	Methamphetamine	449 (31%)	291 (65%)	158 (35%)
	Other	28 (2%)	20 (71%)	8 (29%)
Excessive alcohol consumption	No	915 (64%)	599 (65%)	316 (34%)
	Yes	525 (36%)	332 (63%)	197 (37%)

*Participants identifying transgender excluded from sex-specific stratification due to small sample size (n=3)

Supplementary Table 4: Unadjusted and adjusted analysis of factors associated with current HCV infection among all ETHOS Engage participants with a valid point-of-care HCV RNA result who had recently injected drugs (n=880)

Characteristic		Total valid point-of-care result, n (col%)	Current HCV infection, n (row%)	OR (95% CI)	aOR (95% CI)
Total (N)		880	233 (26%)		
Age at enrolment	<45	502 (57%)	146 (29%)	-ref-	-ref-
	≥45	378 (43%)	87 (23%)	0.76 (0.55, 1.03)	0.72 (0.52, 1.00)
Gender	Male	562 (64%)	152 (27%)	-ref-	-ref-
	Female	316 (36%)	80 (25%)	0.91 (0.66, 1.25)	1.04 (0.75, 1.47)
	Transgender	2 (<1%)	1 (50%)	2.62 (0.16, 42.21)	omitted
Indigenous ethnicity	No	683 (78%)	181 (27%)	-ref-	-ref-
	Yes	197 (22%)	52 (26%)	1.00 (0.69, 1.43)	0.86 (0.59, 1.26)
Homeless	No	761 (86%)	190 (25%)	-ref-	-ref-
	Yes	119 (14%)	43 (36%)	1.71 (1.13, 2.58)	1.56 (1.00, 2.42)
OAT status	Never	158 (18%)	39 (25%)	-ref-	-ref-
	Past	120 (14%)	40 (33%)	1.48 (0.87, 2.52)	1.32 (0.76, 2.28)
	Current	602 (68%)	154 (26%)	1.07 (0.71, 1.61)	0.93 (0.59, 1.47)
Incarceration history	Never	279 (32%)	48 (17%)	-ref-	-ref-
	>1 year ago	422 (49%)	128 (30%)	2.08 (1.41, 3.06)	2.27 (1.53, 3.40)
	Within last year	168 (19%)	57 (34%)	2.50 (1.58, 3.93)	2.61 (1.61, 4.21)
Frequency of injecting	Within last month, <daily	477 (54%)	109 (23%)	-ref-	-ref-
	Within last month, ≥daily	403 (46%)	124 (31%)	1.56 (1.15, 2.12)	1.37 (0.99, 1.88)
Main drug injected in last month	Heroin	296 (34%)	75 (25%)	-ref-	-ref-
	Other opioids	127 (14%)	44 (35%)	1.48 (0.94, 2.35)	1.46 (0.91, 2.34)
	Methamphetamine	431 (49%)	108 (25%)	0.95 (0.67, 1.34)	0.91 (0.62, 1.32)
	Other	26 (3%)	6 (23%)	0.93 (0.36, 2.45)	0.84 (0.31, 2.22)
Excessive alcohol consumption	No	537 (61%)	138 (26%)	-ref-	-ref-
	Yes	341 (39%)	67 (28%)	1.15 (0.84, 1.58)	1.09 (0.80, 1.50)

Main drug injected in last month was removed from adjusted analyses due to collinearity with recency and frequency of injecting

† Not reported for transgender participants

Supplementary Table 5: Unadjusted and adjusted analysis of factors associated with self-reported historical HCV treatment among ETHOS Engage participants who recently injected drugs and were ever eligible for HCV treatment (n=512)

Characteristics		Previous or current HCV infection ,n (row%)	Treated, n (row%)	OR (95% CI)	aOR (95% CI)
Total (N)		512	324 (63%)		
Age at enrolment	<45	276 (52%)	157 (57%)	-ref-	-ref-
	≥45	236 (60%)	167 (71%)	1.83 (1.27, 2.65)	1.71 (1.15, 2.55)
Gender	Male	352 (59%)	232 (66%)	-ref-	-ref-
	Female	158 (48%)	91 (58%)	0.70 (0.48, 1.03)	0.65 (0.43, 1.00)
	Transgender	2 (100%)	1 (50%)	0.52 (0.03, 8.34)	omitted
Indigenous ethnicity	No	410 (57%)	267 (65%)	-ref-	-ref-
	Yes	102 (49%)	57 (56%)	0.68 (0.43, 1.05)	0.72 (0.45, 1.16)
Homeless	No	449 (57%)	297 (66%)	-ref-	-ref-
	Yes	63 (49%)	27 (43%)	0.38 (0.22, 0.66)	0.51 (0.29, 0.91)
OAT status	Never	63 (39%)	27 (43%)	-ref-	-ref-
	Past	72 (57%)	41 (57%)	1.76 (0.89, 3.49)	1.70 (0.83, 3.47)
	Current	377 (60%)	256 (68%)	2.82 (1.63, 4.85)	2.40 (1.32, 4.36)
Incarceration history	Never	118 (41%)	75 (64%)	-ref-	-ref-
	>1 year ago	287 (63%)	186 (64%)	1.05 (0.68, 1.64)	0.89 (0.54, 1.46)
	Within last year	107 (61%)	63 (59%)	0.82 (0.48, 1.40)	0.76 (0.42, 1.39)
Frequency of injecting	Within last month, <daily	273 (55%)	189 (69%)	-ref-	-ref-
	Within last month, ≥daily	439 (56%)	135 (57%)	0.58 (0.40, 0.83)	0.63 (0.43, 0.94)
Main drug injected in last month	Heroin	188 (60%)	132 (70%)	-ref-	-ref-
	Other opioids	83 (63%)	45 (54%)	0.50 (0.29, 0.85)	0.61 (0.34, 1.07)
	Methamphetamine	227 (51%)	139 (61%)	0.67 (0.44, 1.01)	0.81 (0.51, 1.26)
	Other	14 (50%)	8 (57%)	0.57 (0.19, 1.70)	0.42 (0.13, 1.31)
Excessive alcohol consumption[†]	No	310 (55%)	200 (64%)	-ref-	-ref-
	Yes	200 (56%)	123 (62%)	0.88 (0.61, 1.27)	0.97 (0.66, 1.43)

[†] Not reported for transgender participants

Supplementary Table 6: Unadjusted and adjusted analysis of factors associated with self-reported historical HCV treatment among males (n=543), and females (n=242) who have evidence of previous or current HCV infection

Characteristic		Males				Females			
		Previous or current HCV infection, n (row%)	Treated, n (row%)	OR (95% CI)	aOR (95% CI)	Previous or current HCV infection, n (row%)	Treated, n (row%)	OR (95% CI)	aOR (95% CI)
Total		543	372 (69%)			242	147(61%)		
Age at enrolment	<45	264 (54%)	172 (65%)	-ref-	-ref-	126 (41%)	64 (51%)	-ref-	-ref-
	≥45	276 (62%)	200 (72%)	1.35 (0.94, 1.94)	1.14 (0.77, 1.70)	116 (57%)	83 (71%)	2.44 (1.42, 4.15)	2.62 (1.47, 4.66)
Indigenous ethnicity	No	438 (59%)	304 (69%)	-ref-	-ref-	172 (57%)	105 (61%)	-ref-	-ref-
	Yes	105 (55%)	68 (65%)	0.81 (0.52, 1.27)	0.75 (0.46, 1.21)	70 (58%)	42 (60%)	0.95 (0.54, 1.69)	1.07 (0.58, 1.97_
Homeless	No	484 (58%)	344 (71%)	-ref-	-ref-	220 (49%)	136 (62%)	-ref-	-ref-
	Yes	59 (60%)	28 (47%)	0.37 (0.21, 0.64)	0.49 (0.27, 0.88)	22 (38%)	11 (50%)	0.62 (0.26, 1.49)	0.94 (0.36, 2.45)
OAT Status	Never	49 (38%)	20 (41%)	-ref-	-ref-	20 (56%)	9 (45%)	-ref-	-ref-
	Past	63 (55%)	41 (65%)	2.70 (1.25, 5.83)	2.51 (1.13, 5.58)	27 (51%)	12 (44%)	0.98 (0.31, 3.12)	0.88 (0.26, 3.02)
	Current	431 (63%)	311 (72%)	3.75 (2.04, 6.89)	2.86 (1.50, 5.49)	195 (52%)	126 (65%)	2.23 (0.88, 5.65)	1.97 (0.72, 5.40)
Incarceration history	Never	93 (40%)	66 (71%)	-ref-	-ref-	101 (43%)	63 (62%)	-ref-	-ref-
	>1 year ago	322 (65%)	223 (69%)	0.92 (0.56, 1.53)	1.01 (0.59, 1.72)	112 (52%)	68 (61%)	0.93 (0.54, 1.62)	0.78 (0.43, 1.41)
	Within last year	128 (64%)	83 (65%)	0.75 (0.42, 1.34)	0.83 (0.45, 1.53)	29 (49%)	16 (55%)	0.74 (0.32, 1.71)	0.90 (0.36, 2.24)
Recency of injecting	>12 months	79 (56%)	63 (80%)	-ref-	-ref-	38 (52%)	28 (74%)	-ref-	-ref-
	Within 1-12 months	112 (57%)	77 (69%)	0.56 (0.28, 1.10)	0.64 (0.32, 1.28)	46 (43%)	28 (61%)	0.56 (0.22, 1.41)	0.69 (0.26, 1.83)
	Within last month, <daily	188 (57%)	136 (72%)	0.66 (0.35, 1.25)	0.79 (0.41, 1.54)	85 (51%)	53 (63%)	0.61 (0.26, 1.42)	0.85 (0.35, 2.07)
	Within last month, ≥daily	164 (62%)	96 (58%)	0.36 (0.19, 0.67)	0.49 (0.25, 0.95)	74 (46%)	38 (51%)	0.38 (0.16, 0.89)	0.57 (0.22, 1.45)
Main drug injected in last month	None	191 (56%)	140 (73%)	-ref-	omitted	84 (46%)	56 (67%)	-ref-	omitted
	Heroin	127 (65%)	94 (74%)	1.03 (0.62, 1.73)		60 (52%)	37 (62%)	0.80 (0.40, 1.60)	
	Other opioids	58 (67%)	32 (55%)	0.45 (0.24, 0.82)		24 (53%)	13 (54%)	0.59 (0.23, 1.48)	
	Methamphetamine	154 (53%)	99 (64%)	0.66 (0.41, 1.04)		73 (46%)	40 (55%)	0.61 (0.32, 1.16)	
	Other	13 (65%)	7 (54%)	0.43 (0.14, 1.32)		1 (13%)	1 (100%)	-omitted-	
Excessive alcohol consumption	No	347 (58%)	242 (70%)	-ref-	-ref-	148 (47%)	95 (64%)	-ref-	-ref-
	Yes	196 (59%)	130 (66%)	0.85 (0.59, 1.24)	0.92 (0.63, 1.38)	94 (49%)	52 (55%)	0.69 (0.41, 1.17)	0.69 (0.39, 1.21)

Main drug injected in last month was removed from adjusted analyses due to collinearity with recency and frequency of injecting; *Participants who identified as transgender dropped from stratification due to small sample size (n=3); † Not reported for transgender participants

Chapter 3: High hepatitis C treatment uptake among people with recent drug dependence in New South Wales, 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: High HCV treatment among people at most risk of transmission is essential to achieve elimination. We aimed to characterise subpopulations of people with HCV based on drug dependence, to estimate direct-acting antiviral (DAA) uptake in an unrestricted treatment era, and evaluate factors associated with treatment uptake among people with recent drug dependence. **Methods:** HCV notifications in New South Wales, Australia (1995-2017) were linked to opioid agonist therapy (OAT), hospitalisations, incarcerations, HIV notifications, deaths, and prescription databases. Drug dependence was defined as hospitalisation due to injectable drugs or receipt of OAT, with these indicators in 2016-2018 considered recent. Records were weighted to account for spontaneous clearance. Logistic regression was used to analyse factors associated with treatment uptake among those with recent drug dependence. **Results:** 57,467 people were estimated to have chronic HCV throughout the DAA era. Treatment uptake was highest among those with recent (47%), compared to those with distant (38%), and no (33%) drug dependence. Among those with recent drug dependence, treatment was more likely among those with HIV (aOR: 1.71, 95%CI: 1.24, 2.36), recent incarceration (aOR: 1.10, 95%CI: 1.01, 1.19), and history of alcohol use disorder (aOR: 1.22, 95%CI: 1.13, 1.31). Treatment was less likely among women (aOR: 0.78, 95%CI: 0.72, 0.84), Indigenous (aOR: 0.75, 95%CI: 0.69, 0.81), foreign-born (aOR: 0.86, 95%CI: 0.78, 0.96), those with outer-metropolitan notifications (aOR: 0.90, 95%CI: 0.82, 0.98), HBV (aOR: 0.69, 95%CI: 0.59, 0.80), and >1 recent hospitalisation (aOR: 0.91, 95%CI: 0.84, 0.98). **Conclusions:** These data provide evidence of high DAA uptake among people with recent drug dependence, including those incarcerated. Enhancing this encouraging initial uptake among high-risk populations will be essential to achieve HCV elimination.

Keywords: hepatitis C virus; direct acting antiviral therapy; drug dependence; injecting drug use; opioid substitution therapy; data linkage

3.2 Introduction

A decade remains to achieve the World Health Organization's 2030 goal to eliminate hepatitis C virus (HCV) as a global public health threat [133]. Achieving these targets, including the reduction in HCV incidence by 90%, necessitates high testing and treatment uptake among populations who account for the highest incidence and prevalence of infection. People who inject drugs (PWID) are a priority population for HCV elimination, but are an often marginalised with considerable barriers to care [120].

From March 2016, Australian specialists and non-specialists were able to prescribe government-reimbursed direct-acting antiviral (DAA) therapy to all adults with chronic HCV with neither drug and alcohol nor disease stage-related restrictions. Although this type of "unrestricted" DAA access is becoming more common, as drug pricing falls [107], Australia has been an international leader in broad DAA access and HCV elimination [186]. As such, investigating characteristics associated with treatment uptake among PWID in Australia is informative for further elimination efforts nationally and globally.

To determine DAA era treatment uptake and impact among marginalised, key populations, previous studies have used a combination of data derived from mathematical modelling which produces estimates with large uncertainty intervals [95, 187], and small-scale cohort studies prone to selection bias [151, 188]. Recent evidence of HCV treatment uptake among PWID in the DAA era has therefore been limited.

New South Wales (NSW), Australia is one of few settings with well-established, population-based linked databases for all HCV notifications. This study sought to utilise

these linked databases to identify people with HCV notification according to evidence of historical or recent drug dependence and to evaluate the proportion of, and factors associated with, DAA treatment initiation among those with drug dependence.

3.3 Methods

3.3.1 Setting, data sources and record linkages

NSW accounts for approximately 35% of HCV burden [189] and 40% of PWID [59] in Australia. The NSW Notifiable Conditions Information Management System (NCIMS) holds records of all individuals with HCV and hepatitis B virus (HBV) positive serology from 1993. Notification of positive HCV serology was the study inclusion criteria. These records were subsequently linked to the (1) NSW Admitted Patient Data Collection (APDC) database, for inpatient hospital discharges occurring in NSW from 2001, (2) NSW Registry of Birth Deaths, and Marriages, for date of death from 1993, (3) NSW Electronic Recording and Reporting of Controlled Drugs system, for opiate agonist therapy (OAT) authority data from 1985, (4) NSW Bureau of Crime Statistics and Research (BOCSAR) dataset, for dates of incarceration and release from 1994, and (5) National HIV Registry, for new HIV diagnoses made from 1994. The New South Wales Centre for Health Record Linkage used demographic details (including full name, sex, date of birth, and address) to probabilistically and deterministically link records between datasets, as previously described [190]. These datasets underwent a subsequent probabilistic linkage by the Australian Institute of Health and Welfare based on individual Medicare number (unique universal health insurance number) to the Pharmaceutical Benefits Schedule (PBS) dataset which holds HCV therapy dispensing data from 2010.

3.3.2 Study period

For the study period, data were extracted from each database as follows: HCV notifications (1 January 1993-31 December 2017); hospitalisations (1 January 2001-30 June 2018); deaths (1 January 1993-30 June 2018); OAT authority (1 January 1985-19

September 2018); incarcerations (1 January 1994-31 December 2017); HIV notifications (1 January 1985-31 December 2017); HCV treatment (1 January 2010-31 December 2018).

3.3.3 Study population

For all HCV notifications, hospitalisations occurring due to injectable drugs and/or infections indicative of injection drug use(IDU-related hospitalisation henceforth) were identified using the ICD-10 classifications of disease manual (Supplementary Table 1) [191]. As IDU-related hospitalisations are not sensitive enough to capture the wider population of PWID, an indicator of drug dependence was created by combining IDU-related hospitalisations with OAT authority data. IDU-related hospitalisations and/or receipt of OAT occurring between 2016-2018 were considered as indicators of recent drug dependence (i.e. evidence of drug dependence in the DAA era); records with last hospitalisation or OAT dose recorded any time pre-2016 were considered as indicators of distant drug dependence. Three mutually exclusive groups, according to drug dependence, therefore comprise: (1) no, (2) distant, and (3) recent evidence. Within the recent drug dependence group, three mutually exclusive groups comprise those with: (1) IDU-related hospitalisation only, (2) IDU-related hospitalisation and OAT dose, and (3) those with OAT dose only.

3.3.4 Outcome

The primary outcome was first initiation of DAA therapy for HCV occurring between 2016-2018, among (1) the total population, (2) the three broader drug-dependent populations, and (3) the three sub-populations of people with evidence of recent drug

dependence. The secondary outcome was to assess factors associated with treatment uptake among those with evidence of recent drug dependence.

3.3.5 Exclusion criteria

Due to concerns with sensitivity and specificity of early generation HCV antibody assays, records were removed where date of HCV notification occurred prior to 01 January 1995 (n=12,319) [190]. Records with unknown date of birth (n=55), those <18 years by end of follow up (31 December 2018) (n=244), and those whose sex was undetermined (n=409) were excluded.

To allow time for treatment initiation, records were removed if death occurred before 01 June 2016 (n=11,174). Post-mortem notifications were removed (n=20). Records with no Medicare (universal healthcare) number available for PBS (HCV treatment) linkage were excluded (n=9,931). Supplementary Table 2 compares characteristics of records which were linked and unlinked to Medicare. Those who had been prescribed interferon-based therapy with no subsequent HCV treatment were assumed to have cleared HCV infection and were removed (n=1,500). A flowchart describing derivation of the final cohort is presented in Figure 1.

3.3.6 Exposure variables

To ensure treatment eligibility, we categorised age at the end of 2018 (18-29, 30-44, 45-59, ≥60 years). Sex (male, female), and region of residence at time of HCV notification (metropolitan [metro], outer-metro, and rural), were obtained from NCIMS. HIV coinfection status was obtained from the HIV notifications database; due to small numbers (accounting for <0.5% of all records), those with HCV/HBV/HIV coinfection

were reclassified as HCV/HIV coinfection. Recent incarceration (2016-2017) was defined using the BOCSAR. History of hospitalisations occurring due to alcohol use disorder (AUD) [192], and any recent hospitalisation (2016- mid 2018) (none, 1, >1) were obtained using APDC. An algorithm was applied across datasets to identify Indigenous Australian ethnicity (Aboriginal Australian or Torres Strait Islander) and country of birth (Australia, overseas) [193].

3.3.7 Statistical analysis

Our analysis comprised three strands: first, estimations of the treatment eligible population were determined; second, treatment uptake was analysed among the treatment eligible; and third, factors associated with treatment uptake were determined. Analyses one and two were performed among all HCV notifications and subsequently by sub-populations according to drug dependence. The third analysis was restricted to those with evidence of recent drug dependence.

3.3.8 Analysis 1: Estimating the DAA treatment eligible population in NSW, Australia

As the vast majority of HCV notifications are made on the basis of positive anti-HCV antibody (evidence of HCV RNA confirmation is not required), an adjustment was made to account for spontaneous clearance and estimate the population with chronic HCV, the key criteria for treatment eligibility. This adjustment was made in line with published spontaneous clearance rates obtained from linkage data with high coverage RNA testing. These data indicate sex-specific spontaneous clearance rates of 25% among men and 34% among women [12]. Importance weights were applied to each observation based on treatment status and sex, where each observation was weighted 1

if HCV treatment was received (i.e. confirmed chronic infection), and weighted using the following formula for males and females:

$$1.00 - \frac{Total \times spontaneous\ clearance\ rate}{Total - n\ treated}$$

resulting in a weight of 0.65 and 0.56 for each untreated male and female record, respectively.

3.3.9 Analysis 2: DAA uptake, according to drug dependence

Individual treatment initiation data were obtained from PBS. The proportion treated is according to the weighted population of HCV notifications derived in Analysis 1. Treatment uptake was stratified across sub-populations of interest according to drug dependence.

3.3.10 Analysis 3: Factors associated with DAA uptake among people with recent drug dependence

Logistic regression models were used to determine the factors associated with HCV treatment uptake in the DAA era among people with recent drug dependence. An unadjusted model was performed first; all exposures with $p \leq 0.250$ significance, or with known clinical significance, were considered for the adjusted model. The adjusted model was tested for collinearity using variance-covariance matrices, and the model of best fit was deduced using likelihood ratio tests. Both unadjusted and adjusted models were run on the importance-weighted cohort of people with recent drug dependence. Because of sex-specific differences observed in other studies [188], sex-stratifications were performed ad hoc.

3.3.11 Sensitivity analyses

To investigate the effect of weighting on standard errors, a sensitivity analysis was performed comparing importance-weighted results to unweighted results. An additional analysis accounted for sex and treatment variation between sub-populations.

All analyses were performed in STATA v.14.0 [College Station, TX, USA].

3.4 Results

Among 115,669 HCV notifications, 80,017 fulfilled our inclusion criteria (Figure 1). Following removal of those estimated to have spontaneously cleared HCV, 57,467 were estimated to have chronic HCV and therefore eligible for DAA treatment between 2016-2018 (Figure 1). Of these, 54% had no evidence of drug dependence, and 19% and 26% had evidence of distant and recent drug dependence, respectively. Of those with evidence of recent drug dependence, 29% had at least one IDU-related hospitalisation and no OAT, 25% had both IDU-related hospitalisation and OAT, and 47% had only OAT (Table 1).

Figure 1: Derivation of cohort and drug dependence groups

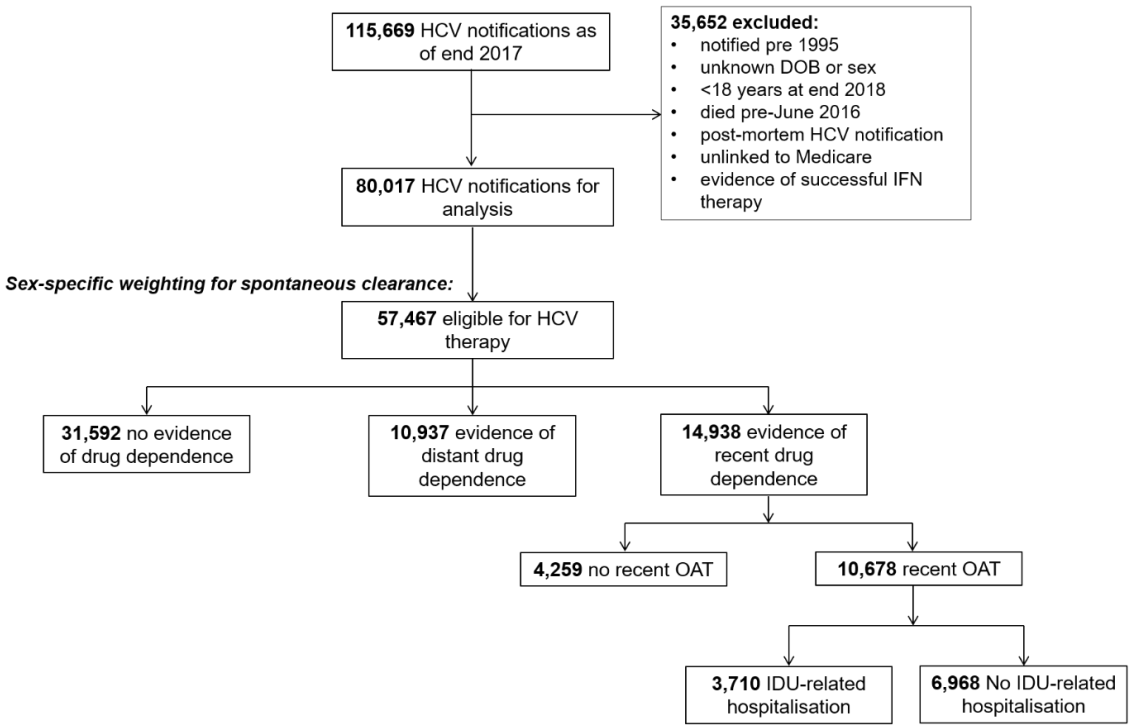


Table 1: Characteristics of NSW people eligible for DAA therapy between 2016-2018 [a], by drug dependence

Characteristic		Total	No evidence of drug dependence, n (col%)	Distant drug dependence, n (col%)	Recent drug dependence, n (col%)	Recent drug dependence sub-populations		
						Hospitalisation only, n (col%)	Hospitalisation and OAT, n (col%)	OAT only, n (col%)
Total, n (row%)		57,467	31,592 (54%)	10,937 (19%)	14,938 (26%)	4,259 (29%)	3,710 (25%)	6,968 (47%)
Age	18-29	2,031 (4%)	963 (3%)	308 (3%)	760 (5%)	273 (6%)	230 (6%)	257 (4%)
	30-44	15,095 (26%)	5,580 (18%)	3,550 (32%)	5,995 (40%)	1,308 (31%)	1,742 (47%)	2,945 (42%)
	45-59	26,312 (46%)	14,748 (47%)	5,191 (47%)	6,373 (43%)	1,833 (43%)	1,457 (39%)	3,083 (44%)
	60+	14,029 (24%)	10,301 (33%)	1,918 (18%)	1,810 (12%)	846 (20%)	281 (8%)	683 (40%)
Sex	Male	37,306 (65%)	19,818 (63%)	7,233 (66%)	10,255 (69%)	2,909 (68%)	2,455 (66%)	4,891 (73%)
	Female	20,161 (35%)	11,775 (37%)	3,703 (34%)	4,682 (31%)	1,350 (32%)	1,255 (34%)	2,077 (27%)
Indigenous Australian ethnicity	No	40,185 (70%)	20,990 (66%)	8,251 (75%)	10,943 (73%)	3,155 (74%)	2,690 (72%)	5,099 (73%)
	Yes	7,475 (13%)	2,002 (6%)	1,943 (18%)	3,523 (24%)	1,035 (24%)	1,014 (27%)	1,473 (21%)
Region of HCV notification	Metro	15,070 (26%)	8,942 (28%)	2,651 (24%)	3,477 (23%)	956 (22%)	909 (25%)	1,612 (23%)
	Outer-metro	18,759 (33%)	10,184 (32%)	3,495 (32%)	5,081 (34%)	1,295 (30%)	1,366 (37%)	2,419 (35%)
	Rural	20,560 (36%)	11,158 (35%)	4,174 (38%)	5,228 (35%)	1,724 (41%)	1,131 (30%)	2,373 (34%)
Country of birth	Australia	38,917 (68%)	16,935 (54%)	9,065 (83%)	12,917 (86%)	3,580 (84%)	3,310 (89%)	6,025 (86%)
	Overseas	10,112 (18%)	6,404 (15%)	1,767 (16%)	1,940 (13%)	667 (16%)	398 (11%)	876 (13%)
Recent incarceration	No	51,730 (90%)	30,698 (97%)	9,812 (90%)	11,219 (75%)	3,243 (76%)	2,438 (66%)	5,538 (79%)
	Yes	5,737 (10%)	895 (3%)	1,124 (10%)	3,718 (25%)	1,016 (24%)	1,273 (34%)	1,429 (21%)
Coinfection status	HCV only	54,545 (95%)	30,222 (96%)	10,330 (94%)	13,993 (94%)	3,979 (93%)	3,467 (93%)	6,574 (94%)
	HCV/HBV	2,189 (4%)	985 (3%)	431 (4%)	773 (5%)	180 (4%)	209 (6%)	383 (5%)
	HCV/HIV	732 (1%)	385 (1%)	176 (2%)	172 (1%)	99 (2%)	34 (1%)	37 (1%)
History of AUD	No	45,834 (80%)	28,900 (91%)	7,169 (66%)	9,765 (65%)	2,105 (49%)	2,060 (56%)	5,601 (80%)
	Yes	11,632 (20%)	2,692 (9%)	3,767 (34%)	5,172 (35%)	2,154 (51%)	1,650 (44%)	1,367 (20%)
Recent hospitalisation	None	36,151 (63%)	23,502 (74%)	7,282 (67%)	5,367 (36%)	NA	NA	5,367 (77%)
	1 episode	8,874 (15%)	4,314 (14%)	1,682 (15%)	2,878 (19%)	887 (21%)	964 (26%)	1,027 (15%)
	>1 episodes	12,441 (22%)	3,777 (12%)	1,973 (18%)	6,692 (45%)	3,372 (79%)	2,746 (74%)	574 (8%)

[a] Missing data for Indigenous Australian ethnicity, region of HCV notification, and country of birth not shown

3.4.1 DAA uptake

Among the DAA treatment eligible population in 2016-2018, 38% initiated therapy. The highest treatment uptake was among those with recent drug dependence (47%), followed by those with distant (38%), and no drug dependence (33%) (Table 2, Figure 2). General practitioners had authorised the majority of DAA therapy dispensed in NSW to those with evidence of recent drug dependence (53%), compared to those with distant (47%) and no evidence of drug dependence (37%) (Supplementary Table 3). The vast majority of those treated with DAA therapy with recent (86%), distant (88%), and no evidence of drug dependence (89%) received their total prescribed course (Supplementary Table 4). Among those with recent drug dependence (n=14,938), DAA therapy was highest among those with HIV (62%), males (49%), those notified in metropolitan regions (49%), and those with a history of AUD (49%). The sub-population of those with recent drug dependence with the highest treatment uptake was those with both an IDU-related hospitalisation and OAT in the DAA era (49%), followed by those who had only received OAT (47%), and those who only had IDU-related hospitalisation (43%) (Table 2, Figure 3). DAA therapy was consistently higher among males compared to females (Supplementary Table 5, Supplementary Figure 1).

Table 2: DAA uptake among NSW people [a], by drug dependence, and by recent OAT and hospitalisation status [b], 2016-2018

Characteristic		Total	No evidence of drug dependence	Distant drug dependence	Recent drug dependence	Recent drug dependence sub-populations		
						Hospitalisation only	Hospitalisation and OAT	OAT only
Total		21,570 (38%)	10,434 (33%)	4,187 (38%)	6,949 (47%)	1,820 (43%)	1,825 (49%)	3,304 (47%)
Age	18-29	832 (41%)	326 (34%)	137 (45%)	367 (48%)	133 (49%)	116 (50%)	118 (46%)
	30-44	4,676 (38%)	1,569 (28%)	1,335 (38%)	2,772 (46%)	570 (44%)	847 (49%)	1,355 (46%)
	45-59	9,929 (38%)	4,937 (33%)	2,012 (39%)	2,980 (47%)	788 (42%)	721 (49%)	1,471 (48%)
	60+	5,133 (37%)	3,602 (35%)	701 (37%)	830 (46%)	329 (39%)	141 (50%)	360 (53%)
Sex	Male	14,435 (39%)	6,624 (33%)	2,815 (39%)	4,996 (49%)	1,229 (45%)	1,293 (53%)	2,404 (49%)
	Female	7,135 (35%)	3,810 (32%)	1,372 (37%)	1,953 (42%)	521 (39%)	532 (42%)	900 (43%)
Indigenous Australian ethnicity	No	16,216 (40%)	7,681 (37%)	3,256 (39%)	5,279 (48%)	1,388 (44%)	1378 (51%)	2,513 (49%)
	Yes	2,805 (38%)	656 (33%)	668 (34%)	1,481 (42%)	403 (39%)	445 (44%)	633 (43%)
Region of HCV notification	Metro	5,408 (36%)	2685 (30%)	1,031 (39%)	1,692 (49%)	425 (45%)	474 (52%)	793 (49%)
	Outer-metro	6,501 (35%)	2794 (29%)	1,220 (35%)	2,307 (45%)	524 (40%)	665 (49%)	1,118 (46%)
	Rural	8,611 (42%)	4451 (40%)	1,721 (41%)	2,439 (47%)	754 (44%)	543 (48%)	1,142 (48%)
Country of birth	Australia	16,167 (42%)	6,541 (39%)	3,568 (39%)	6,058 (47%)	1,555 (43%)	1630 (49%)	2,873 (48%)
	Overseas	3,440 (34%)	1,996 (31%)	584 (33%)	860 (44%)	260 (39%)	194 (49%)	406 (46%)
Recent incarceration	No	18,951 (37%)	10,059 (33%)	3,736 (38%)	5,256 (46%)	1,376 (42%)	1184 (49%)	2,596 (47%)
	Yes	2,619 (46%)	375 (42%)	451 (40%)	1,793 (48%)	444 (44%)	641 (50%)	708 (50%)
Coinfection status	HCV only	20,542 (38%)	10,032 (33%)	3,959 (38%)	6,551 (47%)	1,697 (43%)	1728 (50%)	3,126 (48%)
	HCV/HBV	627 (29%)	213 (22%)	122 (28%)	292 (38%)	62 (34%)	74 (35%)	156 (41%)
	HCV/HIV	401 (55%)	189 (49%)	106 (60%)	106 (62%)	61 (62%)	23 (68%)	22 (59%)
History of AUD	No	16,301 (36%)	9,288 (32%)	2,622 (37%)	4,391 (45%)	838 (40%)	949 (46%)	2,604 (46%)
	Yes	5,215 (50%)	1,146 (43%)	1,565 (42%)	2,558 (49%)	982 (46%)	876 (53%)	700 (51%)
Recent hospitalisation	None	12,297 (34%)	7,119 (30%)	2,672 (37%)	2,506 (47%)	NA	NA	2,506 (47%)
	1 episode	3,793 (43%)	1,761 (41%)	692 (41%)	1,240 (46%)	374 (42%)	460 (48%)	506 (49%)
	>1 episodes	5,840 (47%)	1,554 (41%)	823 (42%)	3,103 (46%)	1,446 (43%)	1365 (50%)	292 (51%)

a Denominators for assessing treatment uptake proportion are in Table 1

[b] Missing data for Indigenous Australian ethnicity, region of HCV notification, and country of birth not shown

Figure 2: Number of NSW people with HCV notification eligible for DAA therapy in beginning of the DAA era (2016) and at end of follow up (2018) among those with (A) no drug dependence, (B) distant drug dependence, and (C) recent drug dependence

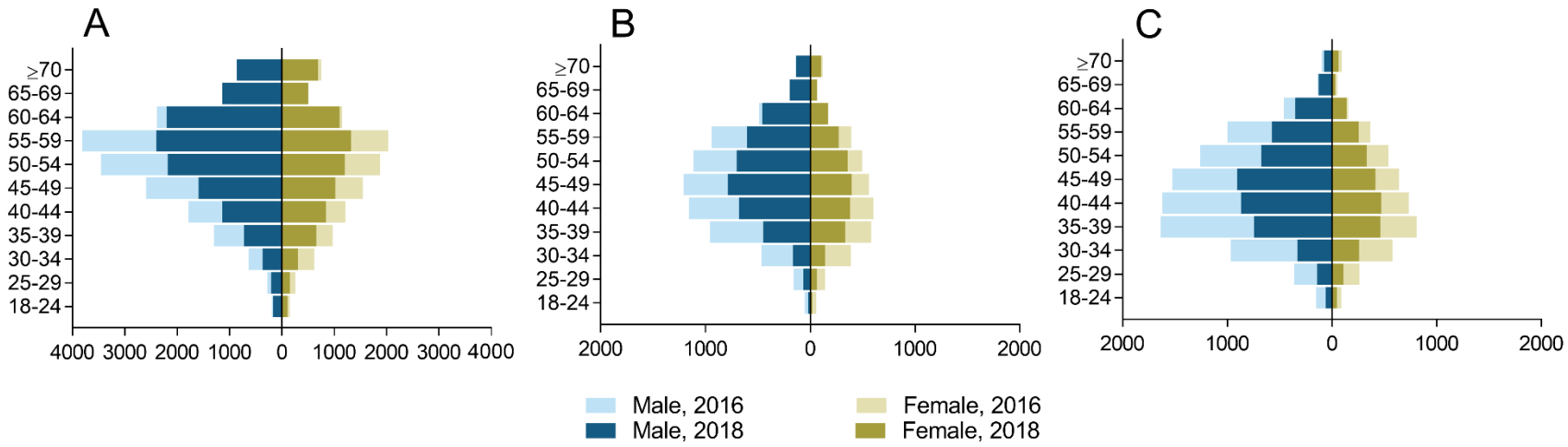
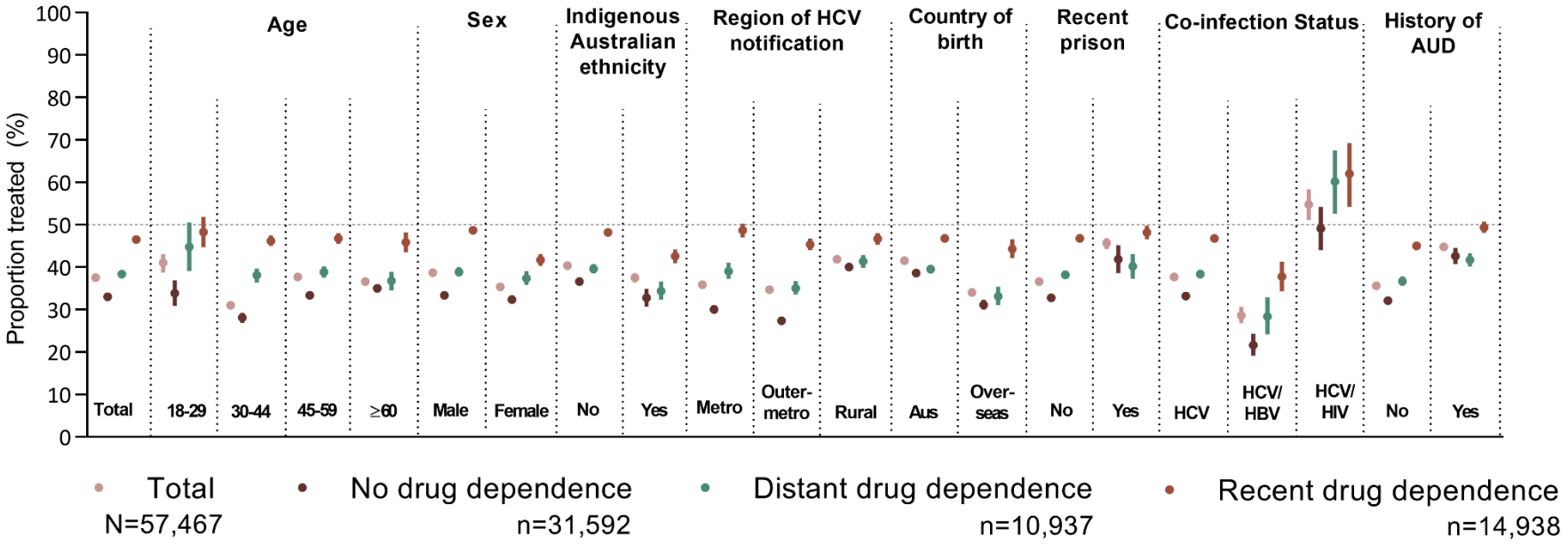


Figure 3: DAA therapy uptake among NSW people [a], overall and by drug dependence, 2016-2018



[a] Missing data for Indigenous Australian ethnicity, region of HCV notifications, and country of birth not shown

3.4.2 Factors associated with DAA uptake among people with evidence of recent drug dependence

All covariates were included in the adjusted model. After adjusting, DAA uptake was less likely among females (aOR: 0.78, 95%CI: 0.72, 0.84), and among those: with Indigenous Australian ethnicity (aOR: 0.75, 95%CI: 0.69, 0.81), HCV notified in outer-metropolitan regions (aOR: 0.90, 95%CI: 0.82, 0.98), born overseas (aOR: 0.86, 95%CI: 0.78, 0.96), with HBV (aOR: 0.69, 95%CI: 0.59, 0.80), and who had been hospitalised more than once during the DAA era (aOR: 0.91, 95%CI: 0.84, 0.98). Treatment uptake was more likely among those: with HIV (aOR: 1.71, 95%CI: 1.13, 2.31), incarcerated in the DAA era (aOR: 1.10, 95%CI: 1.01, 1.19), and with a history of AUD (aOR: 1.22, 95%CI: 1.13, 1.31) (Table 3).

Table 3: Factors associated with DAA uptake among NSW people with evidence of recent drug dependence [a]

Characteristic		OR	95%CI	p	aOR	95%CI	p
Age	18-29	1.11	0.93, 1.31	0.244	1.17	0.97, 1.41	0.094
	30-44	1.02	0.92, 1.13	0.743	1.02	0.91, 1.15	0.711
	45-59	1.04	0.94, 1.15	0.465	1.03	0.92, 1.14	0.655
	60+	-reference-			-reference-		
Sex	Male	-reference-			-reference-		
	Female	0.76	0.70, 0.81	<0.001	0.78	0.72, 0.84	<0.001
Indigenous Australian ethnicity	No	-reference-			-reference-		
	Yes	0.78	0.72, 0.84	<0.001	0.75	0.69, 0.81	<0.001
Region of HCV notification	Metro	-reference-			-reference-		
	Outer-metro	0.88	0.80, 0.96	0.003	0.90	0.82, 0.98	0.021
	Rural	0.92	0.85, 1.00	0.065	0.94	0.86, 1.03	0.178
Country of birth	Australia	-reference-			-reference-		
	Overseas	0.91	0.82, 0.99	0.033	0.86	0.78, 0.86	0.005
Recent incarceration	No	-reference-			-reference-		
	Yes	1.09	1.01, 1.18	0.017	1.10	1.01, 1.19	0.035
Coinfection status	HCV only	-reference-			-reference-		
	HCV/HBV	0.69	0.59, 0.80	<0.001	0.69	0.59, 0.80	<0.001
	HCV/HIV	1.83	1.33, 2.51	<0.001	1.71	1.24, 2.36	0.001
History of AUD	No	-reference-			-reference-		
	Yes	1.20	1.12, 1.28	<0.001	1.22	1.13, 1.31	<0.001
Recent hospitalisation	None	-reference-			-reference-		
	1 episode	0.99	0.90, 1.08	0.873	0.95	0.86, 1.04	0.251
	>1 episodes	0.99	0.92, 1.06	0.717	0.91	0.84, 0.98	0.020

a Missing data for Indigenous Australian ethnicity, region of HCV notification, and country of birth not shown

Among males with evidence of recent drug dependence, DAA uptake was less likely among those: with Indigenous Australian ethnicity (aOR: 0.72, 95%CI: 0.65, 0.79), HCV notified in outer-metropolitan regions, (aOR: 0.86, 95%CI: 0.77, 0.95), born overseas (aOR: 0.83, 95%CI: 0.74, 0.93), and with HBV (aOR: 0.66, 95%CI: 0.57, 0.80). Treatment was more likely among younger males (18-29 years) (aOR: 1.25, 95%CI: 1.00, 1.27), and those with HIV (aOR: 1.71, 95%CI: 1.22, 2.39), incarcerated in the DAA era (aOR: 1.11, 95%CI: 1.01, 1.22), and with a history of AUD (aOR: 1.19, 95%CI: 1.03, 1.30) (Supplementary Table 6).

Among women with evidence of recent drug dependence, DAA uptake was less likely among those: with Indigenous Australian ethnicity (aOR: 0.82, 95%CI: 0.71, 0.94), and hospitalised more than once during the DAA era (aOR: 0.86, 95%CI: 0.74, 0.99). DAA uptake was more likely among women who had a history of AUD (aOR: 1.27, 95%CI: 1.11, 1.45).

3.4.3 Sensitivity analyses

The factor most impacted by importance-weighting was sex; however, the significance of this factor was unchanged after weighting. Importance-weighting slightly increased the range of 95% confidence intervals but did not affect the significance of factors associated with treatment uptake (Supplementary Tables 7-9). Applying subgroup-specific weights did not significantly change results (Supplementary Tables 10-13).

3.5 Discussion

Our study provides evidence that the Australian public health approach to HCV — unrestricted DAA therapy access for all adults with chronic HCV — is reaching marginalised populations with drug dependence. Encouragingly for HCV elimination, between 2016-2018, DAA uptake was higher among those with evidence of recent drug dependence compared to those with distant or no evidence. Although receipt of OAT during the DAA era was associated with the highest treatment uptake, even those with injecting-related hospitalisation and no OAT had higher uptake than populations without recent drug dependence. Furthermore, a history of incarceration during the DAA era (2016-2017) was associated with uptake.

The relatively high DAA uptake among more marginalised "high-risk" populations indicates that HCV elimination efforts, particularly those targeted at reduction of HCV incidence, are on-track. Australian modelling studies have indicated the potential to achieve substantial reductions in population-level prevalence and incidence before 2030 through maintained primary prevention and DAA therapy, despite declines in annual uptake [95]. These models used the assumption that treatment rates were comparable in high-risk and low-risk populations. Based on our results, these models may have under-estimated the impact of DAA therapy on HCV incidence in Australia. Empirical evidence of reduction in chronic HCV through high DAA uptake among PWID has been reported through Australian annual needle and syringe program (NSP) surveillance, with a halving of the HCV RNA prevalence between 2015-2017 [151].

Due to the initial high cost of DAA therapies and subsequent reimbursement restrictions, many countries faced obstacles to provide early, universal access to

populations with ongoing risk behaviour or with mild liver disease [107]. In contrast, provision of unrestricted DAA therapy coupled with services which have significant interface with PWID and other key populations such as prisoners and people living with HIV, places Australia at the forefront of HCV elimination, particularly among marginalised populations. With notable exceptions of Iceland (population 364,000) [194], Georgia [195], and more recently Scotland [196], few countries have been able to implement a comprehensive treatment as prevention strategy which enhances testing, diagnosis, and treatment among PWID.

Women were less likely to have initiated treatment than men, particularly those of childbearing age, a result which has been corroborated by previous Australian evidence [188]. Women who inject drugs experience multiple stigmas and increased marginalisation contributing to a higher vulnerability and disengagement with health services [197]. To better understand the potential impact of childbirth on HCV treatment uptake, subsequent analyses will assess timing of HCV screening, confirmatory testing, and treatment in relation to pregnancy and delivery. Strategies which aim to reduce vulnerabilities incurred among women who inject drugs, including adequate antenatal HCV screening and other hospital-based interventions will be key.

Among people with evidence of recent drug dependence, there were several factors associated with DAA therapy uptake. The strongest association was observed among those with a coinfection, where HIV was associated with higher treatment uptake, and HBV coinfection associated with lower uptake. Previous work has demonstrated the positive impact of increased clinical service contact among people living with HIV coinfection on engagement with the HCV cascade of care, including treatment uptake

[198]. Conversely, it would appear that despite guidance to prioritise people with liver disease progression cofactors for DAA therapy [105, 199], prescribers may remain concerned about the association between DAA therapy and HBV reactivation [200].

Additional factors associated with lower DAA therapy uptake among those with recent drug dependence include Indigenous Australian ethnicity, non-Australian country of birth, an HCV notification made in outer-metro regions, and more than one hospitalisation between 2016-June 2018. Culturally appropriate interventions which address the complex intersectionality of ethnicity and mental health outcomes caused by inherited historical traumas have been shown to enhance engagement with HCV care [201]. Implementing these interventions on a national scale will be required to ensure equitable elimination of HCV. Considering evidence of an association between non-Australian country of birth and development of HCC [202], it is imperative to enhance linkage to HCV care in health settings which may encounter high frequency of people born outside of Australia. Barriers to access to DAA prescribing in outer-metro areas may also need to be addressed, including increasing the general practitioner prescribing capacity.

Lastly, majority of people with evidence of recent drug dependence had been hospitalised (for any cause), between 2016-2018. Among those with recent drug dependence, treatment uptake was lowest among those with no OAT. Additionally, those hospitalised more than once for any cause were less likely to have received DAA therapy than those who were never hospitalised. Hospital admissions serve as a potential juncture between healthcare and PWID to commence linkage to HCV care. As such, further investigation is underway into length and type of hospitalisations incurred

by this population to guide strategies for provision of enhanced HCV care during hospitalisation.

Two markers of marginalisation were associated with higher DAA therapy uptake: recent incarceration and history of AUD. Prisons have been utilised in Australia as a key setting for HCV testing and treatment; however, this population is dynamic with 43,000 people incarcerated at any given time in Australia and a large amount of recidivism [94]. Increased coverage of harm reduction in the prison setting will be an important factor in preventing potential re-infection as people cycle through the prison system. The association of AUD and chronic liver disease, including a common contributor to liver cirrhosis [203], means this population may have been in contact with hepatologists and prioritised for DAA therapy.

There is a clear need to develop and implement HCV awareness campaigns and strategies which focus on engaging those with no and distant evidence of drug dependence, including through primary care practitioner training. This is particularly important given these populations tend to be older and therefore at higher risk of liver disease progression [202]. Further understanding of the factors associated with DAA therapy uptake among those with no and distant evidence of drug dependence should be explored.

There are limitations that should be considered within our findings. First, although NSW is the largest jurisdiction in Australia (35% of population), our findings may not be nationally representative. It is reassuring that overall DAA uptake in Australia is similar to NSW [204]. In addition, the annual Australian NSP survey evaluates HCV

treatment uptake among PWID and shows similar uptake in NSW and Australia [205]. Second, administrative datasets have limitations. The inclusion of those receiving OAT in a broader "drug dependence" population with hospitalisations should have enhanced the sensitivity for the drug dependent population, albeit with some specificity reduction. The recent drug dependent population in NSW is likely to have been underestimated; however, people attending hospital for IDU-related complications are likely more marginalised than the overall PWID population, so the high treatment uptake found among this group is particularly encouraging. Third, as HCV notifications are largely on basis of HCV antibody detection, we adjusted for spontaneous clearance. Given our estimates of spontaneous clearance were conservative, DAA uptake would be higher in the setting of higher spontaneous clearance adjustments. This could partly explain lower DAA uptake among females. Finally, we have decided to focus on treatment initiation, yet the gaps highlighted here may reflect similar discrepancies in earlier stages of HCV care which should be further explored. Likewise, while the large majority (86%) of those who started DAA therapy received a complete course of therapy, PBS records dispensing and we cannot guarantee full adherence and subsequent sustained viral response.

3.5.1 Conclusion

These results are encouraging with regard to equity of access to DAA therapy, but further strategies are required to engage key populations and facilitate elimination [117]. Innovative strategies to enhance linkage to care including HCV screening and same-day DAA initiation through utilisation of point-of-care technologies are required. Lastly, the provision of DAA therapy in settings which regularly interface with PWID, such as NSPs, drug treatment clinics, prisons, and inpatient hospital settings, is imperative.

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Declaration of interests

GD reports grants from Gilead, Abbvie, Merck, and Bristol-Myers Squibb, personal fees from Gilead, Abbvie, and Merck, and non-financial support from Gilead, Abbvie, and Merck, outside the submitted work. JGrebely reports grants from Merck , grants from Cepheid, during the conduct of the study; grants and personal fees from Abbvie, grants and personal fees from Gilead Sciences, grants and personal fees from Merck , grants and personal fees from Cepheid, grants from Hologic, grants from Indivior, outside the submitted work. ML reports grants from Gilead, ViiV Healthcare and Janssen outside the submitted work. MK reports receiving grants from Boehringer Ingelheim, Hologic, Merck, Roche Molecular Systems, and Siemens Healthcare Diagnostics outside of the submitted work. JGeorge reports funding from MSD, Abbvie, BMS, Pharmaxis, Norvartis, Cincera, and Bayer outside the submitted work. BH reports grants from NSW Health and Cancer Council NSW. LD has received investigator-initiated untied educational grants for studies of opioid medications in

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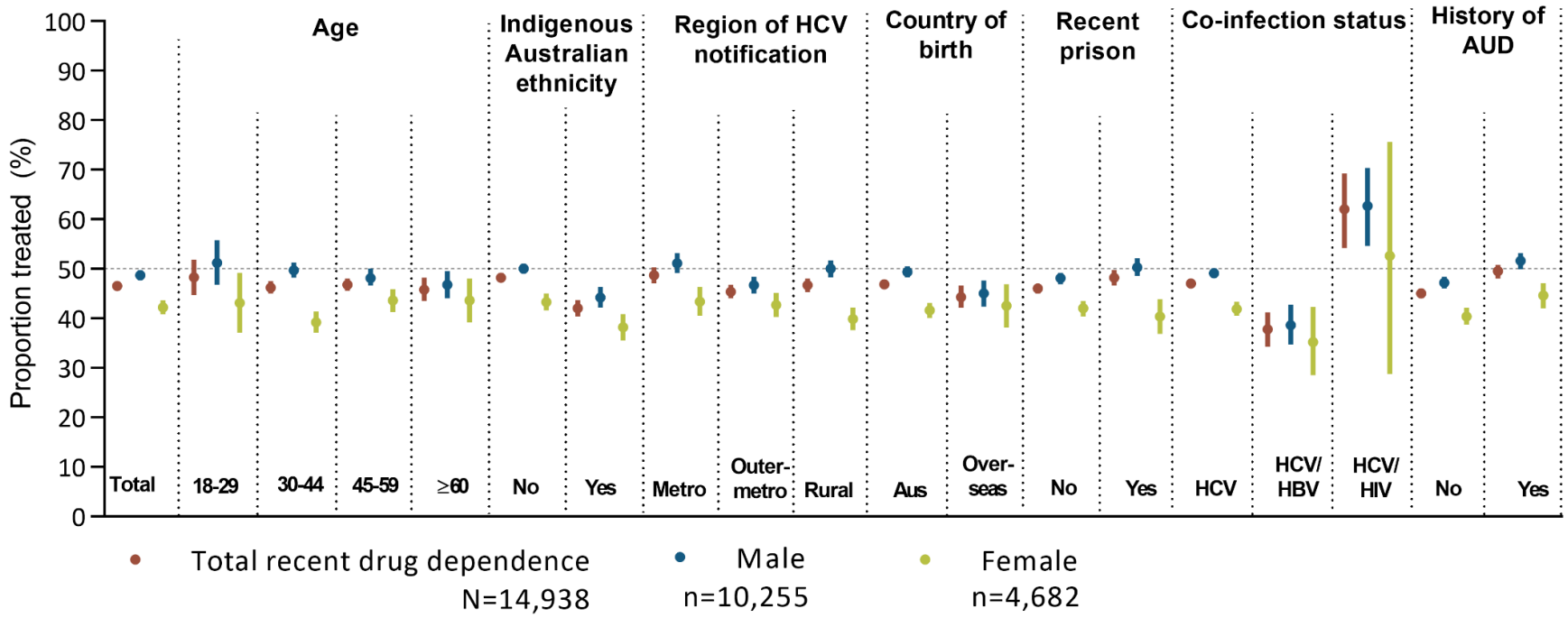
Supplementary Figure 1: DAA uptake among NSW people with evidence of recent drug dependence between 2016-2018 [a], by sex



[a] Missing data for Indigenous Australian ethnicity, Region of HCV notification, and country of birth not shown

Supplementary Table 1: ICD-10 definitions used to identify injecting drug use-related hospital presentations among all NSW people with an HCV notification

ICD-10	Description
A40	Streptococcal sepsis
A41	Other sepsis
A48.0	Other bacterial diseases, not elsewhere classified (gas gangrene)
B37.6	Candidiasis, candida endocarditis
F11	Mental and behavioural disorders due to use of opioids
F13	Mental and behavioural disorders due to sedatives or hypnotics
F14	Mental and behavioural disorders due to use of cocaine
F15	Mental and behavioural disorders due to use of other stimulants, including caffeine
F19	Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances
G06	Intracranial and intraspinal abscess and granuloma
G09	Sequelae of inflammatory disease of central nervous system
I26.9	Pulmonary embolism, pulmonary embolism without mention of acute or pulmonale
I33	Acute and subacute endocarditis
I34	Nonrheumatic mitral valve disorders
I35	Nonrheumatic aortic valve disorders
I36	Nonrheumatic tricuspid valve disorders
I37	Pulmonary valve disorders
I38	Endocarditis, valve unspecified
I39	Endocarditis and heart valve disorders in diseases classified elsewhere
I40.0	Acute myocarditis, infective myocarditis
I80	Phlebitis and thrombophlebitis
K63.0	Other diseases of the intestine, abscess of intestine
K65.0	Peritonitis, acute peritonitis
K75.0	Other inflammatory liver disease, abscess of liver
L02	Cutaneous abscess, furuncle and carbuncle
L03	Cellulitis
L97	Ulcer of lower limb, not elsewhere classified
L98.8	Other disorders of skin and subcutaneous tissue, not elsewhere classified, other specified disorders of skin and subcutaneous tissue
M54.0	Dorsalgia, panniculitis affecting regions of neck and back
M72.6	Fibroblastic disorders, necrotizing fasciitis
M79.3	Other soft tissue disorders, not elsewhere classified (panniculitis, unspecified)
M86	Osteomyelitis
M89.9	Other disorders of bone, disorder of bone, unspecified
N10	Acute tubulo-interstitial nephritis
R02	Gangrene, not elsewhere classified
R57.2	Shock, not elsewhere classified, septic shock
R65.1	Systemic Inflammatory Response Syndrome of infectious origin with organ failure
R65.9	Systemic Inflammatory Response Syndrome, unspecified
R78.1	Finding of opiate drug in blood
R78.2	Finding of cocaine in blood
T38.7	Androgens and anabolic congeners
T40.0	Poisoning by narcotics and psychodysleptics, opium
T40.1	Poisoning by narcotics and psychodysleptics, heroin
T40.2	Poisoning by narcotics and psychodysleptics, other opioids (codeine/morphine)
T40.3	Poisoning by narcotics and psychodysleptics, methadone
T40.4	Poisoning by narcotics and psychodysleptics, other synthetic narcotics (pethidine)
T40.5	Poisoning by narcotics and psychodysleptics, cocaine
T40.6	Poisoning by narcotics and psychodysleptics, other and unspecified narcotics

T40.8	Poisoning by narcotics and psychodysleptics, lysergide (LSD)
T41.2	Poisoning by anaesthetics and therapeutic gases, other and unspecified general anaesthetics
T42.3	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs, barbiturates
T42.4	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs, benzodiazepines
T42.5	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs, mixed antiepileptics, not elsewhere classified
T42.6	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs, other antiepileptic and sedative-hypnotic drugs
T42.7	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs, antiepileptic and sedative-hypnotic drugs, unspecified
T42.8	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs, antiparkinsonism drugs and other central muscle-tone depressants
T43.6	Poisoning by psychotropic drugs, not elsewhere classified, psychostimulants with abuse potential
T43.8	Poisoning by psychotropic drugs, not elsewhere classified, other psychotropic drugs, not elsewhere classified
T43.9	Poisoning by psychotropic drugs, not elsewhere classified, psychotropic drug, unspecified
T50.7	Poisoning by psychotropic drugs, not elsewhere classified, analeptics and opioid receptor antagonists
X41	Accidental poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified
X61	Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified
Y11	Poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified, undetermined intent

Supplementary Table 2: Characteristics of those linked and unlinked to Medicare (universal healthcare) dataset holding HCV treatment information

Characteristic		Medicare linked, n (col%)	Medicare unlinked, n (col%)
Total, n(row%)		80,017 (89%)	9,931 (11%)
Age	18-29	2,800 (4%)	580 (6%)
	30-44	21,129 (26%)	3,516 (35%)
	45-59	36,530 (46%)	4,073 (41%)
	60+	19,558 (24%)	1,762 (18%)
Sex	Male	49,621 (62%)	7,570 (76%)
	Female	30,396 (38%)	2,361 (24%)
Indigenous Australian ethnicity	No	55,275 (69%)	3,739 (38%)
	Yes	10,432 (13%)	1,391 (14%)
	NK	14,310 (18%)	4,801 (48%)
Region of HCV notification	Metro	21,163 (26%)	3,373 (34%)
	Outer-metro	26,483 (33%)	1,180 (12%)
	Rural	28,104 (3%)	1,213 (12%)
	NK	4,267 (5%)	4,165 (42%)
Country of birth	Australia	53,212 (67%)	4,310 (43%)
	Overseas	14,323 (18%)	815 (8%)
	NK	12,482 (16%)	4,806 (48%)
Recent incarceration	No	72,432 (91%)	9,075 (91%)
	Yes	7,585 (9%)	856 (9%)
Coinfection status	HCV only	75,959 (95%)	9546 (96%)
	HCV/HBV	3,140 (4%)	272 (3%)
	HCV/HIV	918 (1%)	113 (1%)
History of AUD	No	64,497 (81%)	9,400 (95%)
	Yes	15,520 (19%)	531 (5%)
Drug Dependence	None	44,955 (56%)	7,850 (79%)
	Past	15,148 (19%)	851 (9%)
	Recent	19,914 (25%)	1,230 (12%)

Supplementary Table 3: Prescriber type among total courses of courses DAA therapy dispensed [a] in NSW (2016-2018), by drug dependence

Prescriber type	No evidence of drug dependence, n (col%)	Distant drug dependence, n (col%)	Recent drug dependence, n (col%)
General Practitioner	4,204 (37%)	2,139 (47%)	4,014 (53%)
Gastroenterologist/Hepatologist	5,142 (45%)	1,583 (35%)	1,997 (27%)
Infectious Disease Specialist	638 (6%)	302 (7%)	484 (6%)
Addiction Specialist	29 (<1%)	22 (<1%)	302 (4%)
Other Specialist	1,452 (13%)	532 (12%)	696 (9%)
Nurse Practitioner	5 (<1%)	6 (<1%)	30 (<1%)
Total[a]	11,470	4,584	7,523

[a] Includes all courses of DAA therapy dispensed between 01 March 2016 – 31 December 2018

Supplementary Table 4: Number and proportion of NSW people who received a full course of therapy (treatment completion) among the latest prescribed course [a], by drug dependence

Treatment completion	No evidence of drug dependence, n (col%)	Distant drug dependence, n (col%)	Recent drug dependence, n (col%)
No	1,097 (11%)	505 (12%)	932 (14%)
Yes	9,160 (89%)	3,578 (88%)	5,763 (86%)
Total[a]	10,257	4,083	6,725

[a] Does not include courses of DAA therapy with ≥1 month left in prescription duration

Supplementary Table 5: DAA uptake among NSW people with evidence of recent drug dependence [a], by sex

Characteristic		Male		Female	
		Treatment eligible, N_1 (col%)	Treatment uptake, n (%N_1)	Treatment eligible, N_2 (col%)	Treatment uptake, n (%N_2)
Total		10,255	4,996 (49%)	4,682	1,953 (42%)
Age	18-29	486 (5%)	249 (51%)	274 (6%)	118 (43%)
	30-44	3,992 (39%)	1,985 (50%)	2,004 (43%)	787 (39%)
	45-59	4,482 (44%)	2,156 (48%)	1,890 (40%)	824 (44%)
	60+	1,296 (13%)	606 (47%)	514 (11%)	224 (43%)
Indigenous Australian ethnicity	No	7,657 (75%)	3,856 (50%)	3,286 (70%)	1,423 (43%)
	Yes	2,230(22%)	987 (44%)	1,293 (28%)	494 (38%)
Region of HCV notification	Metro	2,352 (23%)	1,203 (51%)	1,126 (24%)	489 (43%)
	Outer-metro	3,442 (34%)	1,607 (47%)	1,639 (35%)	700 (43%)
	Rural	3,492 (34%)	1,746 (50%)	1,736 (37%)	693 (40%)
Country of birth	Australia	8,768 86%)	4,333 (49%)	4,148 (89%)	1,725 (42%)
	Overseas	1,434(14%)	645 (45%)	506 (11%)	215 (42%)
Recent incarceration	No	7,329 (71%)	3,523 (48%)	3,890 (83%)	1,633 (42%)
	Yes	2,926 (29%)	1,473 (50%)	792 (17%)	320 (40%)
Coinfection status	HCV only	9,525 (93%)	4,677 (49%)	4,468 (95%)	1,874 (42%)
	HCV/HBV	577 (6%)	223 (39%)	196 (4%)	69 (35%)
	HCV/HIV	153 (1%)	96 (63%)	19 (<1%)	10 (53%)
History of AUD	No	6,571 (64%)	3,101 (47%)	3,195 (68%)	1,290 (40%)
	Yes	3,684 (36%)	1,895 (51%)	1,488 (32%)	663 (45%)
Recent hospitalisation	None	3,791 (37%)	1,828 (48%)	1,576 (34%)	678 (43%)
	1 episode	1,962 (19%)	866 (44%)	916 (20%)	374 (41%)
	>1 episodes	4,502 (44%)	2,202 (49%)	2,190 (47%)	901 (41%)

[a] Missing data for Indigenous Australian ethnicity, region of HCV notification, and country of birth not shown

Supplementary Table 6: Factors associated with DAA uptake among NSW people with evidence of recent drug dependence [a], by sex

		Male						Female					
Characteristic		OR	95%CI	p	aOR	95%CI	p	OR	95%CI	p	aOR	95%CI	p
Age	18-29	1.20	0.97, 1.47	0.088	1.25	1.00, 1.27	0.048	0.98	0.72, 1.32	0.912	1.05	0.76, 1.43	0.777
	30-44	1.13	1.00, 1.28	0.057	1.13	0.66, 1.29	0.069	0.84	0.70, 1.01	0.078	0.83	0.68, 1.03	0.090
	45-59	1.06	0.94, 1.18	0.369	1.05	0.92, 1.19	0.469	1.00	0.82, 1.22	0.983	0.98	0.80, 1.20	0.840
	60+	-reference-			-reference-			-reference-			-reference-		
Indigenous Australian ethnicity	No	-reference-			-reference-			-reference-			-reference-		
	Yes	0.78	0.71, 0.86	<0.001	0.72	0.65, 0.79	<0.001	0.81	0.71, 0.92	0.002	0.82	0.71, 0.94	0.005
Region of HCV notification	Metro	-reference-			-reference-						-reference-		
	Outer-metro	0.84	0.75, 0.93	0.001	0.76	0.77, 0.95	0.005	0.97	0.83, 1.31	0.705	0.99	0.85, 1.16	0.921
	Rural	0.95	0.86, 1.06	0.376	0.97	0.87, 1.08	0.543	0.67	0.74, 1.01	0.062	0.89	0.76, 1.04	0.144
Country of birth	Australia	-reference-			-reference-			-reference-			-reference-		
	Overseas	0.84	0.75, 0.94	0.002	0.83	0.74, 0.93	0.002	1.04	0.86, 1.24	0.711	0.96	0.79, 1.17	0.709
Recent incarceration	No	-reference-			-reference-			-reference-			-reference-		
	Yes	1.09	1.00, 1.19	0.040	1.11	1.01, 1.22	0.029	0.94	0.80, 1.10	0.418	1.00	0.85, 1.19	0.960
Coinfection status	HCV only	-reference-			-reference-			-reference-			-reference-		
	HCV/HBV	0.65	0.55, 0.78	<0.001	0.67	0.57, 0.80	<0.001	0.75	0.56, 1.02	0.065	0.76	0.56, 1.02	0.071
	HCV/HIV	1.74	1.25, 2.42	0.001	1.71	1.22, 2.39	0.002	1.65	0.66, 4.13	0.287	1.70	0.67, 4.28	0.262
History of AUD	No				-reference-			-reference-			-reference-		
	Yes	1.18	1.09, 1.29	<0.001	1.19	1.03, 1.30	<0.001	1.17	1.50, 1.35	0.007	1.27	1.11, 1.45	<0.001
Recent hospitalisation	None	-reference-			-reference-			-reference-			-reference-		
	1 episode	1.04	0.93, 1.16	0.495	0.98	0.88, 1.01	0.732	0.91	0.77, 1.08	0.281	0.88	0.75, 0.99	0.133
	>1 episodes	1.03	0.94, 1.12	0.531	0.94	0.85, 1.03	0.171	0.93	0.81, 1.05	0.245	0.90	0.71, 1.13	0.035

[a] Missing data for Indigenous Australian ethnicity, region of HCV notification, and country of birth not shown

Supplementary Table 7: Characteristics of NSW population eligible for DAA therapy between 2016-2018 [a], unweighted

Characteristic		Total	No evidence of drug dependence, n (col%)	Distant drug dependence, n (col%)	Recent drug dependence, n (col%)	Recent drug dependence sub-populations		
						Hospitalisation only, n (col%)	Hospitalisation and OAT, n (col%)	OAT only, n (col%)
Total, n(row%)		80,017 (%)	44,955 (56%)	15,148 (19%)	19,914 (25%)	5,778 (29%)	4,904 (25%)	9,232 (46%)
Age	18-29	2,800 (4%)	1,372 (3%)	418 (3%)	1,010 (5%)	362 (6%)	304 (6%)	344 (4%)
	30-44	21,129 (26%)	8,186 (18%)	4,912 (32%)	8,031 (40%)	1,774 (31%)	2,319 (47%)	3,938 (43%)
	45-59	36,530 (46%)	20,912 (47%)	7,155 (47%)	8,463 (43%)	2,474 (43%)	1,915 (39%)	4,074 (44%)
	60+	19,558 (24%)	14,485 (32%)	2,663 (18%)	2,410 (12%)	1,168 (20%)	366 (7%)	876 (10%)
Sex	Male	49,621 (62%)	26,922 (60%)	9,612 (63%)	13,087 (66%)	3,776 (65%)	3,081 (63%)	6,230 (67%)
	Female	30,396 (38%)	18,033 (40%)	5,536 (37%)	6,827 (34%)	2,002 (35%)	1,823 (37%)	3,002 (33%)
Indigenous Australian ethnicity	No	55,275 (69%)	29,447 (66%)	11,374 (75%)	14,454 (73%)	4,250 (74%)	3,511 (72%)	6,693 (73%)
	Yes	10,432 (13%)	2,859 (6%)	2,753 (18%)	4,820 (24%)	1,434 (25%)	1,385 (28%)	2,001 (22%)
Region of HCV notification	Metro	21,163 (26%)	12,908 (29%)	3,659 (24%)	4,596 (23%)	1,286 (22%)	1,187 (24%)	2,123 (23%)
	Outer-metro	26,483 (33%)	14,754 (33%)	4,922 (32%)	6,807 (34%)	1,775 (31%)	1,813 (37%)	3,219 (35%)
	Rural	28,104 (3%)	15,399 (34%)	5,717 (38%)	6,988 (35%)	2,336 (40%)	1,507 (31%)	3,145 (34%)
Country of birth	Australia	53,212 (67%)	23,498 (42%)	12,505 (73%)	17,209 (49%)	4,843 (84%)	4,381 (89%)	7,985 (86%)
	Overseas	14,323 (18%)	9,232 (21%)	2,497 (16%)	2,594 (13%)	919 (16%)	521 (11%)	1,154 (13%)
Recent incarceration	No	72,432 (91%)	43,762 (97%)	13,628 (90%)	15,042 (76%)	4,416 (76%)	3,247 (66%)	7,379 (80%)
	Yes	7,585 (9%)	1,193 (3%)	1,520 (10%)	4,872 (24%)	1,362 (24%)	1,657 (34%)	1,853 (20%)
Coinfection status	HCV only	75,959 (95%)	43,002 (96%)	14,315 (95%)	18,642 (74%)	5,405 (94%)	4,571 (93%)	8,666 (94%)
	HCV/HBV	3,140 (4%)	1,459 (3%)	618 (4%)	1,063 (5%)	252 (4%)	292 (6%)	519 (6%)
	HCV/HIV	918 (1%)	494 (1%)	215 (1%)	209 (1%)	121 (2%)	41 (1%)	47 (<1%)
History of AUD	No	64,497 (81%)	41,333 (92%)	10,034 (66%)	13,130 (66%)	2,905 (50%)	2,768 (56%)	7,484 (81%)
	Yes	15,520 (19%)	3,622 (8%)	5,114 (34%)	6,784 (34%)	2,873 (50%)	2,136 (44%)	1,775 (19%)
Recent hospitalisation	None	51,077 (64%)	33,813 (75%)	10,434 (67%)	7,130 (36%)	NA	NA	7,130 (77%)
	1 episode	12,094 (15%)	5,948 (13%)	2,305 (15%)	3,841 (19%)	1,207 (21%)	1,281 (26%)	1,353 (15%)
	>1 episodes	16,846 (21%)	5,194 (12%)	2,709 (18%)	8,943 (45%)	4,571 (79%)	3,623 (74%)	749 (8%)

[a] Missing data for Indigenous Australian ethnicity, region of HCV notification, and country of birth not shown

Supplementary Table 8: DAA uptake [a] among NSW people [b], by drug dependence, unweighted

Characteristic		Total	No evidence of drug dependence	Distant drug dependence	Recent drug dependence	Recent drug dependence sub-populations		
						Hospitalisation only	Hospitalisation and OAT	OAT only
Total		21,570 (27%)	10,434 (23%)	4,187 (28%)	6,949 (35%)	1,820 (31%)	1825 (37%)	3,304 (36%)
Age	18-29	832 (30%)	326 (24%)	137 (33%)	367 (36%)	133 (37%)	116 (38%)	118 (34%)
	30-44	4,676 (27%)	1569 (19%)	1,335 (27%)	2,772 (35%)	570 (32%)	847 (37%)	1,355 (34%)
	45-59	9,929 (27%)	4937 (24%)	2,012 (28%)	2,980 (35%)	788 (32%)	721 (38%)	1,471 (36%)
	60+	5,133 (26%)	3,602 (25%)	701 (26%)	830 (34%)	329 (28%)	141 (38%)	360 (41%)
Sex	Male	14,435 (29%)	6,624 (25%)	2,815 (29%)	4,996 (38%)	1,229 (34%)	1,293 (42%)	2,404 (39%)
	Female	7,135 (23%)	3,810 (21%)	1,372 (25%)	1,953 (29%)	521 (26%)	532 (29%)	900 (30%)
Indigenous Australian ethnicity	No	16,216 (29%)	7,681 (26%)	3,256 (29%)	5,279 (37%)	1,388 (33%)	1,378 (39%)	2,513 (38%)
	Yes	2,805 (27%)	656 (23%)	668 (24%)	1,481 (31%)	403 (28%)	445 (32%)	633 (32%)
Region of HCV notification	Metro	5,408 (26%)	2,685 (21%)	1,031 (28%)	1,692 (37%)	425 (33%)	474 (40%)	793 (37%)
	Outer-metro	6,501 (24%)	2,974 (20%)	1,220 (25%)	2,307 (34%)	524 (30%)	665 (37%)	1,118 (35%)
	Rural	8,611 (31%)	4,451 (29%)	1,721 (30%)	2,439 (35%)	754 (32%)	543 (36%)	1,142 (36%)
Country of birth	Australia	16,167 (30%)	6,541 (28%)	3,568 (29%)	6,058 (35%)	1,555 (32%)	1,630 (37%)	2,873 (36%)
	Overseas	3,440 (24%)	1,996 (22%)	584 (23%)	860 (33%)	260 (28%)	194 (37%)	406 (35%)
Recent incarceration	No	18,951 (26%)	10,059 (23%)	3,736 (27%)	5,256 (34%)	1,376 (31%)	1,184 (36%)	2,596 (35%)
	Yes	2,619 (35%)	375 (31%)	451 (30%)	1,793 (37%)	444 (33%)	641 (39%)	708 (38%)
Coinfection status	HCV only	20,542 (27%)	10,032 (23%)	3,959 (28%)	6,551 (35%)	1,697 (31%)	1,728 (38%)	3,126 (36%)
	HCV/HBV	627 (20%)	213 (15%)	122 (20%)	292 (27%)	62 (25%)	74 (25%)	156 (30%)
	HCV/HIV	401 (44%)	189 (38%)	106 (49%)	106 (51%)	61 (50%)	23 (56%)	22 (47%)
History of AUD	No	16,301 (25%)	9,288 (22%)	2,622 (26%)	7,391 (33%)	838 (29%)	949 (34%)	2,604 (35%)
	Yes	5,215 (34%)	1,146 (32%)	1,565 (31%)	2,558 (38%)	982 (34%)	876 (41%)	700 (39%)
Recent hospitalisation	None	12,297 (24%)	7,119 (21%)	2,672 (26%)	2,506 (35%)	NA	NA	2,506 (35%)
	1 episode	3,793 (31%)	1,761 (30%)	692 (30%)	1,240 (35%)	374 (31%)	460 (36%)	506 (37%)
	>1 episodes	5,840 (33%)	1,554 (30%)	823 (30%)	3,103 (35%)	1,446 (32%)	1,365 (38%)	292 (39%)

[a] Denominators for assessing treatment uptake proportion are in Supplementary Table 7

[b] Missing data for Indigenous Australian ethnicity, region of HCV notification, and country of birth not shown

Supplementary Table 9: Factors associated with DAA uptake among NSW people [a] with evidence of recent drug dependence, unweighted

Characteristic		OR	95%CI	p	OR	95%CI	p
Age	18-29	1.09	0.93, 1.27	0.274	1.17	1.00, 1.38	0.056
	30-44	1.01	0.91, 1.10	0.916	1.02	0.92, 1.13	0.679
	45-59	1.04	0.94, 1.14	0.456	1.03	0.93, 1.13	0.616
	60+	-reference-			-reference-		
Sex	Male	-reference-			-reference-		
	Female	0.65	0.61, 0.69	<0.001	0.66	0.62, 0.70	<0.001
Indigenous Australian ethnicity	No	-reference-			-reference-		
	Yes	0.77	0.72, 0.83	<0.001	0.75	0.69, 0.81	<0.001
Region of HCV notification	Metro	-reference-			-reference-		
	Outer-metro	0.88	0.81, 0.95	0.001	0.90	0.83, 0.97	0.010
	Rural	0.92	0.85, 0.99	0.035	0.94	0.87, 1.02	0.124
Country of birth	Australia	-reference-			-reference-		
	Overseas	0.91	0.84, 0.99	0.040	0.88	0.79, 0.95	0.002
Recent incarceration	No	-reference-			-reference-		
	Yes	1.12	1.04, 1.19	0.001	1.10	1.02, 1.18	0.017
Coinfection status	HCV only	-reference-			-reference-		
	HCV/HBV	0.70	0.61, 0.80	<0.001	0.69	0.60, 0.79	<0.001
	HCV/HIV	1.90	1.45, 2.50	<0.001	1.70	1.29, 2.24	<0.001
History of AUD	No	-reference-			-reference-		
	Yes	1.20	1.13, 1.28	<0.001	1.21	1.14, 1.30	<0.001
Recent hospitalisation	None	-reference-			-reference-		
	1 episode	0.98	0.91, 1.07	0.753	0.95	0.87, 1.03	0.210
	>1 episodes	0.98	0.92, 1.05	0.543	0.91	0.85. 0.98	0.010

[a] Missing data for Indigenous Australian ethnicity, region of HCV notification, and country of birth not shown

Supplementary Table 10: Derivation of importance weights

Population	Total	Treated	Weight
Total, male	49,636	14,435	0.65
Total, female	30,403	7,135	0.56
No evidence of drug dependence, male	26,930	6,624	0.67
No evidence of drug dependence, female	18,036	3,810	0.57
Distant drug dependence, male	9,612	2,815	0.65
Distant drug dependence, female	5,537	1,372	0.55
Recent drug dependence, male	13,094	4,996	0.60
Recent drug dependence, female	6,830	1,953	0.51
Recent drug dependence, hospitalisation only, male	3,780	1,299	0.62
Recent drug dependence, hospitalisation only, female	2,004	521	0.54
Recent drug dependence, hospitalisation and OAT, male	3,083	1,293	0.52
Recent drug dependence, hospitalisation and OAT, female	1,824	532	0.57
Recent drug dependence, OAT only, male	6,231	2,404	0.51
Recent drug dependence, OAT only female	3,002	900	0.59

Supplementary Table 11: Characteristics of NSW people eligible for DAA therapy between 2016-2018 [a], by to drug dependence and subgroup-specific weighted for spontaneous clearance

Characteristic		Total	No evidence of drug dependence, n (col%)	Distant drug dependence, n (col%)	Recent drug dependence, n (col%)	Recent drug dependence sub-populations		
						Hospitalisation only, n (col%)	Hospitalisation and OAT, n (col%)	OAT only, n (col%)
Total, n (row%)		58,481	32,148 (%)	10,896 (19%)	14,295 (26%)	4,159 (29%)	3,517 (25%)	6,634 (47%)
Age	18-29	2,031 (4%)	980 (3%)	306 (3%)	728 (5%)	267 (6%)	219 (6%)	245 (4%)
	30-44	15,098 (26%)	5,680 (18%)	3,506 (32%)	5,734 (40%)	1,278 (31%)	1,652 (47%)	2,800 (42%)
	45-59	26,316 (46%)	15,007 (47%)	5,173 (47%)	6,100 (43%)	1,789 (43%)	1,380 (39%)	2,935 (44%)
	60+	14,035 (24%)	10,480 (33%)	1,911 (18%)	1,734 (12%)	826 (20%)	266 (8%)	654 (40%)
Sex	Male	37,315 (65%)	20,229 (63%)	7,233 (66%)	9,855 (69%)	2,837 (68%)	2,313 (66%)	4,661 (73%)
	Female	20,165 (35%)	11,918 (37%)	3,663 (34%)	4,440 (31%)	1,322 (32%)	1,204 (34%)	1,972 (27%)
Indigenous Australian ethnicity	No	40,194 (70%)	21,336 (66%)	8,252 (75%)	10,489 (73%)	3,082 (74%)	2,553 (72%)	4,863 (73%)
	Yes	7,478 (13%)	2,038 (6%)	1,942 (18%)	3,353 (24%)	1,010 (24%)	958 (27%)	1,396 (21%)
Region of HCV notification	Metro	15,073 (26%)	9,104 (28%)	2,641 (24%)	3,333 (23%)	933 (22%)	866 (25%)	1,537 (23%)
	Outer-metro	18,763 (33%)	10,372 (32%)	3,480 (32%)	3,858 (34%)	1,264 (30%)	1,295 (37%)	2,300 (35%)
	Rural	20,565 (36%)	11,334 (35%)	4,158 (38%)	5,004 (35%)	1,686 (41%)	1,071 (30%)	2,261 (34%)
Country of birth	Australia	38,926 (68%)	17,209 (54%)	9,031 (83%)	12,364 (86%)	3,497 (84%)	3,140 (89%)	5,738 (86%)
	Overseas	10,113 (18%)	6,516 (15%)	1,761 (16%)	1,855 (13%)	651 (16%)	376 (11%)	832 (13%)
Recent incarceration	No	52,741 (90%)	31,238 (97%)	9,774 (90%)	10,729 (75%)	3,166 (76%)	2,313 (66%)	5,270 (79%)
	Yes	5,740 (10%)	910 (3%)	1,122 (10%)	3,566 (25%)	993 (24%)	1,204 (34%)	1,364 (21%)
Coinfection status	HCV only	54,559 (95%)	30,751 (96%)	10,290 (94%)	13,394 (94%)	3,886 (93%)	3,289 (93%)	6,235 (94%)
	HCV/HBV	2,189 (4%)	1,006 (3%)	430 (4%)	734 (5%)	173 (4%)	195 (6%)	362 (5%)
	HCV/HIV	732 (1%)	391 (1%)	176 (2%)	166 (1%)	98 (2%)	33 (1%)	36 (1%)
History of AUD	No	45,845 (80%)	29,441 (91%)	7,139 (66%)	9,333 (65%)	2,054 (49%)	1,948 (56%)	5,328 (80%)
	Yes	11,635 (20%)	2,736 (9%)	3,757 (34%)	4,962 (35%)	2,105 (51%)	1,570 (44%)	1,306 (20%)
Recent hospitalisation	None	36,156 (63%)	23,931 (74%)	7,256 (67%)	5,137 (36%)	NA	NA	5,106 (77%)
	1 episode	8,878 (15%)	4,379 (14%)	1,675 (15%)	2,756 (19%)	877 (21%)	913 (26%)	980 (15%)
	>1 episodes	12,447 (22%)	3,837 (12%)	1,964 (18%)	6,402 (45%)	3,292 (79%)	2,650 (74%)	548 (8%)

[a] Missing data for Indigenous Australian ethnicity, region of HCV notification, and country of birth not shown

Supplementary Table 12: DAA uptake [a], by drug dependence, and by recent OAT and hospitalisation status [b], 2016-2018, subgroup-specific weighted for spontaneous clearance

Characteristic		Total	No evidence of drug dependence	Distant drug dependence	Recent drug dependence	Recent drug dependence sub-populations		
						Hospitalisation only	Hospitalisation and OAT	OAT only
Total		21,570 (38%)	10,434 (32%)	4,187 (38%)	6,949 (49%)	1,820 (44%)	1,825 (52%)	3,304 (50%)
Age	18-29	832 (41%)	326 (33%)	137 (45%)	367 (50%)	133 (50%)	116 (53%)	118 (48%)
	30-44	4,676 (38%)	1569 (28%)	1,335 (38%)	2,772 (48%)	570 (45%)	847 (51%)	1,355 (48%)
	45-59	9,929 (38%)	4937 (33%)	2,012 (39%)	2,980 (49%)	788 (44%)	721 (52%)	1,471 (50%)
	60+	5,133 (37%)	3,602 (34%)	701 (37%)	830 (48%)	329 (40%)	141 (53%)	360 (55%)
Sex	Male	14,435 (39%)	6,624 (33%)	2,815 (39%)	4,996 (51%)	1,229 (46%)	1,293 (56%)	2,404 (52%)
	Female	7,135 (35%)	3,810 (32%)	1,372 (37%)	1,953 (44%)	521 (39%)	532 (44%)	900 (46%)
Indigenous Australian ethnicity	No	16,216 (40%)	7,681 (36%)	3,256 (40%)	5,279 (50%)	1,388 (45%)	1378 (54%)	2,513 (52%)
	Yes	2,805 (38%)	656 (32%)	668 (34%)	1,481 (44%)	403 (40%)	445 (46%)	633 (45%)
Region of HCV notification	Metro	5,408 (36%)	2685 (29%)	1,031 (39%)	1,692 (51%)	425 (46%)	474 (55%)	793 (52%)
	Outer-metro	6,501 (35%)	2794 (29%)	1,220 (35%)	2,307 (60%)	524 (41%)	665 (51%)	1,118 (49%)
	Rural	8,611 (42%)	4451 (39%)	1,721 (41%)	2,439 (49%)	754 (45%)	543 (51%)	1,142 (51%)
Country of birth	Australia	16,167 (42%)	6,541 (38%)	3,568 (40%)	6,058 (49%)	1,555 (44%)	1630 (52%)	2,873 (50%)
	Overseas	3,440 (34%)	1,996 (31%)	584 (33%)	860 (46%)	260 (40%)	194 (52%)	406 (49%)
Recent incarceration	No	18,951 (37%)	10,059 (32%)	3,736 (38%)	5,256 (48%)	1,376 (43%)	1184 (51%)	2,596 (49%)
	Yes	2,619 (46%)	375 (41%)	451 (40%)	1,793 (50%)	444 (45%)	641 (53%)	708 (52%)
Coinfection status	HCV only	20,542 (38%)	10,032 (33%)	3,959 (38%)	6,551 (49%)	1,697 (44%)	1728 (53%)	3,126 (50%)
	HCV/HBV	627 (29%)	213 (21%)	122 (28%)	292 (40%)	62 (35%)	74 (38%)	156 (43%)
	HCV/HIV	401 (55%)	189 (48%)	106 (60%)	106 (64%)	61 (62%)	23 (70%)	22 (61%)
History of AUD	No	16,301 (36%)	9,288 (32%)	2,622 (37%)	7,391 (47%)	838 (41%)	949 (49%)	2,604 (49%)
	Yes	5,215 (50%)	1,146 (42%)	1,565 (42%)	2,558 (52%)	982 (47%)	876 (56%)	700 (54%)
Recent hospitalisation	None	12,297 (34%)	7,119 (30%)	2,672 (37%)	2,506 (49%)	NA	NA	2,506 (49%)
	1 episode	3,793 (43%)	1,761 (40%)	692 (41%)	1,240 (49%)	374 (43%)	460 (50%)	506 (52%)
	>1 episodes	5,840 (44%)	1,554 (41%)	823 (42%)	3,103 (48%)	1,446 (44%)	1365 (52%)	292 (53%)

[a] Denominators for assessing treatment uptake proportion are in Supplementary Table 11

[b] Missing data for Indigenous Australian ethnicity, region of HCV notification, and country of birth not shown

Supplementary Table 13: Factors associated with DAA uptake among people with evidence of recent drug dependence [a], subgroup-specific weighted for spontaneous clearance

Characteristic		OR	95%CI	P	aOR	95%CI	p
Age	18-29	1.07	0.93, 1.31	0.248	1.17	0.97, 1.40	0.094
	30-44	1.01	0.92, 1.13	0.733	1.02	0.91, 1.45	0.711
	45-59	1.04	0.93, 1.15	0.471	1.02	0.92, 1.14	0.655
	60+	-reference-			-reference-		
Sex	Male	-reference-			-reference-		
	Female	0.76	0.71, 0.82	<0.001	0.78	0.72, 0.83	<0.001
Indigenous Australian ethnicity	No	-reference-			-reference-		
	Yes	0.78	0.72, 0.84	<0.001	0.75	0.69, 0.81	<0.001
Region of HCV notification	Metro	-reference-			-reference-		
	Outer-metro	0.88	0.80, 0.96	0.004	0.90	0.82, 0.98	0.021
	Rural	0.92	0.84, 1.00	0.071	0.94	0.86, 1.03	0.178
Country of birth	Australia	-reference-			-reference-		
	Overseas	0.90	0.82, 0.99	0.035	0.86	0.78, 0.96	0.005
Recent incarceration	No	-reference-			-reference-		
	Yes	1.09	1.01, 1.79	0.022	1.10	1.01, 1.19	0.035
Coinfection status	HCV only	-reference-			-reference-		
	HCV/HBV	0.69	0.59, 0.81	<0.001	0.69	0.57, 0.80	<0.001
	HCV/HIV	1.83	1.33, 2.51	<0.001	1.71	1.24, 2.36	0.001
History of AUD	No	-reference-			-reference-		
	Yes	1.20	1.12, 1.28	<0.001	1.21	1.13, 1.31	<0.001
Recent hospitalisation	None	-reference-			-reference-		
	1 episode	0.99	0.91, 1.09	0.884	0.95	0.86, 1.04	0.254
	>1 episodes	0.99	0.92, 1.06	0.734	0.91	0.94, 0.98	0.020

[a] Missing data for Indigenous Australian ethnicity, region of HCV notification, and country of birth not shown

Chapter 4: Opportunities to enhance linkage to hepatitis C care among hospitalised people with recent drug dependence in New South Wales, Australia: A population-based linkage study

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Declaration

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4.1 Abstract

Background: People who inject drugs are at greater risk of hepatitis C virus (HCV) infection and hospitalisation, yet admissions are not utilised for HCV treatment initiation. We aimed to assess the extent to which people with HCV notification, including those with evidence of recent drug dependence, are hospitalised while eligible for direct-acting antiviral (DAA) therapy, and treatment uptake according to hospitalisation in the DAA era. **Methods:** We conducted a longitudinal, population-based cohort study of people living with HCV in the DAA era (March 2016-December 2018) through analysis of linked databases in New South Wales, Australia. Kaplan Meier estimates were used to report HCV treatment uptake by frequency, length, and cause-specific hospitalisation. **Results:** Among 57,467 people, 14,938 (26%) had evidence of recent drug dependence, 50% (n=7,506) of whom were hospitalised while DAA eligible. Incidence of selected cause-specific hospitalisation was highest for mental health-related (15.84 per 100 person-years [PY]), drug-related (15.20 per 100PY), and injection-related infectious disease (9.15 per 100PY) hospitalisations, and lowest for alcohol use disorder (4.58 per 100PY) and liver-related (3.13 per 100PY). 65% (n=4,898) of those hospitalised had been admitted $\geq$2 times and 46% (n=3,437) were hospitalised $\geq$7 days. By the end of 2018, DAA therapy was lowest for those hospitalised $\geq$2 times, for $\geq$7 days, and those whose first admission was for injection-related infectious disease, mental health disorders, and drug-related complications. **Conclusions:** Among people who have evidence of recent drug dependence, frequent hospitalisation—particularly mental health, drug, and alcohol admissions—presents an opportunity for engagement in HCV care.

Keywords: hepatitis C virus; direct acting antiviral therapy; drug dependence; injecting drug use; inpatient hospitalisation; data linkage

4.2 Introduction

Progress toward achieving hepatitis C virus (HCV) elimination targets [206] in the next decade hinges on enhanced public health action to reach key populations who may face barriers to traditional standard of care [120], particularly people who inject drugs (PWID). Although PWID account for the majority of HCV disease burden and transmission in many countries, access to highly curative direct-acting antiviral (DAA) therapy has been restricted in many settings, limiting uptake [38, 105]. In contrast, Australia has provided unrestricted access to DAA therapy to all adults infected with HCV from March 2016. Previous research has demonstrated the successes of this approach in delivery of equitable treatment access among people with recent drug dependence, yet gaps remain [188, 207, 208].

Systems which interface with PWID—including drug treatment clinics [137], community health centres [168, 209], community pharmacies [137] needle syringe programs (NSP) [210], and prisons [211, 212]—remain successful settings to increase HCV education, testing, and treatment uptake. Nevertheless, there remains a group of PWID who are not engaged with HCV care through these services, or who do not access these services on a regular basis [207]. Recent data have shown that HCV treatment uptake was lower among those with recent drug dependence who had been hospitalised more than one time during the DAA era, compared to those never hospitalised [208]. As such, inpatient hospital wards have been recognised as a potential setting to enhance linkage to HCV care and progress toward elimination [199].

Herein, we aim to assess the extent to which people with HCV notification, including those with evidence of recent injection drug use (IDU), are hospitalised while eligible for DAA therapy, and treatment uptake according to hospitalisation in the DAA era. In doing so, we aim to evaluate the potential for inpatient hospitalisation as an opportunity to engage PWID with HCV care.

4.3 Methods

4.3.1 Setting

New South Wales (NSW), Australia accounts for approximately 35% of HCV burden [192] and 40% of PWID [59] nationally, and is one of few settings internationally with well-established infrastructure for linking positive HCV serology notifications to administrative databases.

4.3.2 Data sources and record linkages

The methods which utilise linked datasets to define populations of people with HCV infection and drug dependence have been previously described [208]. In brief, a master dataset was established using data sources which were probabilistically and deterministically linked (using full name, sex, date of birth, and address) to the NSW Notifiable Conditions Information Management System (NCIMS). NCIMS holds individual records of HCV and hepatitis B virus (HBV) positive serology. A record of positive HCV serology was the inclusion criteria for this study. These HCV notifications were linked to (1) inpatient hospitalisation discharge (NSW Admitted Patient Data Collection), (2) deaths (NSW Registry of Birth Deaths, and Marriages), (3) opioid agonist therapy (OAT) authority (NSW Electronic Recording and Reporting of Controlled Drugs system), (4) incarcerations (NSW Bureau of Crime Statistics and Research), and (5) HIV diagnosis (National HIV Database). Using the same set of identifying information, HCV notifications were also linked to HCV treatment database (Pharmaceutical Benefits Schedule [PBS]) [208]. Record linkages were undertaken by the New South Wales Centre for Health Record Linkage and the Australian Institute of Health and Welfare Data Integration Services Centre.

4.3.3 Study period

For the study period, data were extracted from each database as follows: HCV notifications (1 January 1993-31 December 2017); hospitalisations (1 January 2001-30 June 2018); deaths (1 January 1993-30 June 2018); OAT authority (1 January 1985-19 September 2018); incarcerations (1 January 1994-31 December 2017); HIV diagnosis (1 January 1985-31 December 2017); PBS (1 January 2010-31 December 2018).

4.3.4 Study population

Evidence of drug dependence was defined by hospital admissions due to IDU and/or infections indicative of IDU (IDU-related hospitalisation) (Supplementary Table 1), or receipt of OAT. Hospital admissions were coded using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), at primary or secondary (including up to 50 secondary diagnostic fields) diagnosis at hospitalisation [208]. Receipt of OAT or IDU-related hospitalisation occurring between 2016-2018 was considered recent, records with last hospitalisation or OAT dose recorded any time pre-2016 were considered distant. As HCV notifications are based on positive serology (HCV antibody), importance weights were applied to individual records to account for sex-specific rates of spontaneous clearance using previously published linkage data with high coverage RNA testing [12, 188]. Each observation with recorded HCV treatment (confirmed chronic infection) was weighted 1, and each observation with no recorded HCV treatment was weighted using a 25% and 34% spontaneous clearance rate for men and women, respectively [12]:

$$1.00 - \frac{Total \times spontaneous\ clearance\ rate}{Total - n\ treated}$$

resulting in a weight for each untreated male of 0.65 and each untreated female of 0.56.

4.3.4 Exclusion Criteria

Due to concerns with sensitivity and specificity of early generation HCV antibody assays, records were removed where date of HCV notification occurred prior to 01 January 1995 (n=12,319) [208]. Records with unknown date of birth (n=55), those <18 years by end of follow up (31 December 2018) (n=244), and those with unknown sex (n=409) were excluded.

To allow time for treatment initiation, records were removed if death occurred before 01 June 2016 (n=11,174). Post-mortem notifications were removed (n=20). Records with no Medicare (universal healthcare) number available for PBS (HCV treatment) linkage were excluded (n=9,931). Those without sufficient information to link to Medicare could include some temporary and undocumented migrants and those HCV notified in an anonymous testing service. The characteristics of those with and without Medicare number are compared in Supplementary Table 2 [208]. Those who had been prescribed interferon-based therapy with no subsequent HCV treatment were assumed to have cleared HCV infection and were removed (n=1,500) (Figure 1).

Admissions with a primary diagnosis relating to dialysis (ICD-10 code Z46) were excluded, given each episode of dialysis is coded as a separate admission, leading to high numbers of admissions (n=15,064) among a small amount of people receiving dialysis (n=97).

4.3.5 Outcome

The primary outcome of this study was to describe hospital-related characteristics, including frequency, length, and cause-specific hospitalisation among people eligible for DAA therapy and according to drug dependence (none, distant, recent). The secondary outcome was DAA therapy uptake among those with evidence of recent drug dependence by hospital-related characteristics.

4.3.6 Exposure variables

Characteristics considered in the hospitalisation analyses included year of birth (1989-2000, 1988-1974, 1959-1973, ≤1958), sex (male, female), Indigenous Australian (Australian Aboriginal or Torres Strait Islander), region of residence at time of HCV notification (metropolitan [metro], outer-metro, and rural), country of birth (Australia, overseas), recent incarceration (2016-2017), and coinfection status (HCV/HBV, HCV/HIV). Due to a small number of records with HCV/HBV/HIV coinfection (relating to <0.5% of total notifications), these were classified as HCV/HIV coinfection [208].

The main exposures of interest in DAA uptake analyses comprised hospital-based characteristics: maximum frequency (never hospitalised, 1, ≥2), maximum length of stay (never hospitalised, <7 days, ≥7 days [long-stay]), and primary diagnosis of cause-specific hospitalisations. After identifying trends in hospitalisation by major ICD-10 chapter (based on primary diagnosis), these broad diagnoses were recoded to identify more specific cause-specific hospitalisations. Cause-specific hospitalisations included hospital episodes with primary diagnosis relating to mental health disorders, alcohol use

disorder (AUD) [192], drug use, liver complications, and injection-related infectious diseases (Supplementary Table 3).

4.3.7 Statistical analysis

We performed two analyses. Hospitalisations were only considered while an individual was DAA treatment naive. Observation time for hospitalisation commenced 1 March 2016, date of HCV notification, or date of 18th birthday and ended on date of DAA treatment initiation, date of death or 30 June 2018. Follow up time for commencement of DAA therapy started 1 March 2016, date of HCV notification, or date of 18th birthday and ended on date of DAA treatment initiation, date of death, or 31 December 2018. Date of HCV notification was reset to the day before DAA therapy for those records where date of treatment preceded date of notification (46/6949, 0.6% of all treatment episodes occurring among those with recent drug dependence).

4.3.8 Analysis 1: Hospitalisations by drug dependence

First, the number and primary cause of hospitalisation was assessed using major ICD-10 chapters for each population according to drug dependence. Furthermore, the number and cause of long-stay hospitalisation ($\geq$7 days in duration) was assessed using major ICD-10 chapters for each population according to drug dependence. After recoding hospitalisations into cause-specific diagnoses, the incidence (per 100 person-years) of each hospital admission and corresponding 95% CIs were calculated assuming a Poisson distribution.

4.3.9 Analysis 2: DAA uptake by drug dependence

The estimated proportion of people with HCV notification who initiated DAA therapy at yearly time points between was assessed using Kaplan Meier failure curves. First, DAA uptake was assessed for all people by drug dependence. Subsequently, among people with evidence of recent drug dependence, DAA uptake was assessed by three hospital-related characteristics (frequency, length of stay, and primary diagnosis of first cause-specific hospitalisation).

4.3.10 Sensitivity and supplementary analyses

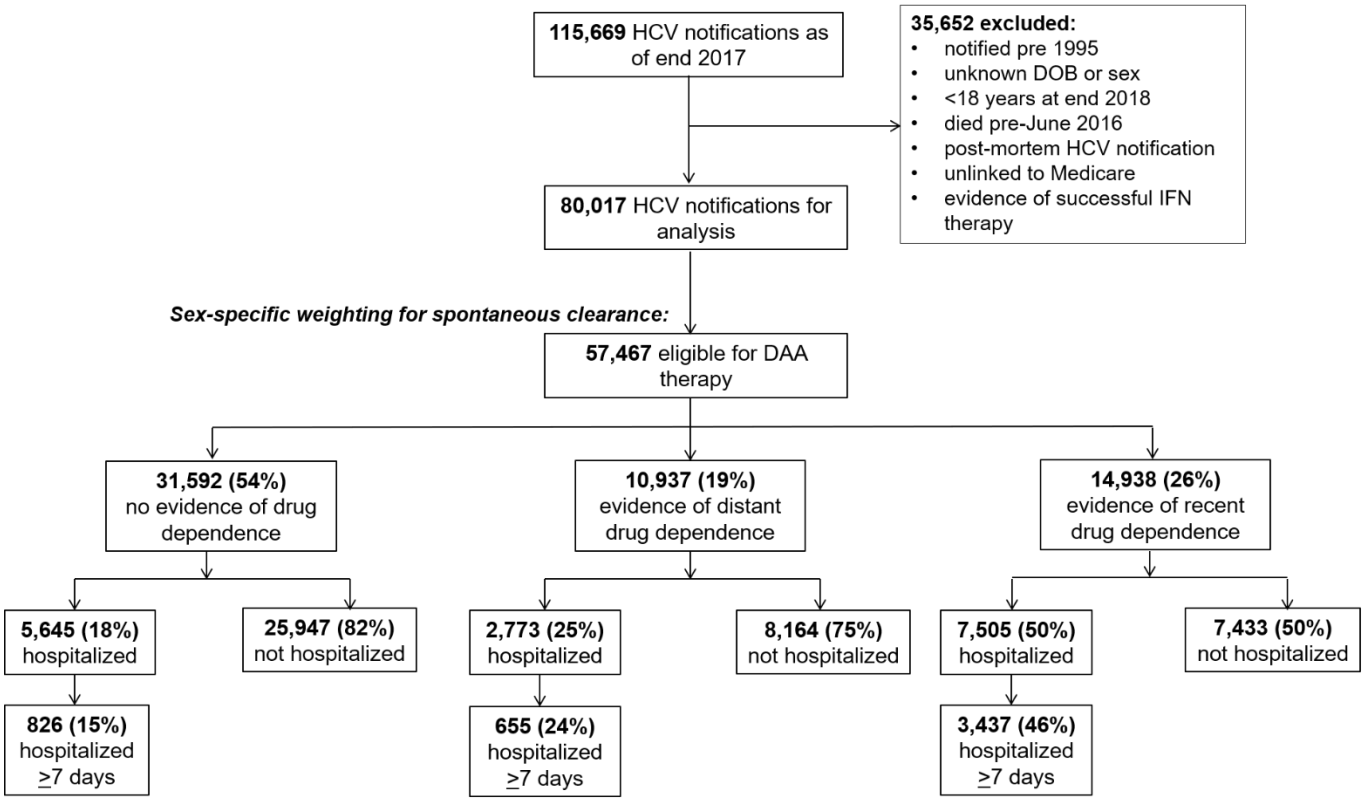
To better understand the impact of long-stay hospitalisation, a supplementary analysis was performed to assess DAA uptake by frequency of long-stay hospitalisation.

Analyses were conducted using STATA version 16.0 [College Station, TX, USA].

4.4 Results:

Among 57,467 people eligible for DAA therapy, 54% (n=31,592) had no evidence, and 19% (n=10,937) and 26% (n=14,938) had evidence of distant and recent drug dependence, respectively (Figure 1).

Figure 1: Cohort derivation, NSW people with HCV notification ever eligible for DAA therapy



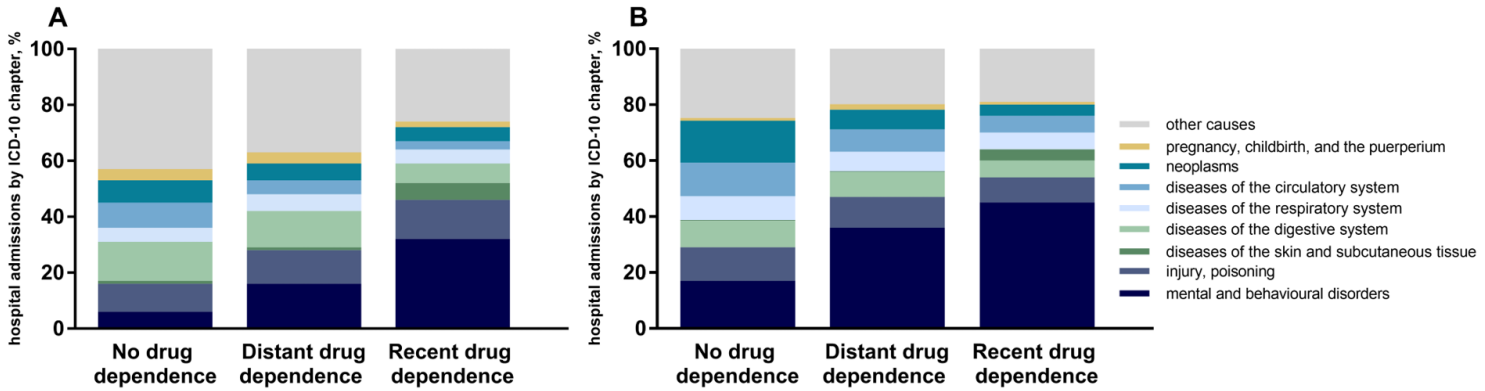
4.4.5 Hospitalisations by drug dependence

A total of 7,505 people with recent drug dependence accounted for 27,650 hospital episodes, relating to a median number of 2 (interquartile range [IQR]: 1,4) and a maximum of 121 hospitalisations. Those with distant drug dependence incurred a median 1 (IQR: 1,3) (6,572 episodes among 2,773 hospitalised individuals) and a maximum of 74 hospitalisations. Those with no evidence of drug dependence incurred a median of 1 (IQR: 1,2) (12,051 episodes among 5,645 hospitalised individuals) and a maximum of 42 hospitalisations. Mental and behavioural disorders was the most common cause for hospitalisation among those with recent drug dependence (31%). With the exception of other causes, mental and behavioural disorders was the most common cause for hospitalisation among those with distant drug dependence (17%), while diseases of the digestive system was most common among those without drug dependence (15%) (Figure 2A; Supplementary Table 4).

Incidence of cause-specific hospitalisations for all major categories, including liver-related hospitalisation, was higher among those with recent compared to those with distant and no drug dependence (Figure 3). Among those with recent drug dependence, hospitalisations relating to mental health disorders were highest (15.84 [95%CI: 15.42, 16.28] per 100 PY), followed by drug-related (15.20 [95%CI: 14.78, 15.63] per 100 PY), injection-related infectious disease (9.15 [95%CI: 8.82, 9.50] per 100 PY), AUD (4.58 [95%CI: 4.34, 4.83] per 100 PY) and liver-related hospitalisation (3.13 [95%CI: 2.93, 3.34] per 100 PY). Among those with distant drug dependence the highest incidence of cause-specific hospitalisation was for mental health disorders (3.37 [95%CI: 3.10, 3.57] per 100 PY). The cause-specific hospitalisation with the highest

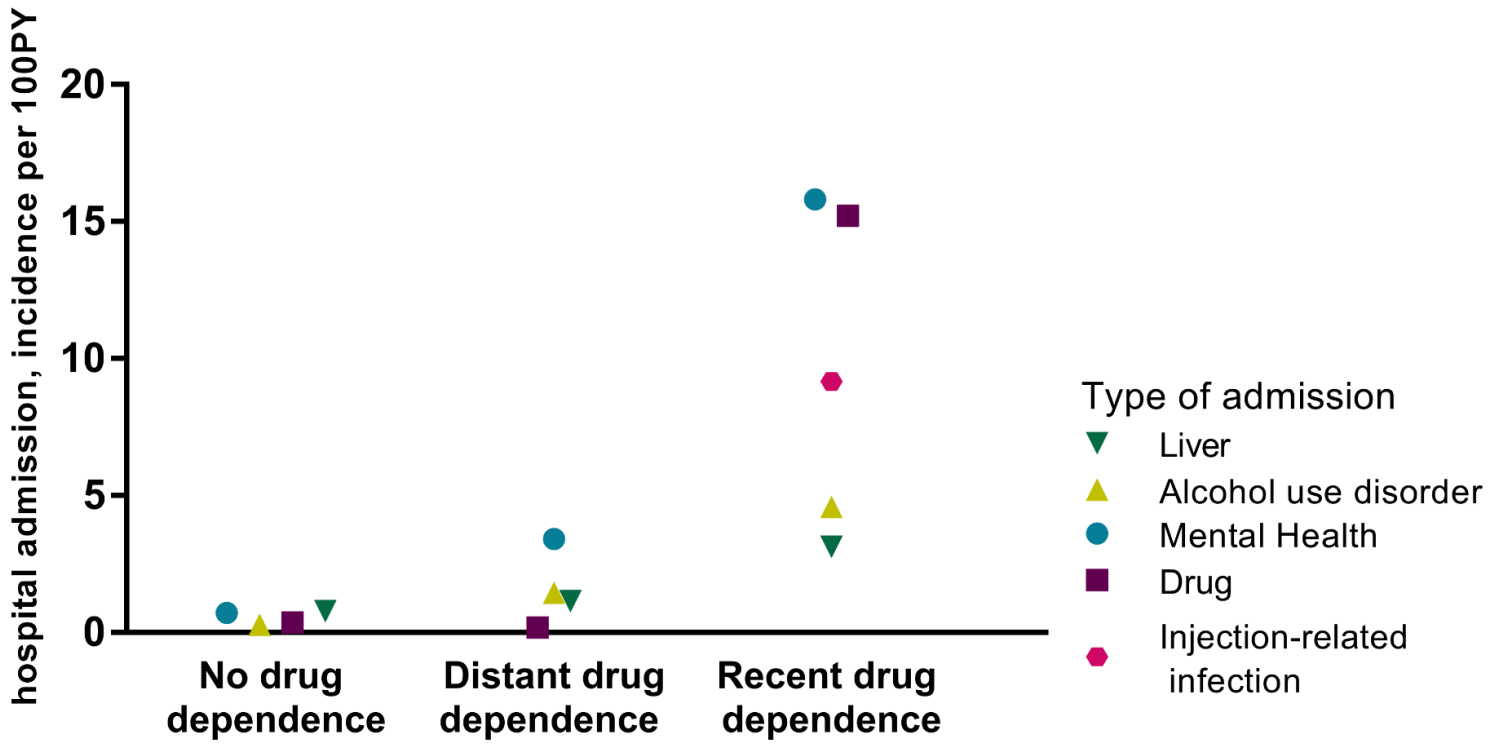
incidence among those with no evidence of drug dependence was for liver-related disorders (0.78 [95%CI: 0.72, 0.85] per 100 PY) (Figure 3; Supplementary Table 5).

Figure 2: Reasons for (A) all hospitalisations and (B) hospitalisations lasting ≥7 days among NSW people eligible for DAA therapy occuring between 01 March and 30 June 2018, among those with no (n=31,592), distant (n=10,937) and recent (n=14,938) drug dependence



	A			B		
	No drug dependence	Distant drug dependence	Recent drug dependence	No drug dependence	Distant drug dependence	Recent drug dependence
Individuals hospitalised:	5,645	2,773	7,505	826	655	3,437
Hospital episodes:	12,051	6,572	27,650	1,215	1,021	7,021
Maximum episodes:	42	74	121	9	9	31

Figure 3: Incidence of cause-specific hospitalisation among those estimated to have chronic HCV in the DAA era in NSW, Australia, by drug dependence



4.4.5.1 Long-stay hospitalisation by drug dependence

People with recent drug dependence were most likely to have had a long-stay hospitalisation (lasting ≥7 days) (46% of all hospitalised, n=3,437), compared to those with distant (24%, n=655) and no (15%, n=826) drug dependence. A total of 3,437 people with recent drug dependence accounted for 7,021 long-stay hospital episodes, equivalent to a median 2 (IQR: 1,4) and maximum of 31 hospitalisations. Those with distant drug dependence incurred a median 1 (IQR: 1,3) and maximum of 9 long-stay hospitalisations per person (1,021 episodes among 655 hospitalised individuals), and those with no evidence of drug dependence incurred a median of 1 (IQR: 1,2) and maximum of 9 long-stay hospitalisations per person (1,215 episodes among 826 hospitalised individuals). Mental and behavioural disorders was the most common cause for long-stay hospitalisation among those with recent drug dependence (45%) and among those with distant drug dependence (36%). With the exception of other causes, mental and behavioural disorders was most common among those without drug dependence (17%) (Figure 2B, Supplementary Table 4).

4.4.6 DAA uptake

The overall Kaplan Meier estimate of DAA uptake by the end of follow up was 38.1% (95%CI: 37.7%, 38.5%) (Supplementary Table 6).

4.4.7 DAA uptake by drug dependence

Within the first year of the DAA era, DAA uptake was highest among those with no evidence of drug dependence; however, at the end of follow up, DAA uptake remained greatest among those with recent (47.7%, 95%CI: 46.9%, 48.6%) compared to those with distant (38.8%, 95%CI: 37.8%, 39.7%) and no (33.4%, 95%CI: 32.9%, 33.9%) evidence of drug dependence (Supplementary Table 6, Supplementary Figure 1).

4.4.8 DAA uptake among those with evidence of recent drug dependence

The demographic characteristics of those with recent drug dependence by hospital-related characteristics are presented in Tables 1 and 2. Among those with recent drug dependence, DAA uptake was highest among those who were never hospitalised in the DAA era, a result that was sustained throughout observation time and by the end of follow up (57.7%, 95%CI: 56.6%, 58.9%) (Figure 4A/B, Supplementary Table 7).

Among those with evidence of recent drug dependence (n=14,938), 17% (n=2,608) had been hospitalised only once and 33% (n=4,898) had been hospitalised twice or more (Table 1). At the end of follow up, people with 1 hospitalisation had a higher DAA uptake compared to those with ≥2 hospital episodes during observation time (42.8%, 95%CI: 40.9%, 44.8%; 35.5%, 95%CI: 34.1%, 36.9%, respectively). (Figure 4A, Supplementary Table 7).

Twenty seven percent (n=4,069) of those with recent drug dependence had a hospital duration <7 days and 23% (n=3,437) had been hospitalised ≥7 days (Table 1). At the end of follow up, those who had been hospitalised for a duration <7 days (39.3%, 95%CI: 37.7%, 40.8%) had higher DAA uptake than those who had been hospitalised ≥7 days (36.6%,95%CI: 34.9%, 38.3%) (Figure 4B, Supplementary Table 7).

Among those with recent drug dependence who had been hospitalised while DAA treatment eligible (n=7,505), the most common primary diagnosis of the first cause-specific hospitalisation was for drug-related complications (22%, n=1,628), followed by

injection-related infectious diseases (19%, n=1,397), mental health disorders (15%, n=1,098), AUD (5%, n=367) and liver-related complications (3%, n=237) (Table 2).

By the end of follow up, DAA uptake was highest among those who were first hospitalised for liver-related complications (45.3%, 95%CI: 38.0, 53.4) followed by those first hospitalised for AUD (42.6%, 95%CI: 37.3%, 48.2%), drug use-related complications (40.3%, 95%CI: 37.8, 48.2%), mental health disorder (40.2%, 37.2%, 43.3%), and lowest among those first hospitalised for injection-related infectious disease (30.1%, 95%CI: 28.3%, 33.4%) (Figure 4C, Supplementary Table 6).

There was a marked relationship between DAA uptake and frequency of long-stay hospitalisation. Compared to DAA uptake among those without hospitalisation (56%) and no hospitalisations for ≥7 days (38%), uptake progressively declined among those hospitalised once for ≥7 days (38%, 701/1,861), twice (34%, 265/774), three times (29%, 99/341), and four or more times (26%, 118/461) (Supplementary Figure 2).

Table 1: Maximum frequency and length of hospitalisation occurring before end of follow up [a] among NSW people with HCV notification and evidence of recent drug dependence

Characteristic		Total	Never hospitalised, n (col%)	Hospitalisation characteristic			
				Number of times hospitalised [a], n (col%)		Length of hospitalisation [a], n (col%)	
				1	**≥2**	**<7 days**	**≥7 days**
Total, n (row%)		14,938	7,432 (50%)	2,608 (17%)	4,898 (33%)	4,069 (27%)	3,437 (23%)
Year of birth	1989-2000	760 (5%)	324 (5%)	154 (6%)	281 (6%)	260 (6%)	175 (5%)
	1974-1988	5,995 (40%)	3,062 (41%)	1,056 (40%)	1,877 (38%)	1645 (40%)	1,287 (37%)
	1959-1973	6,373 (43%)	3,259 (44%)	1,107 (42%)	2,006 (41%)	1711 (42%)	1,402 (41%)
	≤1958	1,810 (12%)	787 (11%)	290 (11%)	734 (15%)	452 (11%)	572 (17%)
Sex	Male	10,255 (69%)	5,321 (72%)	1,732 (66%)	3,202 (65%)	2,669 (66%)	2,265 (66%)
	Female	4,682 (31%)	2,111 (28%)	876 (34%)	1,696 (35%)	1,399 (34%)	1,172 (34%)
Indigenous Australian ethnicity	No	10,943 (73%)	5,535 (74%)	1,927 (74%)	3,481 (71%)	2,910 (72%)	2,498 (73%)
	Yes	3,523 (24%)	1,488 (20%)	689 (26%)	1,366 (28%)	1,219 (28%)	906 (26%)
Region of HCV notification	Metro	3,477 (23%)	1,768 (24%)	575 (22%)	1,134 (23%)	851 (21%)	857 (25%)
	Outer Metro	5,081 (34%)	2,493 (34%)	876 (34%)	1,712 (35%)	1,397 (34%)	1,190 (35%)
	Regional/Rural	5,228 (35%)	2,575 (35%)	746 (36%)	1,697 (35%)	1,484 (36%)	1,159 (34%)
Country of birth	Australia	12,917 (86%)	6,398 (86%)	2,280 (87%)	4,238 (87%)	3,589 (88%)	2,929 (85%)
	Overseas	1,940 (13%)	961 (13%)	321 (12%)	658 (13%)	475 (12%)	504 (15%)
Recent incarceration	No	11,219 (75%)	5,937 (80%)	1,879 (72%)	3,402 (69%)	1,831 (70%)	2,450 (71%)
	Yes	3,718 (25%)	1,495 (20%)	728 (28%)	1,495 (31%)	1,237 (30%)	986 (29%)
Coinfection status	HCV mono	13,993 (94%)	6,989 (94%)	2,427 (93%)	4,577 (93%)	3,799 (93%)	3,204 (93%)
	HCV/HBV	773 (5%)	373 (5%)	149 (6%)	250 (5%)	216 (5%)	183 (5%)
	HCV/HIV	172 (1%)	70 (1%)	32 (1%)	70 (1%)	53 (1%)	49 (1%)

[a] Maximum number and maximum length of hospitalisation occurring while individual was DAA treatment eligible (i.e. beginning 01 March 2016 or date of HCV notification if after, and ends at DAA treatment initiation, death, or 30 June 2018).

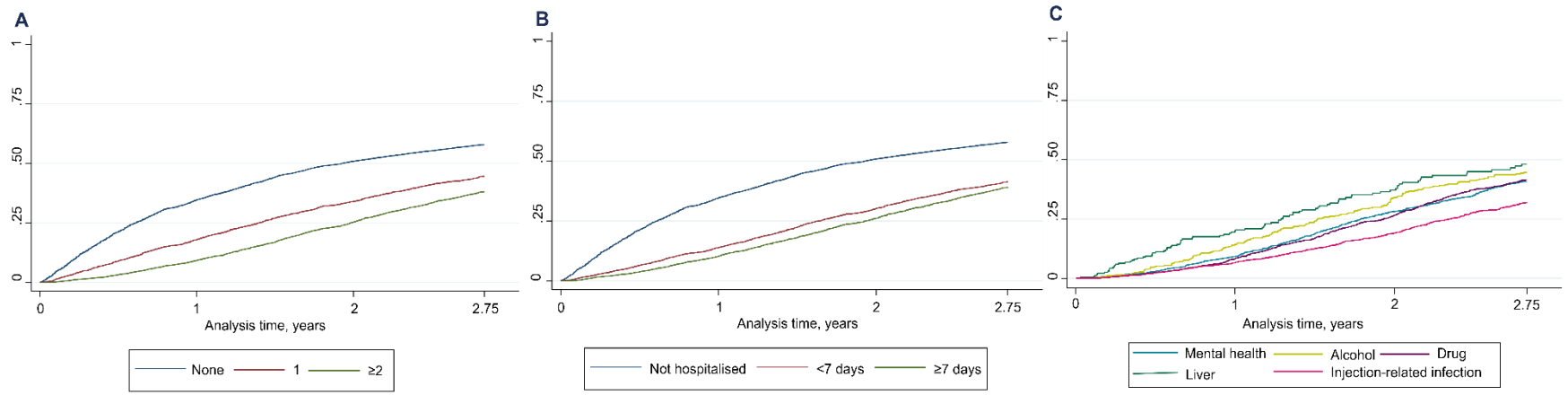
Table 2: Primary diagnosis at first hospitalisation before end of follow up [a] among NSW people with HCV notification and evidence of recent drug dependence (n=14,938)

Characteristic		Primary diagnosis at first hospitalisation, n (col%)				
		Mental health disorder, n (col%)	**AUD,** n (col%)	**Drug** [b]**,** n (col%)	**Liver,** n (col%)	**Injection-related infectious disease,** n (col%)
Total, n(row%)		1,098 (7%)	367 (2%)	1,628 (11%)	237 (2%)	1,397 (9%)
Year of birth	1989-2000	66 (6%)	11 (3%)	151 (9%)		57 (4%)
	1974-1988	543 (49%)	128 (35%)	827 (51%)	29 (12%) [c]	443 (32%)
	1959-1973	417 (38%)	197 (54%)	585 (36%)	123 (52%)	608 (44%)
	≤1958	72 (7%)	31 (8%)	66 (4%)	84 (35%)	289 (21%)
Sex	Male	736 (67%)	273 (74%)	1,071 (66%)	182 (77%)	910 (65%)
	Female	362 (33%)	94 (26%)	558 (34%)	54 (23%)	486 (35%)
ATSI	No	749 (68%)	252 (69%)	1,126 (69%)	198 (84%)	1,019 (73%)
	Yes	337 (31%)	109 (30%)	493 (30%)	37 (16%)	361 (26%)
Region of HCV notification	Metro	270 (25%)	88 (24%)	398 (24%)	48 (20%)	288 (21%)
	Outer Metro	337 (31%)	136 (37%)	563 (35%)	85 (36%)	490 (35%)
	Regional/Rural	398 (36%)	128 (35%)	515 (32%)	95 (40%)	521 (37%)
Country of birth	Australia	959 (87%)	327 (89%)	1,461 (90%)	188 (79%)	1,145 (82%)
	Overseas	138 (13%)	39 (11%)	166 (10%)	49 (21%)	220 (16%)
Recent incarceration	No	705 (64%)	260 (71%)	939 (58%)	213 (90%)	1,066 (76%)
	Yes	393 (36%)	106 (29%)	689 (42%)	24 (10%)	331 (24%)
Coinfection status	HCV mono	1,027 (94%)	342 (93%)	1,522 (93%)	217 (92%)	1,313 (94%)
	HCV/HBV	54 (5%)	18 (5%)	80 (5%)		66 (5%)
	HCV/HIV	17 (2%)	7 (2%)	27 (2%)	20 (8%) [c]	19 (1%)

[a] Primary diagnosis at first hospitalisation occurring while individual was DAA treatment eligible (i.e. beginning 01 March 2016 or date of HCV notification if after, and ends at DAA treatment initiation, death, or 30 June 2018), related ICD-10 codes in Supplementary Table 2

[b] relates to injection and non-injection drug use; [c] Cells combined due to data governance guidelines requiring suppression of individual cells which relate to ≤5 unique observations

Figure 4: Kaplan Meier curves depicting estimated time (years) to DAA treatment initiation among people with evidence of recent drug dependence and who are estimated to have chronic HCV in the DAA era in NSW, Australia, by **(A)** number of hospitalisations, **(B)** maximum length of hospitalisation and **(C)** primary diagnosis at first cause-specific hospitalisation before end of follow up



4.5 Discussion:

The comprehensive evaluation of rates and patterns of hospitalisation among people with drug dependence in our study provides the feasibility for substantially increased DAA therapy uptake through optimising the inpatient setting for HCV screening and treatment initiation. The utilisation of hospitalisations for HCV therapy is a growing area of research interest [199], making these results important in the context of optimising HCV elimination strategies through the inpatient setting. Although HCV treatment uptake among people with drug dependence has been relatively high in the DAA era in Australia, our study demonstrated that those with more frequent (≥2 visits) and long-stay (≥7 days) hospitalisations had lower treatment uptake. These sub-populations with higher rates of largely drug-related admissions are likely higher-risk and more highly marginalised, including many with unstable accommodation [213].

The primary diagnosis at first hospitalisation in the DAA era was associated with DAA uptake, with diagnoses relating to mental health, drug use, and injection-related infectious diseases less likely to have received treatment by the end of follow up than those hospitalised for alcohol and liver-related morbidity. Given high frequency of injection-related infectious disease among Australian PWID [206], the lower treatment uptake in those hospitalised for these complications is discouraging. Women account for a disproportionate amount of injection-related infectious diseases [206], therefore closing sex-related discrepancies in DAA uptake found in previous Australian studies [188, 208] should be facilitated by inpatient HCV treatment.

Psychiatric admissions provide further opportunity to diagnose and treat HCV. While our results suggest progress in reaching populations with mental health disorders, they also highlight the need for increased intervention within mental health settings. Given psychiatric comorbidities remain a barrier to DAA therapy in this and other studies [168], and psychiatrists have significantly lesser competency of HCV therapy compared to other medical specialties [214], innovative strategies may be required. Targeted educational sessions within psychiatry wards have been shown to positively transform HIV-related knowledge among providers and patients [215]. Similar educational interventions may be useful to remodel standard of care in inpatient psychiatric wards to reach key populations.

A further key finding was the "dose-response" nature that number of long-stay admissions had in lowering DAA therapy uptake, despite more time within the health service. Each interaction between PWID and clinical services serves as a potential opportunity to initiate HCV care. Hospital-based HCV screening initiatives both at the local [205, 216] and national [217] levels have demonstrated increased diagnosis and linkage to care among people admitted to hospital and emergency departments, but have cited less linkage to care among those with longer admissions and significant loss to follow up after patient discharge [217]. Simplified engagement and reduction of loss to follow up may be partially mitigated by utilisation of fingerstick point-of-care diagnostic and non-invasive liver imaging technology [216], enacting health policy which allows dispensing of DAA therapy from hospital pharmacy, and prescription of shorter course, pan-genotypic DAA regimens.

This study has limitations which should be considered. The limitations surrounding the methodology and utilisation of administrative datasets in NSW to characterise people with drug dependence have been previously described in detail [208]. Using these datasets to identify people with drug dependence has potentially impacted our results in three ways: (1) while the inclusion of people receiving OAT and expanding the definition of our key population from PWID to those with "drug dependence" increased sensitivity, it is likely that we have underestimated the true population of people with drug dependence in NSW, (2) some people may have been receiving OAT for chronic pain management and thus misclassified as drug dependent, but given the large majority of people in Australia have acquired HCV through injecting drug use, this is likely to be a small minority, and (3) as a large proportion of people with drug dependence were identified on the basis of hospitalisation, the frequency of hospitalisations reported in this group is likely somewhat overestimated. Despite this, using these methods characterises a group of the overall PWID population in NSW who are likely more marginalised and understanding the gaps in treatment uptake among the most marginalised PWID is paramount. An analysis which further stratifies OAT by patterns of engagement will be explored in a future study. Furthermore, this study did not account for the timely relationship between hospitalisation and initiation onto DAA therapy which is the focus of a subsequent analysis.

4.5.1 Conclusion

In an era of unrestricted DAA therapy, there remains a population of people with drug dependence who are not engaged with HCV therapy but remain engaged with health services. Innovative strategies to educate a range of practitioners across medical specialities on HCV risk and therapies and enhancing current standard of inpatient care

to include provision of DAA therapy will be critical in ensuring equitable HCV elimination.

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Disclaimer

All inferences, opinions, and conclusions drawn in this publication are those of the author(s), and do not necessarily reflect the opinions or policies of the Australian Government Department of Health.

Declaration of interests

GD reports grants from Gilead, Abbvie, Merck, and Bristol-Myers Squibb, personal fees from Gilead, Abbvie, and Merck, and non-financial support from Gilead, Abbvie, and Merck, outside the submitted work. JG reports grants from Merck, grants from Cepheid, during the conduct of the study; grants and personal fees from Abbvie, grants and personal fees from Gilead Sciences, grants and personal fees from Merck, grants and personal fees from Cepheid, grants from Hologic, grants from Indivior, outside the submitted work. ML reports grants from Gilead Sciences, Janssen Cilag and ViiV Healthcare outside the submitted work. All remaining authors have no potential conflicts to declare.

Supplementary Table 1: ICD-10 definitions used to identify injecting drug use-related hospital presentations among all NSW people with an HCV notification

ICD-10	Description
A40	Streptococcal sepsis
A41	Other sepsis
A48.0	Other bacterial diseases, not elsewhere classified (gas gangrene)
B37.6	Candidiasis, candida endocarditis
F11	Mental and behavioural disorders due to use of opioids
F13	Mental and behavioural disorders due to sedatives or hypnotics
F14	Mental and behavioural disorders due to use of cocaine
F15	Mental and behavioural disorders due to use of other stimulants, including caffeine
F19	Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances
G06	Intracranial and intraspinal abscess and granuloma
G09	Sequelae of inflammatory disease of central nervous system
I26.9	Pulmonary embolism, pulmonary embolism without mention of acute or pulmonale
I33	Acute and subacute endocarditis
I34	Nonrheumatic mitral valve disorders
I35	Nonrheumatic aortic valve disorders
I36	Nonrheumatic tricuspid valve disorders
I37	Pulmonary valve disorders
I38	Endocarditis, valve unspecified
I39	Endocarditis and heart valve disorders in diseases classified elsewhere
I40.0	Acute myocarditis, infective myocarditis
I80	Phlebitis and thrombophlebitis
K63.0	Other diseases of the intestine, abscess of intestine
K65.0	Peritonitis, acute peritonitis
K75.0	Other inflammatory liver disease, abscess of liver
L02	Cutaneous abscess, furuncle and carbuncle
L03	Cellulitis
L97	Ulcer of lower limb, not elsewhere classified
L98.8	Other disorders of skin and subcutaneous tissue, not elsewhere classified, other specified disorders of skin and subcutaneous tissue
M54.0	Dorsalgia, panniculitis affecting regions of neck and back
M72.6	Fibroblastic disorders, necrotizing fasciitis
M79.3	Other soft tissue disorders, not elsewhere classified (panniculitis, unspecified)
M86	Osteomyelitis
M89.9	Other disorders of bone, disorder of bone, unspecified
N10	Acute tubulo-interstitial nephritis
R02	Gangrene, not elsewhere classified
R57.2	Shock, not elsewhere classified, septic shock
R65.1	Systemic Inflammatory Response Syndrome of infectious origin with organ failure
R65.9	Systemic Inflammatory Response Syndrome, unspecified
R78.1	Finding of opiate drug in blood
R78.2	Finding of cocaine in blood
T38.7	Androgens and anabolic congeners
T40.0	Poisoning by narcotics and psychodysleptics, opium
T40.1	Poisoning by narcotics and psychodysleptics, heroin

T40.2	Poisoning by narcotics and psychodysleptics, other opioids (codeine/morphine)
T40.3	Poisoning by narcotics and psychodysleptics, methadone
T40.4	Poisoning by narcotics and psychodysleptics, other synthetic narcotics (pethidine)
T40.5	Poisoning by narcotics and psychodysleptics, cocaine
T40.6	Poisoning by narcotics and psychodysleptics, other and unspecified narcotics
T40.8	Poisoning by narcotics and psychodysleptics, lysergide (LSD)
T41.2	Poisoning by anaesthetics and therapeutic gases, other and unspecified general anaesthetics
T42.3	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs, barbiturates
T42.4	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs, benzodiazepines
T42.5	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs, mixed antiepileptics, not elsewhere classified
T42.6	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs, other antiepileptic and sedative-hypnotic drugs
T42.7	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs, antiepileptic and sedative-hypnotic drugs, unspecified
T42.8	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs, antiparkinsonism drugs and other central muscle-tone depressants
T43.6	Poisoning by psychotropic drugs, not elsewhere classified, psychostimulants with abuse potential
T43.8	Poisoning by psychotropic drugs, not elsewhere classified, other psychotropic drugs, not elsewhere classified
T43.9	Poisoning by psychotropic drugs, not elsewhere classified, psychotropic drug, unspecified
T50.7	Poisoning by psychotropic drugs, not elsewhere classified, analeptics and opioid receptor antagonists
X41	Accidental poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified
X61	Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified
Y11	Poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified, undetermined intent

Supplementary Table 2: Characteristics of those linked and unlinked to Medicare (universal healthcare) dataset holding HCV treatment information

Characteristic		Medicare linked, n (col%)	Medicare unlinked, n (col%)
Total, n(row%)		80,017 (89%)	9,931 (11%)
Age	18-29	2,800 (4%)	580 (6%)
	30-44	21,129 (26%)	3,516 (35%)
	45-59	36,530 (46%)	4,073 (41%)
	60+	19,558 (24%)	1,762 (18%)
Sex	Male	49,621 (62%)	7,570 (76%)
	Female	30,396 (38%)	2,361 (24%)
Indigenous Australian ethnicity	No	55,275 (69%)	3,739 (38%)
	Yes	10,432 (13%)	1,391 (14%)
	NK	14,310 (18%)	4,801 (48%)
Region of HCV notification	Metro	21,163 (26%)	3,373 (34%)
	Outer-metro	26,483 (33%)	1,180 (12%)
	Rural	28,104 (3%)	1,213 (12%)
	NK	4,267 (5%)	4,165 (42%)
Country of birth	Australia	53,212 (67%)	4,310 (43%)
	Overseas	14,323 (18%)	815 (8%)
	NK	12,482 (16%)	4,806 (48%)
Recent incarceration	No	72,432 (91%)	9,075 (91%)
	Yes	7,585 (9%)	856 (9%)
Coinfection status	HCV only	75,959 (95%)	9546 (96%)
	HCV/HBV	3,140 (4%)	272 (3%)
	HCV/HIV	918 (1%)	113 (1%)
History of AUD	No	64,497 (81%)	9,400 (95%)
	Yes	15,520 (19%)	531 (5%)
Drug Dependence	None	44,955 (56%)	7,850 (79%)
	Past	15,148 (19%)	851 (9%)
	Recent	19,914 (25%)	1,230 (12%)

Supplementary Table 3: ICD-10 definitions used to identify hospitalisations occurring due to (A) mental health disorder (B) AUD (C) drug (D) liver and (E) injection-related infectious disease among all NSW people with an HCV notification

ICD-10	Description
A. Mental health disorder	
F0	Dementia in Alzheimer disease
F2	Schizophrenia, schizotypal and delusional disorders
F3	Mood (affective) disorders
F4	Neurotic, stress-related and somatoform disorders
F5	Behavioural syndromes associated with physiological disturbances and physical factors
F6	Disorders of adult personality and behaviour
F7	Mental retardation
F8	Disorders of psychological development
F9	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence
R44	Other symptoms and signs involving general sensations and perceptions
R45.8	Other symptoms and signs involving emotional state, suicidal ideation and attempt
B. Alcohol use disorder	
E24.4	Alcohol-induced pseudo-Cushing syndrome
F10	Mental and behavioural disorders due to use of alcohol
G31.2	Degeneration of nervous system due to alcohol
G62.1	Alcoholic polyneuropathy
G72.1	Alcoholic myopathy
I42.6	Alcoholic cardiomyopathy
Z50.2	Alcoholic rehabilitation
Z71.4	Alcohol abuse counselling and surveillance
C. Drug use (injecting and non-injecting)	
F11	Mental and behavioural disorders due to use of opioids
F12	Mental and behavioural disorders due to use of cannabinoids
F13	Mental and behavioural disorders due to use of sedatives or hypnotics
F14	Mental and behavioural disorders due to use of cocaine
F15	Mental and behavioural disorders due to use of other stimulants, including caffeine
F16	Mental and behavioural disorders due to use of hallucinogens
F18	Mental and behavioural disorders due to use of volatile solvents
F19	Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances
O35.5	Maternal care for (suspected) damage to foetus by drugs
P04.4	Foetus and newborn affected by maternal use of drugs of addiction
R78.1	Finding of opiate drug in blood
R78.2	Finding of cocaine in blood
R78.3	Finding of hallucinogen in blood
R78.4	Finding of other drugs of addictive potential in blood
R78.5	Finding of psychotropic drug in blood
T38.7	Poisoning by androgens and anabolic congeners
T40	Poisoning by narcotics and psychodysleptics
T41.2	Poisoning by other and unspecified general anaesthetics
T42.4	Poisoning by benzodiazepines
T42.5	Poisoning by mixed antiepileptics, not elsewhere classified
T42.6	Poisoning by other antiepileptic and sedative-hypnotic drugs

T42.7	Poisoning by antiepileptic and sedative-hypnotic drugs, unspecified
T42.8	Poisoning by antiparkinsonism drugs and other central muscle-tone depressants
T43.5	Poisoning by other and unspecified antipsychotics and neuroleptics
T43.6	Poisoning by psychostimulants with abuse potential
T43.8	Poisoning by other psychotropic drugs, not otherwise classified
T43.9	Poisoning by other psychotropic drugs, unspecified
T50.7	Poisoning by analeptics and opioid receptor antagonists
T52	Toxic effect of organic solvents
T53	Toxic effect of halogen derivatives of aliphatic and aromatic hydrocarbons
T59.0	Toxic effect of nitrogen oxides
T59.8	Toxic effect of other specified gases, fumes and vapours
Z04.0	Blood-alcohol and blood-drug test
Z50.3	Drug rehabilitation
Z71.5	Drug abuse counselling and surveillance
D. Liver	
B15	Acute hepatitis A
B16	Acute hepatitis B
B17	Other acute viral hepatitis
B18	Chronic viral hepatitis
B19	Unspecified viral hepatitis
B94.2	Sequelae of viral hepatitis
C22.0	Liber cell carcinoma
K70	Alcoholic liver disease
K71	Toxic liver disease
K72	Hepatic failure, not elsewhere classified
K73	Chronic hepatitis, not elsewhere classified
K74	Fibrosis and cirrhosis of liver
K75	Other inflammatory liver diseases
K76	Other diseases of liver
K77	Liver disorders in diseases classified elsewhere
I85.0	Oesophageal varices with bleeding
I98.21	Oesophageal varices without bleeding in diseases classified elsewhere
I98.3	Oesophageal varices with bleeding in diseases classified elsewhere
R18	Ascites
E. Injecting-related infectious disease	
A40	Streptococcal sepsis
A41	Other sepsis
A48.0	Other bacterial diseases, not elsewhere classified (gas gangrene)
B37.6	Candidiasis, candida endocarditis
G06	Intracranial and intraspinal abscess and granuloma
G09	Sequelae of inflammatory disease of central nervous system
I26.9	Pulmonary embolism, pulmonary embolism without mention of acute or pulmonale
I33	Acute and subacute endocarditis
I34	Nonrheumatic mitral valve disorders
I35	Nonrheumatic aortic valve disorders
I36	Nonrheumatic tricuspid valve disorders
I37	Pulmonary valve disorders
I38	Endocarditis, valve unspecified
I39	Endocarditis and heart valve disorders in diseases classified elsewhere
I40.0	Acute myocarditis, infective myocarditis

I80	Phlebitis and thrombophlebitis
K63.0	Other diseases of the intestine, abscess of intestine
K65.0	Peritonitis, acute peritonitis
K75.0	Other inflammatory liver disease, abscess of liver
L02	Cutaneous abscess, furuncle and carbuncle
L03	Cellulitis
L97	Ulcer of lower limb, not elsewhere classified
L98.8	Other disorders of skin and subcutaneous tissue, not elsewhere classified, other specified disorders of skin and subcutaneous tissue
M54.0	Dorsalgia, panniculitis affecting regions of neck and back
M72.6	Fibroblastic disorders, necrotizing fasciitis
M79.3	Other soft tissue disorders, not elsewhere classified (panniculitis, unspecified)
M86	Osteomyelitis
M89.9	Other disorders of bone, disorder of bone, unspecified
N10	Acute tubulo-interstitial nephritis
R02	Gangrene, not elsewhere classified
R57.2	Shock, not elsewhere classified, septic shock
R65.1	Systemic Inflammatory Response Syndrome of infectious origin with organ failure
R65.9	Systemic Inflammatory Response Syndrome, unspecified

Supplementary Table 4: Number and proportion of hospitalisations according to ICD-10 chapter among people with evidence of recent drug dependence, by all hospitalisations and among long-stay (≥7days) hospitalisations only

ICD-10 Chapter	All hospitalisations [a]		Long-stay hospitalisation only [a]	
	n	%	n	%
Other causes	7,081	26.4	1,352	20.0
Pregnancy, childbirth and the puerperium	499	1.9	100	1.5
Neoplasms	829	3.1	269	4.0
Diseases of the circulatory system	1,248	4.7	396	5.8
Diseases of the respiratory system	1,340	5.0	383	5.6
Diseases of the skin and subcutaneous tissue	1,957	7.3	385	5.7
Diseases of the digestive system	1,633	6.1	258	3.8
Injury, poisoning	3,747	14	631	9.3
Mental and behavioural disorders	8,504	31.7	3,022	44.5

[a] all hospitalisations and long-stay hospitalisations with insufficient diagnostic data (comprising 1% and 3% of all hospitalisations, respectively) not shown

Supplementary Table 5: Incidence (per 100 person-years) of cause-specific hospitalisations

	No evidence of drug dependence	**Distant drug dependence**	**Recent drug dependence**
Mental health	0.71 (0.64, 0.78)	3.37 (3.10, 3.57)	15.84 (15.42, 16.28)
Drug	0.04 (0.02, 0.05)	0.18 (0.12, 0.24)	15.20 (14.78, 15.63)
AUD	0.27 (0.23, 0.32)	1.44 (1.27, 1.59)	4.58 (4.34, 4.83)
Liver	0.78 (0.72, 0.85)	1.14 (1.00, 1.27)	3.13 (2.93, 3.34)
Injection-related infectious disease			9.15 (8.82, 9.50)

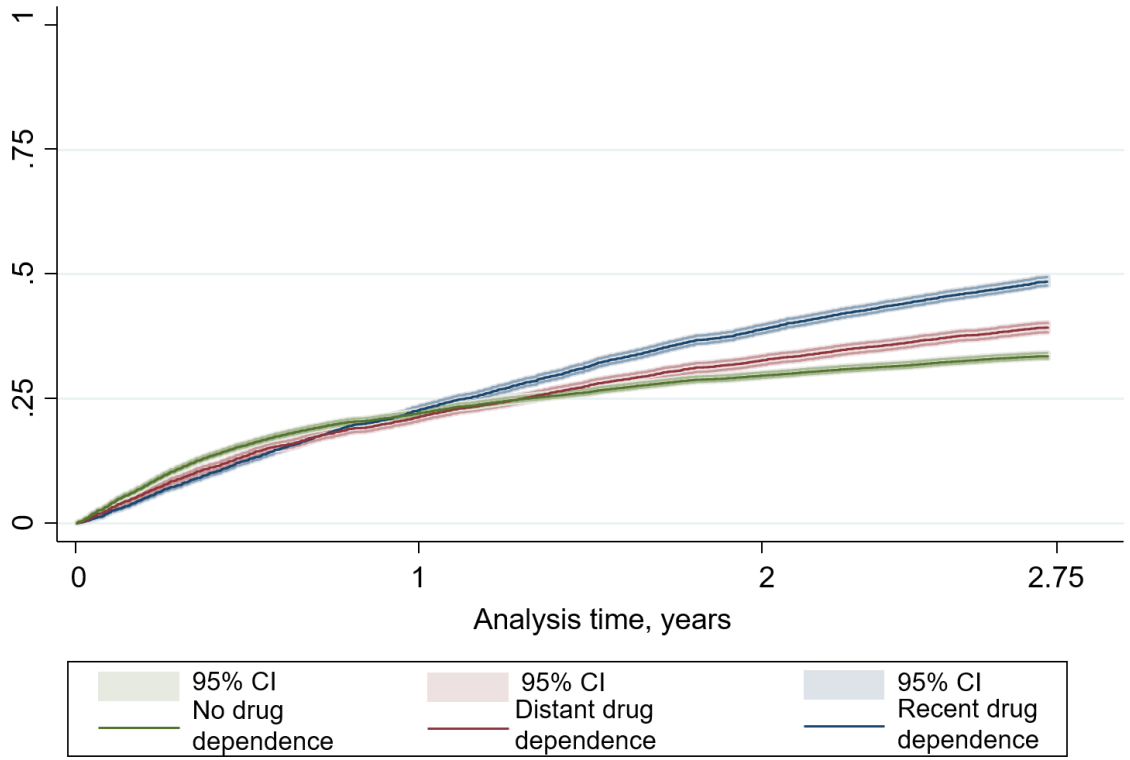
Supplementary Table 6: Kaplan Meier estimated proportions of DAA treatment initiation among NSW people with HCV notification at one and two years after 01 March 2016, and at end of follow up (31 December 2018), overall and by drug dependence

Overall		Follow up time, years		
		1	2	2.75
		22.1 (21.8, 22.5)	32.6 (32.3, 33.0)	38.1 (37.7, 38.5)
Drug Dependence	None	22.1 (21.7, 22.6)	29.7 (29.2, 30.2)	33.4 (32.9, 33.9)
	Distant	21.3 (20.1, 22.1)	32.6 (31.8, 33.5)	38.8 (37.8, 39.7)
	Recent	22.7 (22.1, 23.4)	39.0 (38.2, 39.8)	47.7 (46.9, 48.6)

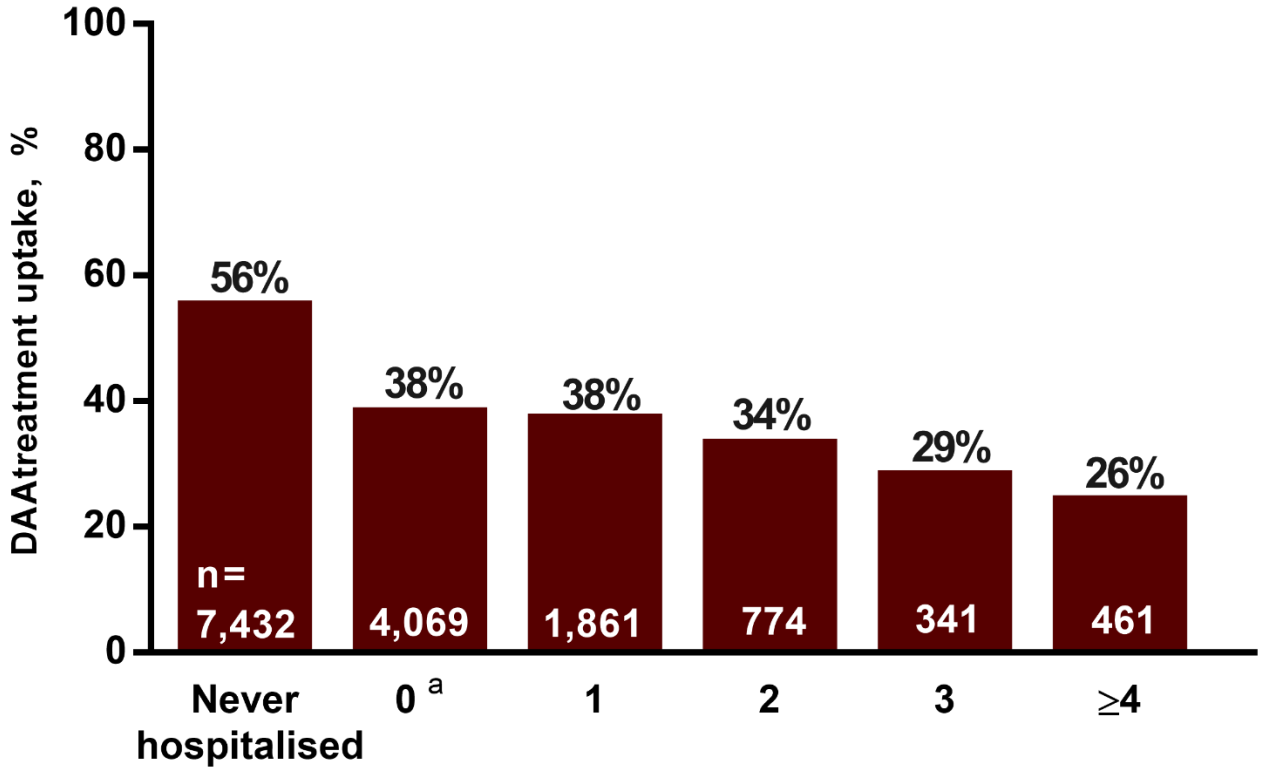
Supplementary Table 7: Kaplan Meier estimated proportions of DAA treatment initiation among NSW people with HCV notification and evidence of recent drug dependence at one and two years after 01 March 2016, and at end of follow up (31 December 2018), by hospitalisation characteristic

Characteristic		Follow up time, years		
		1	2	2.75
No hospitalisation		35.2 (34.1, 36.3)	51.4 (50.2, 52.6)	57.7 (56.6, 58.9)
Freq of hospitalisation	1	16.8 (15.4, 18.3)	33.1 (31.4, 35.0)	42.8 (40.9, 44.8)
	≥2	7.3 (6.6, 8.1)	23.5 (22.4, 24.8)	35.5 (34.1, 36.9)
Length of hospitalisation	0-7 days	12.5 (11.5, 13.5)	28.9 (11.5, 13.6)	39.3 (37.7, 40.8)
	≥7 days	8.4 (7.5, 9.4)	24.5, 23.1, 26.0)	36.6 (34.9, 38.3)
Diagnosis of first hospitalisation	Mental Health	9.1 (7.5, 11.0)	28.5 (25.8, 31.4)	40.2 (37.2, 43.3)
	Drug	8.1 (6.9, 9.6)	26.5 (24.4, 28.7)	40.3 (37.8, 42.8)
	Alcohol	14.4 (11.1, 18.6)	33.8 (28.9, 39.1)	42.6 (37.3, 48.2)
	Liver	19.3 (14.5, 25.4)	37.5 (30.8, 45.0)	45.3 (38.0, 53.4)
	Injection-related infectious disease	6.5 (5.4, 8.0)	19.0 (17.0, 21.2)	30.1 (28.3, 33.4)

Supplementary Figure 1: Kaplan Meier failure curve depicting estimated time to DAA treatment initiation among people who are estimated to have chronic HCV in the DAA era in NSW, Australia



Supplementary Figure 2: DAA uptake among NSW people with HCV notification and evidence of recent drug dependence, by number of long-stay hospital admissions incurred whilst DAA treatment eligible



[a] 0: Ever hospitalised, but never longer than seven-day length of stay between whilst eligible for DAA therapy

Chapter 5: Declining Prevalence of Current HCV Infection and Increased Treatment Uptake Among People Who Inject Drugs: The ETHOS Engage Study

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5.1 Abstract

Background: Evaluating trends in HCV treatment and prevalence is crucial for monitoring elimination efforts. We evaluated the change in the prevalence of current infection and treatment among people who inject drugs (PWID) between 2018-2019 and 2019-2021. **Methods:** ETHOS Engage is an observational cohort study of PWID attending drug treatment clinics and needle and syringe programs in Australia. Participant enrolment occurred over two periods, Wave 1 (May 2018-September 2019, 25 sites) and Wave 2 (November 2019-April 2021, 21 sites), with baseline questionnaire completion and point-of-care HCV RNA testing (Xpert® HCV Viral Load Fingerstick). Using baseline information historic HCV treatment and prevalence of current infection was determined, with logistic regression used to identify factors associated with these outcomes. **Results:** 2,395 individuals were enrolled into ETHOS Engage across the two recruitment waves (55% male, median age 44, 72% current opioid agonist therapy [OAT], and 66% injecting in the last month). HCV prevalence decreased from 24% to 17% between 2018-2019 and 2019-2021, respectively (p=0.003). HCV treatment increased from 66% to 74% between 2018-2019 and 2019-2021, respectively (p<0.001). After adjustment for demographic and behavioural characteristics, there was a reduction in current HCV infection in 2019-2021 (adjusted odds ratio [aOR] 0.62; 95% CI, 0.50-0.77) compared to 2018-2019. Other factors associated with current HCV infection included homelessness (aOR, 1.70; 1.26, 2.30), incarceration (vs. never; not recently: aOR 1.69, 1.31, 2.19; recently: aOR 1.85, 1.35, 2.54), and injecting drug use in the previous month (vs. none; <daily: aOR 2.03; 1.37, 3.02; ≥daily: aOR 2.90; 1.94, 4.32). **Conclusion:** The increase in HCV treatment and decrease in prevalence among PWID provides evidence of further progress towards

HCV elimination. Sub-populations may require additional support to enhance elimination.

Keywords: hepatitis C virus, direct-acting antiviral therapy, hepatitis C virus elimination, people who inject drugs

5.2 Introduction

The World Health Organization has committed to eliminating hepatitis C virus (HCV) as a global public health threat within this decade [218]. People who inject drugs (PWID) incur a disproportionate burden of HCV and continually face barriers to accessing adequate healthcare [120]. Engaging PWID in testing and treatment is key in the pursuit of HCV elimination. Australia is uniquely placed to demonstrate the feasibility of achieving HCV elimination as highly curative direct-acting antiviral therapy (DAA) has been available to all adults, independent of drug and alcohol-related restrictions, since March 2016. Although progress towards improving HCV care among PWID has been achieved in Australia [219, 220], it is critical to understand barriers that continue to impede progress towards enhancing HCV treatment and reducing prevalence to enable the implementation of interventions to facilitate HCV elimination.

Temporal data are optimal for understanding the impact of DAA therapy on the progression toward HCV elimination among PWID. Although studies have evaluated trends in HCV treatment uptake and current infection among PWID [151, 221-223], they are limited by a lack of recent data (published data only provide progress up to 2018) and few studies have evaluated both HCV treatment uptake and current infection. Understanding factors associated with treatment uptake and current infection among PWID can highlight sub-populations with greater barriers to care and facilitate the design of interventions to improve testing and treatment in these sub-populations to facilitate HCV elimination efforts.

This study evaluated progress towards HCV elimination among PWID in Australia in a large, national cohort of PWID recruited from drug treatment and needle and syringe

programs (NSPs) across two recruitment waves during an era of unrestricted HCV DAA therapy. The primary aim of this study was to evaluate the change in the prevalence of current HCV infection and treatment among PWID between 2018-2019 and 2019-2021. A secondary aim was to evaluate factors associated with current HCV infection and HCV treatment among PWID.

5.3 Methods

5.3.1 Data Sources

ETHOS Engage is an observational cohort study. Participants were enrolled across two recruitment waves: Wave 1 (May 2018-September 2019) and Wave 2 (November 2019-June 2021). Participants were recruited from the same opioid agonist therapy (OAT) clinics (Wave 1, n=18; Wave 2, n=16), drug and alcohol clinics (Wave 1, n=3; Wave 2, n=3), and NSPs (Wave 1, n=4; Wave 2, n=2) (Supplementary Table 1). Individuals who were enrolled in both Wave 1 and Wave 2 were identified by two-by-two name code (first two letters of first name and last name) and date of birth.

Inclusion criteria were informed consent, ≥18 years of age, and injecting drug use, either within the last 6 months or lifetime history and current receipt of OAT. Due to contraindications with Fibroscan®, people who were pregnant were excluded from Wave 1. Although study protocol was amended for Wave 2 to include pregnant participants, FibroScan® was withheld for those who were pregnant. The initial study protocol and all subsequent amendments were approved by the Human Research Ethics Committees at St Vincent's Hospital, Sydney (HREC Ref: HREC/17/SVH/113) and the Aboriginal Health and Medical Research Council (HREC Ref: 1279/17).

5.3.2 Procedures

The procedures for ETHOS Engage campaign days have been previously described [220]. In brief, ETHOS Engage was advertised preceding recruitment with posters, cards distributed with injecting equipment and by word of mouth. Recruitment spanned one to five days at each site and included a team of peer workers, university staff, and clinic personnel.

ETHOS Engage campaign days were run in multiple stages. First, participants provided 100µl finger-stick capillary whole-blood to test for HCV RNA using the point-of-care Xpert HCV Viral Load Fingerstick Assay (Cepheid, Sunnyvale, United States; lower limit of quantification 100IU/ml, upper limit of quantification 10^8 log10 IU/ml; 100% sensitivity, 100% specificity) [131]. Participants then self-completed a computer tablet-based questionnaire collecting data on demographics, behavioural risk, and HCV history (testing, infection status, and treatment). Liver fibrosis stage was assessed using transient hepatic elastography (FibroScan®, Echosens, Paris, France), after which participants underwent a brief consultation with appropriate clinical staff. Participation was compensated with a shopping voucher (AUD$30).

In Wave 1, HCV RNA test results were returned to clinics after in-house quality assurance checks since the assay was not yet approved and test results could not be provided to participants. In October 2019, the Therapeutic Goods Administration granted a Clinical Trial Notification for the off-label use of the Xpert HCV Viral Load Fingerstick assay, enabling the provision of HCV RNA test results in Wave 2 to healthcare providers and study participants on campaign days. In September 2020, the Xpert HCV Viral Load Fingerstick assay was fully approved by the Australian Therapeutics Goods Administration.

5.3.3 Outcomes at enrolment baseline

The primary outcome was current HCV infection (HCV RNA detected with the Xpert HCV Viral Load Fingerstick assay). The secondary outcome was self-reported history of HCV treatment among participants who have evidence of past (self-reported history

of HCV treatment) or current HCV infection [220]. Participants who were never infected (HCV RNA undetectable and self-reported as never having been diagnosed with HCV), who had spontaneously cleared (HCV RNA undetectable, self-reported as having been diagnosed with HCV, and self-reported never receiving HCV treatment), and who had suspected HCV reinfection (HCV RNA detectable and self-reported as ever receiving HCV treatment) were also identified.

5.3.4 Statistical analysis

Logistic regression was used to assess the factors associated with (1) current HCV infection, and (2) HCV treatment among those with evidence of previous chronic or current HCV infection. These outcomes were subsequently assessed among participants who had recently injected drugs (previous month). Among those who participated in Wave 1 and Wave 2, the first enrolment was used for logistic regression analyses. Supplementary analyses were also performed to evaluate current HCV infection and treatment uptake among those enrolled in Wave 1 and Wave 2, separately and irrespective of previous participation.

The exposure of interest was recruitment Wave (Wave 1, May 2018 – September 2019; Wave 2, November 2019 – June 2021). Other demographic and behavioural factors hypothesised to be associated with current HCV infection and HCV treatment were determined using previously published ETHOS Engage Wave 1 results [220] and included: (i) age at survey (stratified around median), (ii) gender (male, female, other [non-binary/transgender/other]), (iii) self-identified Aboriginal or Torres Strait Islander, (iv) homelessness in the previous 6 months, (v) OAT status (never, past, within the last month/current), (vi) incarceration history (never, history only [not recent], recent

[assessed within the last 12 months in Wave 1 and last six months in Wave 2]), (vii) recency and frequency of injecting drug use (>1 year ago, within the previous 1-12 months, within the previous month <daily, and ≥daily), and (viii) main drug injected in the last month (none, heroin, other opioids, methamphetamine, other). In analyses among those with injecting drug use in the previous month, injecting-related exposure variables were recoded as recency of injecting (<daily, ≥daily) and main drug injected in the last month (heroin, other opioids, methamphetamine, other).

Association between demographic and behavioural factors and outcomes were analysed in unadjusted analyses. Variables which had significance ≤0.50 at the unadjusted level or known clinical significance were considered for the adjusted model. Collinear variables were removed from adjusted models. All analyses were conducted using Stata 14.0 (StataCorp, College Station, TX, USA).

5.4 Results

5.4.1 Sample characteristics

The sample characteristics by recruitment Wave are presented in Table 1. Overall, 2,395 participants were enrolled. This included 1,443 participants enrolled in ETHOS Engage during 2018-2019 (Wave 1) and 1,211 enrolled during 2019-2021 (Wave 2) (259 participated in both Waves) (Table 1). Among individuals enrolled (n=2,395) 55% were male, the median age was 44, 72% were current receiving OAT and 66% had injected drugs in the last month. Demographics were similar between both recruitment waves (Table 1).

Table 1: Characteristics of people enrolled in ETHOS Engage, by recruitment wave

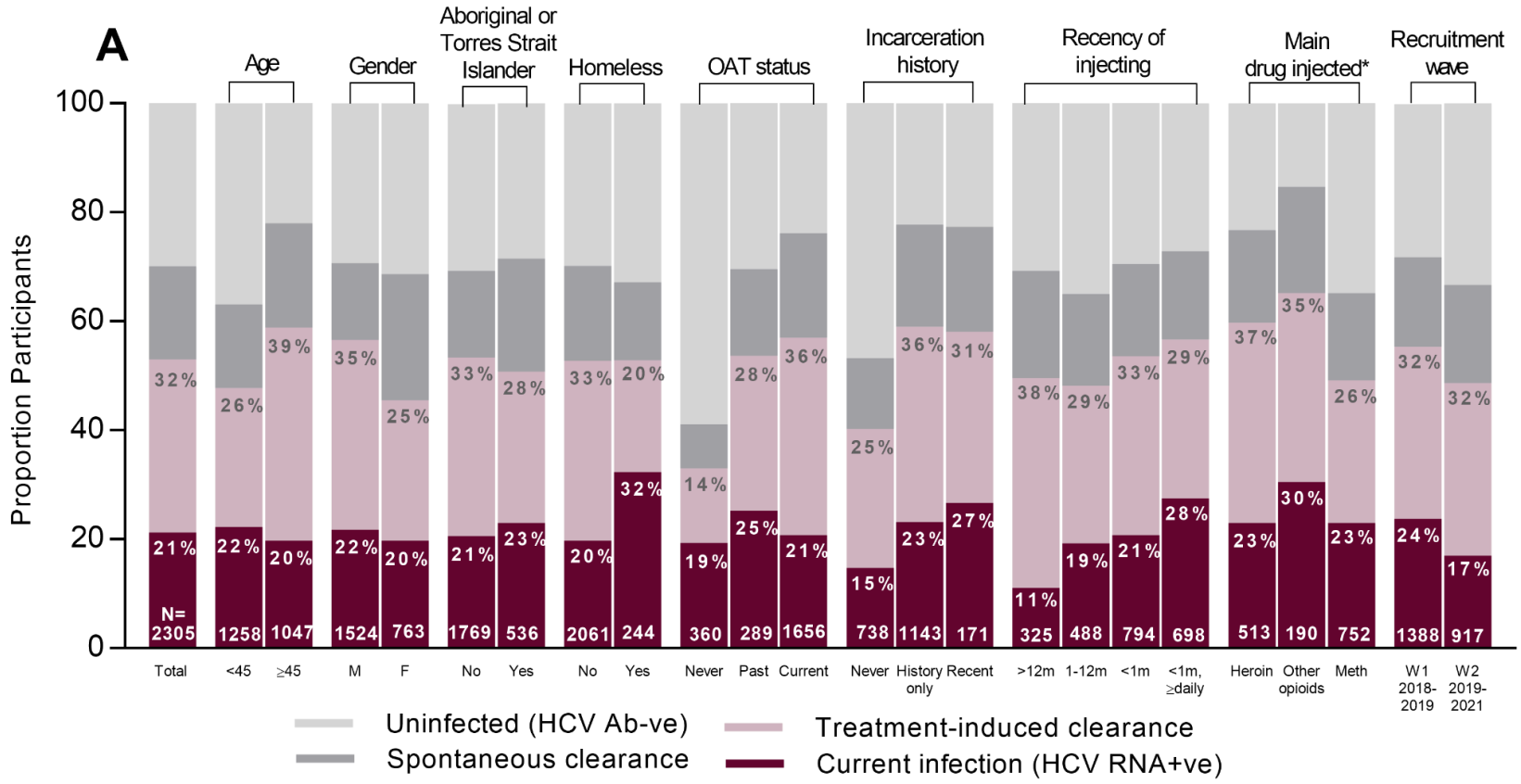
		Overall population	Wave 1 (2018-2019)	Wave 2 (2019-2021)	Participants enrolled in both Wave 1 and Wave 2	Participants only enrolled in Wave 2
Total		2,395	1,443	1,211	259	952
Median age		44	43	44	47	44
Gender	Male	1,591 (66%)	932 (65%)	820 (68%)	161 (62%)	659 (69%)
	Female	786 (33%)	508 (35%)	373 (31%)	95 (37%)	278 (29%)
	Other	18 (1%)	3 (<1%)	18 (2%)	3 (1%)	15 (2%)
Aboriginal or Torres Strait Islander	No	1,840 (76%)	1,106 (77%)	921 (76%)	187 (72%)	734 (77%)
	Yes	555 (23%)	337 (23%)	290 (24%)	72 (28%)	218 (23%)
Homeless	No	2,134 (89%)	1,285 (89%)	1,099 (91%)	250 (97%)	849 (89%)
	Yes	261 (11%)	158 (11%)	112 (9%)	9 (3%)	103 (11%)
OAT status	Never	371 (15%)	205 (14%)	172 (14%)	6 (2%)	166 (17%)
	Past	305 (13%)	168 (12%)	173 (14%)	36 (14%)	137 (14%)
	Current	1,719 (72%)	1,070 (74%)	866 (72%)	217 (84%)	649 (68%)
Incarceration history	Never	771 (32%)	469 (33%)	364 (30%)	62 (24%)	302 (32%)
	History only	1,181 (49%)	715 (50%)	632 (52%)	166 (64%)	466 (49%)
	Recent	443 (19%)	259 (18%)	215 (18%)	31 (12%)	184 (19%)
Recency of injecting	>12 months	334 (14%)	215 (15%)	174 (14%)	55 (21%)	119 (13%)
	Within 1-12 months	506 (21%)	307 (21%)	260 (21%)	61 (24%)	199 (21%)
	Within last month, <daily	822 (34%)	494 (34%)	404 (33%)	76 (29%)	328 (34%)
	Within last month, ≥daily	733 (31%)	427 (30%)	373 (31%)	67 (26%)	306 (32%)
Main drug injected in last month	None	840 (35%)	522 (36%)	434 (36%)	116 (45%)	318 (33%)
	Heroin	535 (22%)	312 (22%)	282 (23%)	59 (23%)	223 (23%)
	Other opioids	201 (8%)	132 (9%)	85 (7%)	16 (6%)	69 (7%)
	Methamphetamine	780 (33%)	450 (31%)	396 (33%)	66 (25%)	330 (35%)
	Other	39 (2%)	27 (2%)	14 (1%)	2 (1%)	12 (1%)

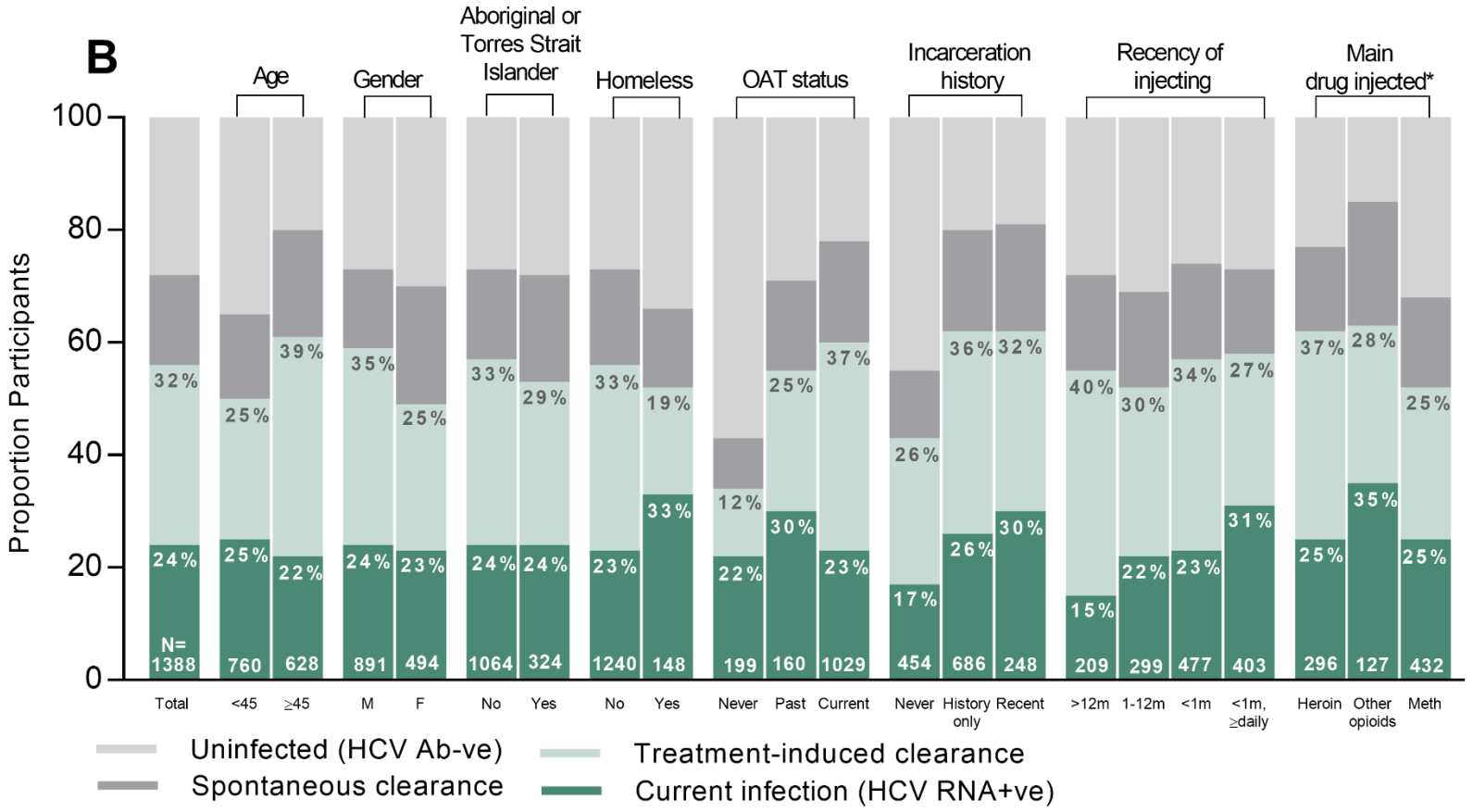
5.4.2 Factors associated with current HCV infection

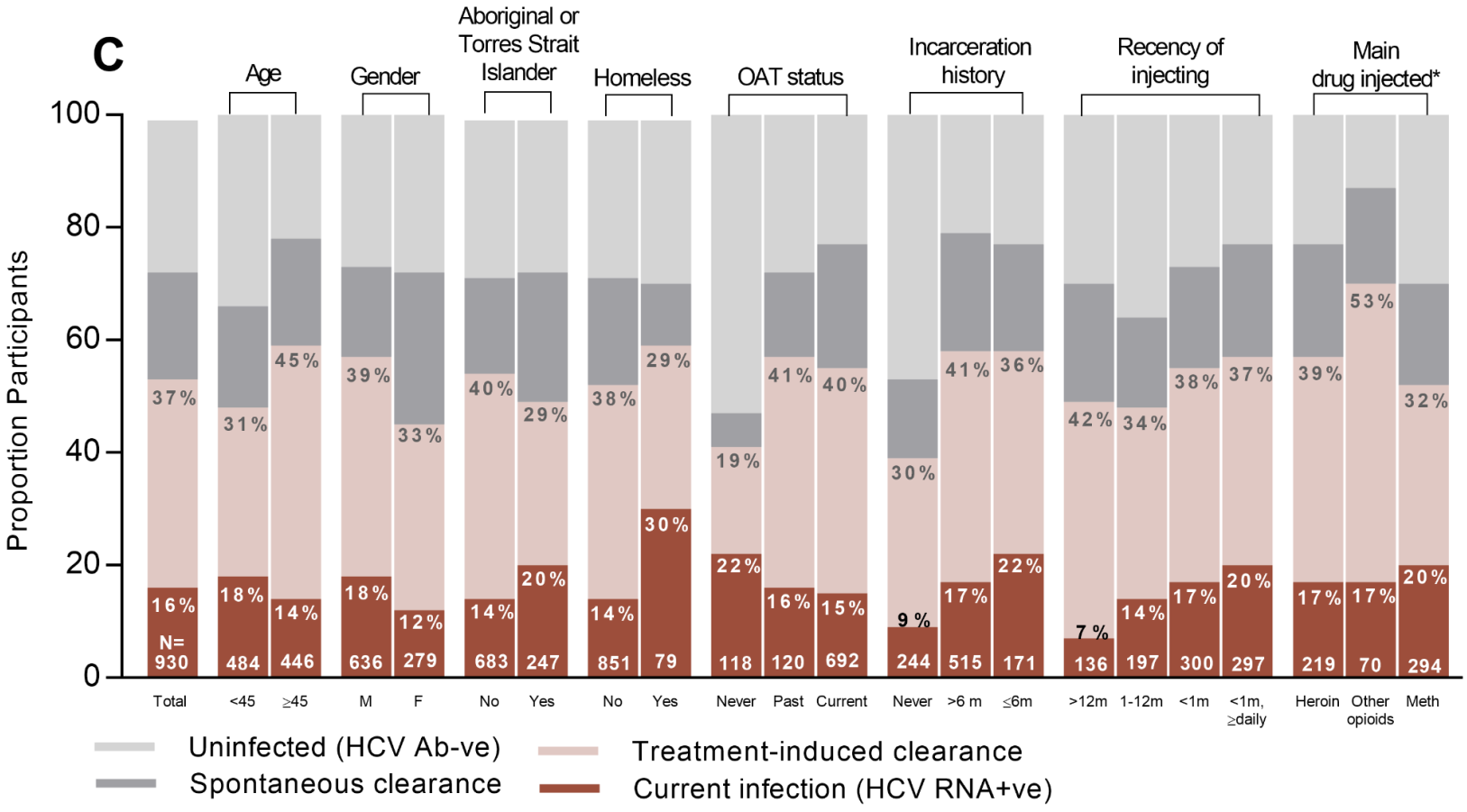
Among participants with valid HCV RNA point-of-care results (n=2,305), prevalence of current HCV infection (HCV RNA detectable) was 21% (Figure 1A), decreasing from 24% (331/1,388) during 2018-2019 to 15% (178/1,166) during 2019-2021 (Supplementary Table 2).

In adjusted analyses, participants recruited between 2019-2021 (Wave 2) were less likely to have current HCV infection than those recruited in 2018-2019 (Wave 1) (aOR: 0.62, 95%CI: 0.50, 0.77) (Table 2). Other factors associated with current HCV infection were homelessness (aOR: 1.70, 95%CI: 1.26, 2.30), incarceration history (vs. never, history only: aOR: 1.69, 95%CI: 1.31, 2.19; recent: aOR: 1.85, 95%CI: 1.35, 2.45), and recency of injecting drugs (vs. injecting in the last year, within 1-12 months ago aOR: 1.88, 95%CI: 1.23, 2.87; <daily in the previous month aOR: 2.03, 95%CI: 1.37, 3.02; ≥daily in the previous month aOR: 2.90, 95%CI: 1.94, 4.32). Current HCV infection was lower across all sub-populations in those recruited during 2019-2021 (Wave 1) compared to those recruited during 2018-2019 (Wave 2) (Figure 1B; Figure 1C; Supplementary Table 2). Among participants recruited during 2019-2021 (Wave 2), those who were homeless, who had a history of incarceration, and who had injected drugs more than one year ago were more likely to have current HCV infection (Supplementary Table 2).

Figure 1: Current HCV infection status among ETHOS Engage participants with known point-of-care HCV RNA, overall (A), and by recruitment Wave 1 (B) and Wave 2 (C)




B
Age
Gender
Aboriginal or Torres Strait Islander
Homeless
OAT status
Incarceration history
Recency of injecting
Main drug injected*
Proportion Participants
100
80
60
40
20
0
32%
25%
39%
24%
25%
22%
N= 1388
760
628
35%
25%
24%
23%
891
494
33%
29%
24%
24%
1064
324
33%
19%
23%
33%
1240
148
12%
25%
37%
22%
30%
23%
199
160
1029
26%
36%
32%
17%
26%
30%
454
686
248
40%
30%
34%
27%
15%
22%
23%
31%
209
299
477
403
37%
28%
25%
35%
25%
296
127
432
Total
<45
≥45
M
F
No
Yes
No
Yes
Never
Past
Current
Never
History only
Recent
>12m
1-12m
<1m
<1m, ≥daily
Heroin
Other opioids
Meth
Uninfected (HCV Ab-ve)
Spontaneous clearance
Treatment-induced clearance
Current infection (HCV RNA+ve)



*main drug injected in the last month
data for transgender and other gender identities not shown due to small numbers ; data for those mainly injecting other drugs in the last month not shown due to small numbers
denominators: A=first enrollment into ETHOS Engage with known HCV RNA result; B=Wave 1 total with known HCV RNA result; C=Wave 2 total with HCV RNA result

5.4.3 Factors associated with current HCV infection among those with recent injecting drug use

Among those with injecting drug use in the previous month with valid HCV RNA results (n=1,492), injecting drugs ≥daily (vs. <daily aOR: 1.33 95%CI: 1.04, 1.72) and injecting opioids other than heroin as their main drug injected (vs. injecting heroin; aOR:1.48, 95%CI: 1.01, 2.17) were associated with current HCV infection (Table 3). Consistent with analyses in the overall population, there was a significant reduction in current HCV infection in 2019-2021 compared to 2018-2019, while homelessness and incarceration history were associated with current HCV infection (Table 3). The factors associated with current HCV infection among those who recently injected who were recruited during 2019-2021 (Wave 2) are presented in Supplementary Tables 3-4.

Table 3: Factors associated with current HCV infection among all ETHOS Engage participants who have recently injected drugs (last month) and have valid HCV RNA point-of-care test results (N=1,492)

Characteristic		Total known HCV RNA result, n (col%)	Current HCV RNA infection, n(row%)	OR (95% CI)	aOR (95% CI)
Total		1,492	357 (24%)		
Age at enrolment	<45	844 (57%)	216 (26%)	-ref-	-ref-
	≥45	648 (43%)	141 (22%)	0.81 (0.63, 1.03)	0.82 (0.63, 1.05)
Gender	Male	988 (66%)	245 (25%)	-ref-	-ref-
	Female	491 (33%)	110 (22%)	0.88 (0.68, 1.13)	0.92 (0.70, 1.21)
	Other	13 (1%)	2 (15%)	0.55 (0.12, 2.50)	0.75 (0.16, 3.45)
Aboriginal or Torres Strait Islander	No	1,155 (77%)	269 (23%)	-ref-	-ref-
	Yes	337 (23%)	88 (26%)	1.16 (0.88, 1.54)	1.07 (0.80, 1.43)
Homeless	No	1,291 (87%)	287 (22%)	-ref-	-ref-
	Yes	201 (13%)	70 (35%)	1.87 (1.36, 2.57)	1.81 (1.30, 2.52)
OAT status	Never	286 (19%)	61 (21%)	-ref-	-ref-
	Past	225 (15%)	65 (29%)	1.50 (1.00, 2.24)	1.32 (0.86, 2.01)
	Current	981 (66%)	231 (24%)	1.14 (0.82, 1.56)	1.05 (0.73, 1.49)
Incarceration history	Never	461 (31%)	76 (16%)	-ref-	-ref-
	History only	740 (47%)	193 (26%)	1.79 (1.33, 2.40)	1.80 (1.32, 2.46)
	Recent	291 (20%)	88 (30%)	2.20 (1.55, 3.11)	2.08 (1.43, 3.03)
Frequency of injecting	<Daily	794 (53%)	165 (21%)	-ref-	-ref-
	≥Daily	698 (47%)	192 (28%)	1.45 (1.14, 1.84)	1.33 (1.04, 1.72)
Main drug injected in last month	Heroin	513 (34%)	118 (23%)	-ref-	-ref-
	Other opioids	190 (13%)	58 (31%)	1.47 (1.01, 2.13)	1.48 (1.01, 2.17)
	Methamphetamine	752 (50%)	173 (23%)	1.00 (0.77, 1.31)	0.96 (0.71, 1.28)
	Other	37 (2%)	8 (22%)	0.92 (0.41, 2.07)	0.84 (0.37, 1.92)
Recruitment wave	Wave 1 (2018-2019)	880 (59%)	233 (26%)	-ref-	-ref-
	Wave 2 (2019-2021)	612 (41%)	124 (20%)	0.71 (0.55, 0.90)	0.69 (0.54, 0.89)

5.4.4 Factors associated with HCV treatment at baseline

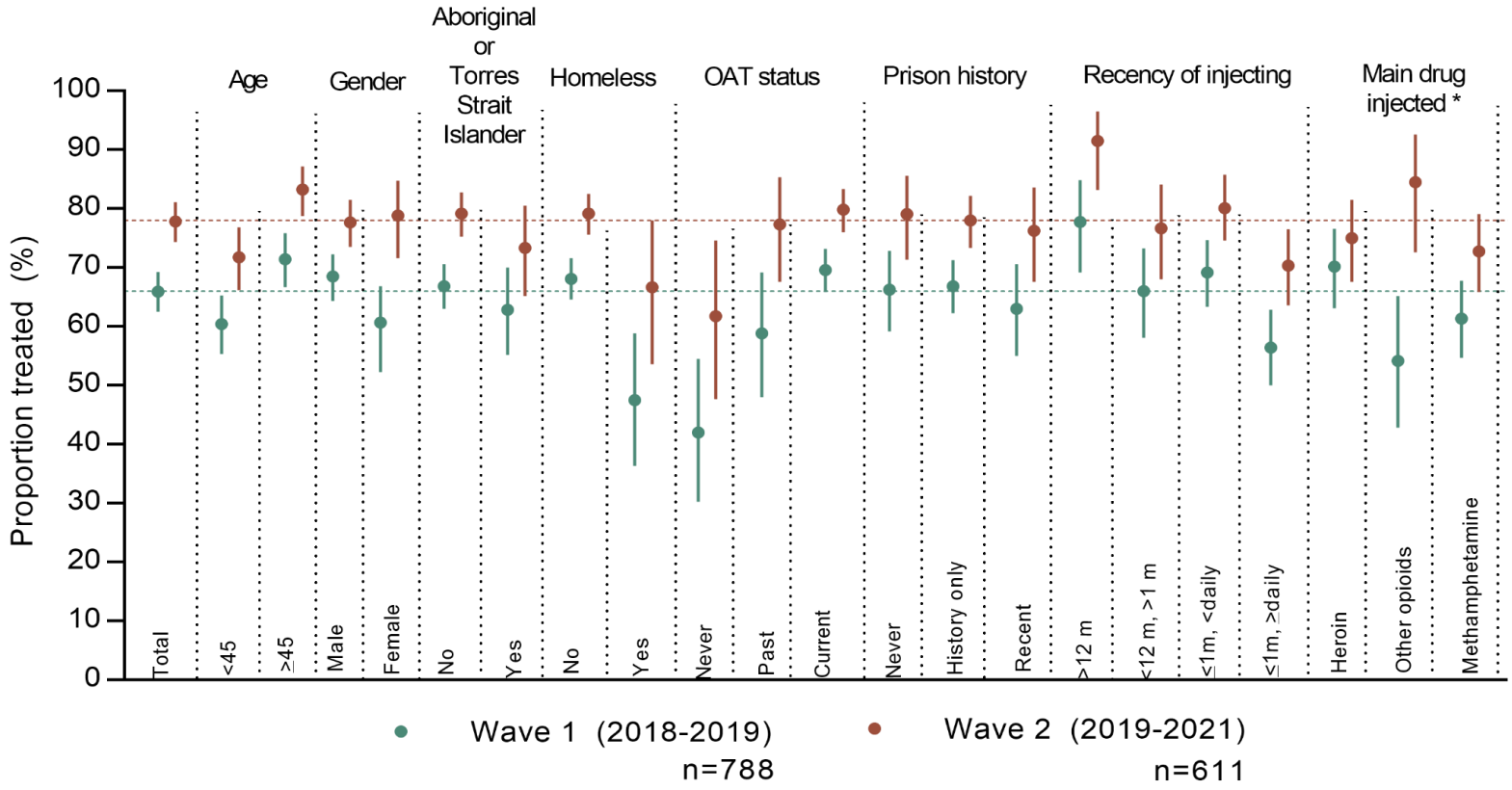
Among participants with evidence of previous chronic or current HCV infection (n=1,250), 69% reported ever receiving HCV treatment (Table 4), increasing from 66% (520/788) during 2018-2019 to 78% (476/611) during 2019-2021 (Supplementary Table 5).

In adjusted analyses, participants recruited between 2019-2021 (Wave 2) were more likely to have received HCV treatment (vs. Wave 1 aOR: 1.61, 95%CI: 1.23, 2.10) (Table 3). Other factors associated with higher previous HCV treatment were age (≥45 aOR: 1.49, 95%CI: 1.16, 1.93) and history of OAT (vs. never received OAT, past OAT aOR: 1.86, 95%CI 1.13, 3.06; current OAT aOR 2.31, 95%CI: 1.53, 3.48). Sex (female vs. male aOR: 0.74, 95%CI: 0.56, 0.99), homelessness (aOR: 0.59, 95%CI: 0.35, 0.92), and recency of injecting drugs (vs. injecting >1 year ago, injecting in the last 1-12 months aOR: 0.57, 95%CI: 0.35, 0.93; injecting ≥ daily aOR: 0.44, 95%CI: 0.28, 0.70) were associated with lower previous HCV treatment (Table 4). Previous HCV treatment was higher across all sub-populations in those recruited during 2019-2021 (Wave 2) compared to those recruited during 2018-2019 (Wave 1) (Figure 2). Among those recruited during 2019-2021 (Wave 2), people who were ≥45 and had ever received OAT were more likely to have previously received treatment and people who had previously injected drugs were less likely to have received treatment (Supplementary Table 6).

Table 4: Factors associated with HCV treatment among all ETHOS Engage participants with evidence of past or current HCV infection (N=1,250)

Characteristic		Previous or current HCV infection, n (col%)	History of HCV treatment, n (row%)	OR (95% CI)	aOR (95% CI)
Total		1,250	862 (69%)		
Age at enrolment	<45	618 (49%)	393 (64%)	-ref-	-ref-
	≥45	632 (51%)	469 (74%)	1.65 (1.29, 2.10)	1.49 (1.16, 1.93)
Gender	Male	890 (71%)	631 (71%)	-ref-	-ref-
	Female	352 (28%)	227 (64%)	0.74 (0.57, 0.97)	0.74 (0.56, 0.99)
	Other	8 (1%)	4 (50%)	0.41 (0.10, 1.65)	0.33 (0.08, 1.36)
Aboriginal or Torres Strait Islander	No	972 (78%)	681 (70%)	-ref-	-ref-
	Yes	278 (22%)	181 (65%)	0.80 (0.60, 1.06)	0.83 (0.61, 1.12)
Homeless	No	1,112 (89%)	787 (71%)	-ref-	-ref-
	Yes	138 (11%)	75 (54%)	0.49 (0.34, 0.70)	0.59 (0.40, 0.86)
OAT status	Never	121 (10%)	60 (50%)	-ref-	-ref-
	Past	161 (13%)	105 (65%)	1.90 (1.18, 3.09)	1.86 (1.13, 3.06)
	Current	968 (77%)	697 (72%)	2.61 (1.78, 3.83)	2.31 (1.53, 3.48)
Incarceration history	Never	305 (24%)	212 (70%)	-ref-	-ref-
	History only	691 (55%)	480 (69%)	1.00 (0.74, 1.34)	0.91 (0.66, 1.25)
	Recent	254 (20%)	170 (67%)	0.89 (0.62, 1.27)	0.93 (0.63, 1.38)
Recency of injecting	>12 months	165 (13%)	134 (81%)	-ref-	-ref-
	Within 1-12 months	243 (19%)	168 (69%)	0.52 (0.32, 0.83)	0.57 (0.35, 0.93)
	Within last month, <daily	436 (35%)	315 (72%)	0.60 (0.39, 0.94)	0.71 (0.45, 1.13)
	Within last month, ≥daily	406 (32%)	245 (60%)	0.35 (0.23, 0.55)	0.44 (0.28, 0.70)
Recruitment wave	Wave 1 (2018-2019)	788 (63%)	520 (66%)	-ref-	-ref-
	Wave 2 (2019-2021)	462 (37%)	342 (74%)	1.47 (1.14, 1.89)	1.61 (1.23, 2.10)

Figure 2: Previous HCV treatment reported among all enrolled ETHOS Engage participants who had current or previous chronic HCV, by recruitment wave



*main drug injected in the last month; data for transgender and other gender identities not shown due to small numbers; data for those mainly injecting other drugs in the last month not shown due to small numbers

5.4.5 Factors associated with HCV treatment among those with recent injecting drug use

Among participants with recent injection drug use who have evidence of past or current HCV infection (n=842), 67% reported ever receiving HCV treatment. Participants who were recruited between 2019-2021 (Wave 2) were more likely to have received HCV treatment (vs. Wave 1 aOR: 1.55, 95%CI: 1.13, 2.12). Age (≥45 aOR: 1.57, 95%CI: 1.15, 2.13) and current OAT (vs. never aOR: 2.15 95%CI: 1.37, 3.39) were significantly associated with higher HCV treatment. Those who were homelessness (aOR: 0.56, 95%CI: 0.36, 0.85) and injecting ≥daily (vs. injecting <daily aOR: 0.58, 95%CI: 0.35, 0.95) were less likely to have previously received HCV treatment (Table 5). The factors associated with HCV treatment among those who recently injected who were recruited during 2019-2021 (Wave 2) are presented in Supplementary Table 7-8.

Table 5: Factors associated with HCV treatment among all ETHOS Engage participants who have recently injected drugs (last month) and have evidence of past or current HCV infection (N=842)

Characteristic		Previous or current HCV infection, n (col%)	History of HCV treatment n, (row%)	OR (95% CI)	aOR (95% CI)
Total		842	560 (67%)		
Age at enrolment	<45	442 (52%)	270 (61%)	-ref-	-ref-
	≥45	400 (48%)	290 (73%)	1.68 (1.26, 2.25)	1.57 (1.15, 2.13)
Gender	Male	599 (71%)	408 (68%)	-ref-	-ref-
	Female	237 (28%)	148 (62%)	0.78 (0.57, 1.07)	0.79 (0.56, 1.22)
	Other	6 (1%)	4 (67%)	0.94 (0.17, 5.15)	0.68 (0.12, 3.88)
Aboriginal or Torres Strait Islander	No	664 (79%)	453 (68%)	-ref-	-ref-
	Yes	178 (21%)	107 (60%)	0.70 (0.50, 0.99)	0.72 (0.50, 1.03)
Homeless	No	729 (87%)	502 (69%)	-ref-	-ref-
	Yes	113 (13%)	58 (51%)	0.48 (0.32, 0.71)	0.56 (0.36, 0.85)
OAT status	Never	107 (13%)	53 (50%)	-ref-	-ref-
	Past	137 (16%)	87 (64%)	1.77 (0.16, 2.97)	1.65 (0.97, 2.83)
	Current	598 (71%)	420 (70%)	2.40 (1.58, 3.65)	2.15 (1.37, 3.39)
Incarceration history	Never	199 (24%)	133 (67%)	-ref-	-ref-
	History only	464 (55%)	312 (67%)	1.02 (0.72, 1.45)	0.96 (0.65, 1.40)
	Recent	179 (21%)	115 (64%)	0.89 (0.58, 1.36)	0.94 (0.59, 1.50)
Frequency of injecting	<Daily	436 (52%)	315 (72%)	-ref-	-ref-
	≥Daily	406 (48%)	245 (60%)	0.58 (0.44, 0.78)	0.62 (0.45, 0.84)
Main drug injected in last month	Heroin	313 (37%)	221 (71%)	-ref-	-ref-
	Other opioids	130 (15%)	83 (64%)	0.73 (0.48, 1.13)	0.83 (0.52, 1.30)
	Methamphetamine	379 (45%)	243 (64%)	0.74 (0.54, 1.03)	0.84 (0.59, 1.19)
	Other	20 (2%)	13 (65%)	0.77 (0.30, 2.00)	0.64 (0.24, 1.71)
Recruitment wave	Wave 1 (2018-2019)	512 (61%)	324 (63%)	-ref-	-ref-
	Wave 2 (2019-2021)	330 (39%)	236 (72%)	1.46 (1.08, 1.96)	1.55 (1.13, 2.12)

5.5 Discussion

In this study of PWID attending drug treatment clinics and NSPs in Australia, a reduction in the proportion with current HCV infection and an increase in the proportion who had received HCV treatment was observed. Although these trends are in line with previous studies [151, 221-223], we have observed these results across all studied sub-populations of PWID and have provided more up-to-date estimates of the impact of DAA therapy on current HCV prevalence among PWID in an era of unrestricted therapy. Importantly, these results have emphasised ongoing gaps in HCV elimination, particularly among priority populations—those who are homeless, who were recently incarcerated, and with recent injecting drug use—thus highlighting populations for increased linkage to treatment and care.

To our knowledge, these are the first temporal HCV infection and treatment results to be reported from data gathered post-2018 [151, 221, 223]. Indeed, these results extend on earlier Australian evidence published soon after the availability of DAAs in Australia (March 2016) demonstrating a decrease in current HCV infection from 43% to 25% and an increase in HCV treatment from 10% to 41% between 2015 and 2017, respectively [151]. It is encouraging that the results observed in this current study demonstrate a continued decrease in the prevalence of HCV infection and increased HCV treatment uptake post-2017. Critically, this study identifies key sub-populations requiring targeted interventions to improve HCV testing and treatment to facilitate HCV elimination and to guide practice and policy nationally and internationally so this progress remains on track.

Participants who reported ≥daily injection drug use were significantly more likely to have current HCV infection, consistent with other studies [220, 224]. However, the current study highlights that this disparity persists after adjusting for period of recruitment. The higher prevalence of current HCV infection in those with more frequent injecting is likely related to increased barriers for engagement in HCV testing and treatment and a higher risk of HCV reinfection following treatment among those with needle/syringe sharing. Given the potential 'treatment as prevention' benefits for reducing viral transmission, people with more frequent injecting should be targeted for treatment [94]. Despite this, HCV treatment uptake was significantly lower among people with more frequent injecting, consistent with previous research [220]. Integration of HCV testing and treatment into community-based settings (e.g. drug treatment, NSP, primary care, etc) could facilitate increased testing for HCV infection in this population [68, 196, 225]. Peer-to-peer education, and tailored care pathways may be effectively delivered to PWID through these settings to enhance HCV treatment [158].

Participants who were homeless were more likely to have current HCV infection and treatment uptake was significantly lower, highlighted the widening gaps in HCV treatment and care in this group. Increased risk of HCV among people who are homeless has been previously reported [226]. These results are worrying but unsurprising, given the competing priorities and multiple barriers incurred among people who are homeless in accessing healthcare [227]. Holistic interventions to improve housing stability may reduce injection-related risk [165] and enhance HCV care [226]. Clearly, there is a need for innovative one-stop community-based

interventions which are integrated with services which interface with people who experience homelessness [165, 226, 227].

History of incarceration was associated with current HCV infection, despite comparable treatment uptake across incarceration categories. This is likely due to higher reinfection among those who have been incarcerated in the recent period, compared to those incarcerated in the past, and those never incarcerated. Prisons have been shown to be settings in which interventions to promote high uptake of HCV treatment can act as a preventative measure against HCV transmission, thus reducing overall incidence and prevalence [228]; however, given the mobile nature of the prison population, criminalisation of drug possession, and high rate of recidivism among PWID, the prison population is often challenging to engage in HCV care [229]. The introduction of point-of-care HCV testing in the prison setting, coupled with reduction in DAA duration and introduction of harm reduction in the prison setting has the potential to significantly reduce current HCV infection in this group [230].

Current OAT was associated with previous HCV treatment. OAT has been shown to improve linkage to HCV treatment among PWID [134, 151], improve knowledge of HCV treatment, [163] and reduce risk of reinfection [7]; however, engaging those who have never been engaged in OAT (including PWID who do not require OAT) remains a priority.

Older participants were more likely to have received treatment than those who were younger, a result corroborated by previous studies [151]. Youth peer-led interventions have the potential to promote HCV treatment and engage younger PWID [231].

Additionally, female participants were less likely to report previous HCV treatment, a result corroborated by previous research [219, 220]. While the treatment gap between men and women may be closing, enhancing HCV treatment and care will require interventions to address the compounding vulnerabilities [232] and higher levels of stigma [233] reported among women who inject drugs.

These results have several public health implications. Despite restriction-free DAA therapy, persistent system, provider, and patient-level barriers hinder HCV care among certain groups of PWID [68, 120]. A range of interventions have been shown to be positively associated with addressing barriers and facilitating engagement with HCV care, including treatment initiation [234]. Electronic medical chart reminders and telehealth are system-level interventions which have been shown to increase HCV care [235]. The latter is particularly vital to integrate in HCV care given the recent need to reduce foot traffic in clinics and adhere to COVID-19 physical distancing requirements. Provider-level barriers can be mitigated by increasing clinical education of general practitioners and those not traditionally involved in HCV care to include HCV-specific training [214]. Furthermore, patient-level barriers can be reduced by providing holistic, integrated healthcare—including embedding HCV care within services already accessed by PWID such as inpatient hospitalisations, primary healthcare services, NSPs, homeless outreach, and mental health facilities [169, 236, 237]. In addition, standard phlebotomy is a barrier recognised amongst both practitioners [238] and patients [118]. The decentralisation of diagnostics and utilisation of innovative diagnostic technology (including dried blood spot and point-of-care testing) is acceptable among PWID [133], has been shown to increase testing, [239] and will be key in reducing attrition from HCV screening to treatment. A combination of these interventions would be optimal to

enhance HCV elimination among PWID and have the potential to close the gaps in current infection and treatment uptake highlighted here.

This study has limitations. First, antibody status and HCV treatment is determined by self-report, but the inferred prevalence found in ETHOS is similar to that of other national cohorts of PWID [240] and the Xpert Viral Load Finger-stick Assay for HCV RNA diagnosis has strengthened this study by allowing characterisation of current HCV infection among a vast majority of participants (>95%). Second, most participants were recruited within an OAT setting, potentially biasing our cohort to people who were already engaged with services and may under-represent the population of PWID who mainly inject stimulants. According to the latest NSP survey in Australia, half of respondents injected ≥daily and nearly half (47%) mainly injected methamphetamine [241]. This oversampling of an engaged PWID population in our study may have resulted in an underestimation of the prevalence of current HCV infection and an overestimation in the proportion of PWID who have received HCV therapy. This sampling bias should not have significantly impacted these results as we have enrolled a high proportion of participants who mainly injected methamphetamine in the last month and participants who injected drugs ≥daily, albeit less than the national estimate. Third, there is slight variation in clinics participating in Wave 1 and Wave 2; however the clinics which did not participate in Wave 2 (n=4) did not yield a high number of participants in Wave 1 (5%, 75/1,443) and thus unlikely to cause significant discrepancies between the cohorts. In addition to reduced number of sites, recruitment for Wave 2 appears to be over a longer period than Wave 1; however, this is due to a six month study suspension (March to September 2020) as a result of COVID-19 prevention and control measures. Finally, the ETHOS Engage survey did not account

for mental health comorbidities and inpatient hospitalisation, factors that have been shown to be associated with lower treatment uptake [242, 243].

5.5.1 Conclusion

The decrease in current HCV infection and increase in history of HCV treatment is certainly a good news story and a testament to the progress that is being made toward eliminating HCV in PWID in Australia. It is concerning, however, that the gaps in current HCV infection are widening, particularly among marginalised groups—thus highlighting crucial populations of PWID who require concerted effort. There is an urgent need for innovative public health interventions to remove barriers to HCV care and equalise progress toward HCV elimination across all communities of PWID.

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5.6 Supplementary Material

Supplementary Table 1: ETHOS Engage recruitment sites, dates, and participation, by recruitment wave

Site name	State	Main function of site	Wave 1 recruitment	Wave 1 N (col %)	Wave 2 recruitment	Wave 2 N (col %)	Participants in Waves 1&2	Time between recruitment waves (mo*)
Rankin Court, Darlinghurst	NSW	OAT	28 – 31 May 2018	107 (7%)	1, 3 – 5 Feb 2021	80 (7%)	24	33
Orana Centre, Wollongong	NSW	DAS	18 – 21 Jun 2018	105 (7%)	15 – 18 Mar 2021	50 (4%)	16	33
Lawrence Avenue Methadone Program, Nowra	NSW	OAT	22 – 30 Jun 2018	38 (3%)	21 June 2021	19 (2%)	8	36
Youth Link, Cairns	QLD	NSP	16 – 19 Jul 2018	105 (7%)	29 Mar – 1 Apr 2021	80 (7%)	6	33
Campbelltown Drug Health Services	NSW	OAT	20 – 22 Aug 2018	49 (3%)	13 – 15 Jan 2020	44 (4%)	15	17
Liverpool Drug Health	NSW	OAT	12 – 19 Sept 2018	100 (7%)	20 – 21 Jan 2020 3 –4 Feb 2020	96 (8%)	33	17
Biala, Brisbane	QLD	NSP	5 – 8 Nov 2018	123 (9%)	11 – 14 Nov 2019	139 (11%)	10	12
Lithgow Opioid Treatment Program	NSW	OAT	21 – 23 Nov 2018	21 (1%)				
Centre for Addiction Medicine, Mt Druitt	NSW	OAT	26 – 29 Nov 2018	62 (4%)	9 – 12 Dec 2019	65 (5%)	24	12
Drug and Alcohol Services, Hunter New England, Newcastle	NSW	OAT	22 Jan 2019 5 Feb 2019 5 Mar 2019	51 (4%)	10 – 11 Mar 2020 4 –5 Mar 2021	65 (5%)	15	13*
Kempsey Drug & Alcohol Service	NSW	OAT	11 – 12 Feb 2019	41 (3%)	28 – 29 Sept 2020	23 (2%)	6	20
Port Macquarie Drug & Alcohol Service	NSW	OAT	13 – 15 Feb 2019	58 (4%)	30 Sept – 2 Oct 2020	44 (4%)	12	20
Coffs Harbour Health Campus	NSW	OAT	20 – 22 Feb 2019	53 (4%)	6 – 9 Oct 2020	22 (2%)	8	20
Drug & Alcohol Services South Australia, North Adelaide	SA	OAT	12 – 13 Mar 2019	42 (3%)	31 May – 1 Jun 2021	40 (3%)	0	27
Drug & Alcohol Services South Australia, Central Adelaide	SA	OAT	14 – 15 Mar 2019	46 (3%)	2 – 3 Jun 2021	40 (3%)	5	27
Riverlands Drug & Alcohol Service, Lismore	NSW	OAT	25 – 27 Mar 2019	52 (4%)	10 – 12 Nov 2020	36 (3%)	5	20
Fleet Street Opioid Treatment Unit, Parramatta	NSW	OAT	13 – 16 May 2019	95 (7%)	17 – 20 Nov 2020	99 (8%)	25	18

Blacktown Opioid Treatment Program	NSW	OAT	20 – 23 May 2019	92 (6%)	26 – 29 Oct 2020	74 (6%)	22	18
Next Step, East Perth	WA	DAS	17 – 19 Jun 2019	56 (4%)	19 – 21 May 2021	80 (7%)	4	23
Next Step, Joondalup	WA	DAS	20 – 21 Jun 2019	24 (2%)	17 – 18 May 2021	16 (1%)	1	23
Woodlands Clinic, Katoomba	NSW	OAT	27 – 28 Jun 2019	22 (2%)				
North Ward Health Campus, Townsville	QLD	NSP	22 – 23 Jul 2019	8 (1%)				
Queensland Injectors Health Network, Townsville	QLD	NSP	24 – 25 Jul 2019	24 (2%)				
Drug & Alcohol Services, Royal North Shore	NSW	OAT	3 – 6 Sept 2019	33 (2%)	12 – 15 Apr 2021	62 (5%)	14	20
Drug & Alcohol Services, Brookvale	NSW	OAT	25 – 27 Sept 2019	36 (2%)	22 – 25 Feb 2021	37 (3%)	6	18

*****time calculated from first recruitment date in Wave 1 to first recruitment in Wave 2; NSW, New South Wales; QLD, Queensland; SA, South Australia; WA, Western Australia; OAT, opioid agonist therapy; NSP, needle and syringe program; DAS, drug and alcohol service

Supplementary Table 1: Current HCV infection among all ETHOS Engage participants with available point-of-care HCV RNA results, by recruitment wave

Characteristic		Wave 1		Wave 2	
		Total valid point-of-care result, n (col%)	Current HCV infection, n (row%)	Total valid point-of-care result, n (col%)	Current HCV infection, n (row%)
Total (N)		1,388	331 (24%)	1,166	178 (15%)
Age at enrolment	<45	760 (55%)	190 (25%)	611 (52%)	104 (17%)
	≥45	628 (45%)	141 (22%)	555 (48%)	74 (13%)
Gender	Male	891 (64%)	216 (24%)	789 (68%)	133 (17%)
	Female	494 (36%)	113 (23%)	359 (31%)	43 (12%)
	Other[†]	3 (<1%)	2 (67%)	18 (2%)	2 (11%)
Aboriginal or Torres Strait Islander	No	1064 (77%)	253 (24%)	885 (76%)	125 (14%)
	Yes	324 (23%)	78 (24%)	281 (24%)	53 (19%)
Homeless	No	1241 (89%)	282 (23%)	1,061 (91%)	148 (14%)
	Yes	147 (11%)	49 (33%)	105 (9%)	30 (29%)
OAT status	Never	199 (14%)	44 (22%)	167 (14%)	28 (17%)
	Past	160 (12%)	48 (30%)	163 (14%)	27 (17%)
	Current	1,029 (74%)	239 (23%)	836 (72%)	123 (15%)
Incarceration history	Never	455 (33%)	77 (17%)	341 (29%)	35 (10%)
	History only	685 (49%)	179 (26%)	619 (53%)	102 (16%)
	Recent	248 (18%)	75 (30%)	206 (18%)	41 (20%)
Recency of injecting	>12 months	209 (15%)	31 (15%)	168 (14%)	9 (5%)
	Within 1-12 months	299 (22%)	67 (22%)	247 (21%)	33 (13%)
	Within last month, <daily	477 (34%)	109 (23%)	390 (33%)	62 (16%)
	Within last month, ≥daily	403 (29%)	124 (31%)	361 (31%)	74 (21%)
Main drug injected in last month	None	508 (37%)	98 (19%)	415 (36%)	42 (10%)
	Heroin	296 (21%)	75 (25%)	274 (24%)	48 (18%)
	Other opioids	127 (9%)	44 (35%)	79 (7%)	14 (18%)
	Methamphetamine	431 (31%)	108 (25%)	384 (33%)	72 (18%)
	Other	26 (2%)	6 (23%)	14 (1%)	2 (14%)

Supplementary Table 2: Unadjusted and adjusted analysis of factors associated with current HCV infection among all ETHOS Engage participants with valid point-of-care HCV RNA results, by recruitment wave

Characteristic		Wave 1		Wave 2	
		OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Age at enrolment	<45	-ref-	-ref-	-ref-	-ref-
	≥45	0.87 (0.68, 1.11)	0.92 (0.71, 1.20)	0.75 (0.54, 1.04)	0.76 (0.55, 1.07)
Gender	Male	-ref-	-ref-	-ref-	-ref-
	Female	0.93 (0.71, 1.20)	1.02 (0.78, 1.36)	0.67 (0.46, 0.97)	0.73 (0.49, 1.08)
	Other[†]	6.25 (0.56, 69.26)	8.00 (0.71, 90.5)	0.62 (0.14, 2.71)	0.60 (0.13, 2.67)
Aboriginal or Torres Strait Islander	No	-ref-	-ref-	-ref-	-ref-
	Yes	1.02 (0.76, 1.36)	0.92 (0.68, 1.25)	1.41 (0.99, 2.01)	1.36 (0.94, 1.96)
Homeless	No	-ref-	-ref-	-ref-	-ref-
	Yes	1.70 (1.18, 2.45)	1.52 (1.04, 2.24)	2.47 (1.56, 3.90)	2.09 (1.30, 3.35)
OAT status	Never	-ref-	-ref-	-ref-	-ref-
	Past	1.51 (0.94, 2.43)	1.39 (0.85, 2.27)	0.99 (0.55, 1.76)	0.88 (0.49, 1.60)
	Current	1.07 (0.74, 1.53)	1.15 (0.78, 1.70)	0.85 (0.55, 1.34)	0.98 (0.61, 1.57)
Incarceration history	Never	-ref-	-ref-	-ref-	-ref-
	History only	1.74 (1.29, 2.34)	1.79 (1.30, 2.45)	1.72 (1.15, 2.60)	1.60 (1.04, 2.46)
	Recent	2.13 (1.48, 3.07)	2.03 (1.38, 3.01)	2.17 (1.33, 3.54)	1.67 (0.99, 2.83)
Recency of injecting	>12 months	-ref-	-ref-	-ref-	-ref-
	Within 1-12 months	1.67 (1.04, 2.66)	1.56 (0.96, 2.52)	2.72 (1.27, 5.85)	2.50 (1.54, 5.45)
	Within last month, <daily	1.70 (1.10, 2.63)	1.57 (1.00, 2.45)	3.33 (1.62, 6.89)	3.01 (1.43, 6.31)
	Within last month, ≥daily	2.55 (1.65, 3.95)	2.30 (1.46, 3.63)	4.56 (2.22, 9.34)	3.75 (1.79, 7.86)
Main drug injected in last month	None	-ref-	omitted	-ref-	omitted
	Heroin	1.42 (1.01, 1.99)		1.89 (1.21, 2.95)	
	Other opioids	2.21 (1.44, 3.29)		1.91 (0.99, 3.70)	
	Methamphetamine	1.40 (1.02, 1.90)		2.04 (1.36, 3.09)	
	Other	1.25 (0.50, 3.20)		1.48 (0.32, 6.84)	

Main drug injected in last month was not included in adjusted analyses due to collinearity with recency and frequency of injecting

Supplementary Table 3: Current HCV infection among ETHOS Engage participants who had evidence of recent injecting and available point-of-care HCV RNA results, by recruitment wave

Characteristic		Wave 1		Wave 2	
		Total valid point-of-care result, n (col%)	Current HCV infection, n (row%)	Total valid point-of-care result, n (col%)	Current HCV infection, n (row%)
Total (N)		880	233 (26%)	751	136 (18%)
Age at enrolment	<45	502 (57%)	146 (29%)	406 (54%)	77 (19%)
	≥45	378 (43%)	87 (23%)	345 (46%)	59 (17%)
Gender	Male	562 (64%)	152 (27%)	519 (69%)	103 (20%)
	Female	316 (36%)	80 (25%)	219 (29%)	32 (15%)
	Other	2 (<1%)	1 (50%)	13 (2%)	1 (8%)
Aboriginal or Torres Strait Islander	No	683 (78%)	181 (27%)	572 (76%)	98 (17%)
	Yes	197 (22%)	52 (26%)	179 (24%)	38 (21%)
Homeless	No	761 (86%)	190 (25%)	660 (88%)	108 (16%)
	Yes	119 (14%)	43 (36%)	91 (12%)	28 (31%)
OAT status	Never	158 (18%)	39 (25%)	132 (18%)	24 (18%)
	Past	120 (14%)	40 (33%)	129 (17%)	26 (20%)
	Current	602 (68%)	154 (26%)	490 (65%)	86 (18%)
Incarceration history	Never	279 (32%)	48 (17%)	208 (28%)	29 (14%)
	History only	422 (49%)	128 (30%)	400 (53%)	75 (19%)
	Recent	168 (19%)	57 (34%)	143 (19%)	32 (22%)
Recency of injecting	<Daily	477 (54%)	109 (23%)	390 (52%)	62 (16%)
	≥Daily	403 (46%)	124 (31%)	361 (48%)	74 (21%)
Main drug injected in last month	Heroin	296 (34%)	75 (25%)	274 (36%)	48 (18%)
	Other opioids	127 (14%)	44 (35%)	79 (11%)	14 (18%)
	Methamphetamine	431 (49%)	108 (25%)	384 (51%)	72 (19%)
	Other	26 (3%)	6 (23%)	14 (2%)	2 (14%)

Supplementary Table 4: Unadjusted and adjusted analysis of factors associated with current HCV infection among ETHOS Engage participants who had evidence of recent injection and valid point-of-care HCV RNA results, by recruitment wave

Characteristic		Wave 1		Wave 2	
		OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Age at enrolment	<45	-ref-	-ref-	-ref-	-ref-
	≥45	0.76 (0.55, 1.03)	0.71 (0.51, 0.99)	0.88 (0.61, 1.28)	0.85 (0.58, 1.26)
Gender	Male	-ref-	-ref-	-ref-	-ref-
	Female	0.91 (0.66, 1.25)	1.05 (0.75, 1.47)	0.69 (0.45, 1.07)	0.71 (0.45, 1.11)
	Other	2.62 (0.16, 42.21)	4.15 (0.25, 68.7)	0.34 (0.04, 2.62)	0.37 (0.05, 2.93)
Aboriginal or Torres Strait Islander	No	-ref-	-ref-	-ref-	-ref-
	Yes	1.00 (0.69, 1.43)	0.86 (0.59, 1.27)	1.30 (0.86, 1.98)	1.26 (0.88, 1.94)
Homeless	No	-ref-	-ref-	-ref-	-ref-
	Yes	1.71 (1.13, 2.58)	1.57 (1.01, 2.43)	2.27 (1.39, 3.71)	2.16 (1.31, 3.57)
OAT status	Never	-ref-	-ref-	-ref-	-ref-
	Past	1.48 (0.87, 2.52)	1.31 (0.76, 2.28)	1.14 (0.61, 2.10)	1.04 (0.54, 1.99)
	Current	1.07 (0.71, 1.61)	0.93 (0.59, 1.47)	0.96 (0.58, 1.57)	0.94 (0.54, 1.63)
Incarceration history	Never	-ref-	-ref-	-ref-	-ref-
	History only	2.08 (1.41, 3.06)	2.24 (1.50, 3.34)	1.42 (0.89, 2.27)	1.34 (0.82, 2.19)
	Recent	2.50 (1.58, 3.93)	2.57 (1.59, 4.16)	1.78 (1.02, 3.10)	1.47 (0.80, 2.69)
Recency of injecting	<Daily	-ref-	-ref-	-ref-	-ref-
	≥Daily	1.56 (1.15, 2.12)	1.35 (0.98, 1.86)	1.36 (0.94, 1.98)	1.24 (0.84, 1.84)
Main drug injected in last month	Heroin	-ref-	-ref-	-ref-	-ref-
	Other opioids	1.48 (0.94, 2.35)	1.49 (0.93, 2.39)	1.01 (0.53, 1.95)	1.11 (0.57, 2.16)
	Methamphetamine	0.95 (0.67, 1.34)	0.91 (0.63, 1.33)	1.09 (0.72, 1.62)	1.05 (0.67, 1.62)
	Other	0.93 (0.36, 2.45)	0.87 (0.33, 2.32)	0.78 (0.17, 3.62)	0.83 (0.18, 3.91)

Supplementary Table 5: HCV treatment uptake among all ETHOS Engage participants with evidence of current or previous HCV RNA infection, by recruitment wave

Characteristics		**Wave 1**		**Wave 2**	
		Previous or current HCV infection, n (row%)*	Treated, n (row%)	Previous or current HCV infection, n (row%)*	Treated, n (row%)
Total (N)		788 (55%)	520 (66%)	611 (50%)	476 (78%)
Age at enrolment	<45	395 (50%)	237 (60%)	287 (45%)	206 (72%)
	≥45	396 (61%)	283 (71%)	324 (57%)	270 (83%)
Gender	Male	543 (58%)	372 (69%)	444 (54%)	345 (77%)
	Female	242 (48%)	147 (61%)	160 (43%)	126 (79%)
	Other	3 (100%)	1 (33%)	7 (39%)	5 (71%)
Aboriginal or Torres Strait Islander	No	613 (55%)	410 (67%)	472 (51%)	374 (79%)
	Yes	175 (52%)	110 (63%)	139 (48%)	102 (73%)
Homeless	No	707 (55%)	481 (68%)	548 (50%)	434 (79%)
	Yes	81 (52%)	39 (48%)	63 (56%)	42 (67%)
OAT status	Never	69 (34%)	29 (42%)	55(32%)	34 (62%)
	Past	90 (54%)	53 (59%)	93 (54%)	72 (77%)
	Current	629 (59%)	438 (70%)	463 (53%)	370 (80%)
Incarceration history	Never	196 (42%)	130 (66%)	139 (38%)	110 (79%)
	History only	435 (61%)	291 (67%)	354 (56%)	276 (78%)
	Recent	157 (61%)	99 (63%)	118 (55%)	90 (76%)
Recency of injecting	>12 months	117 (54%)	91 (78%)	82 (47%)	75 (91%)
	Within 1-12 months	159 (52%)	105 (66%)	116 (45%)	89 (77%)
	Within last month, <daily	273 (55%)	189 (69%)	207 (51%)	167 (81%)
	Within last month, ≥daily	239 (56%)	135 (56%)	206 (55%)	145 (70%)
Main drug injected in last month	None	276 (53%)	196 (71%)	198 (45%)	164 (83%)
	Heroin	188 (60%)	132 (70%)	160 (57%)	120 (75%)
	Other opioids	83 (63%)	45 (54%)	58 (68%)	49 (84%)
	Methamphetamine	228 (51%)	140 (61%)	188 (47%)	137 (73%)

	Other	13 (50%)	7 (54%)	7 (50%)	6 (86%)

*proportion of overall population (Wave 1 N=1,443; Wave 2 N=1,211; all denominators in Supplementary Table 1)

Supplementary Table 6: Unadjusted and adjusted analysis of factors associated with HCV treatment uptake all ETHOS Engage participants with evidence of current or previous HCV RNA infection, by recruitment wave

Characteristic		**Wave 1**		**Wave 2**	
		OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Age at enrolment	<45	-ref-	-ref-	-ref-	-ref-
	≥45	1.63 (1.22, 2.06)	1.45 (1.06, 2.00)	1.97 (1.33, 2.90)	1.89 (1.25, 2.84)
Gender	Male	-ref-	-ref-	-ref-	-ref-
	Female	0.71 (0.52, 0.98)	0.67 (0.48, 0.95)	1.06 (0.69, 1.65)	1.08 (0.67, 1.76)
	Other	0.23 (0.02, 2.55)	0.19 (0.02, 2.17)	0.72 (0.14, 3.75)	0.60 (0.11, 3.25)
Aboriginal or Torres Strait Islander	No	-ref-	-ref-	-ref-	-ref-
	Yes	0.84 (0.59, 1.19)	0.88 (0.60, 1.27)	0.72 (0.47, 1.12)	0.72 (0.45, 1.14)
Homeless	No	-ref-	-ref-	-ref-	-ref-
	Yes	0.44 (0.27, 0.69)	0.59 (0.35, 0.92)	0.52 (0.30, 0.92)	0.62 (0.34, 1.12)
OAT status	Never	-ref-	-ref-	-ref-	-ref-
	Past	1.97 (1.04, 3.73)	1.85 (0.96, 3.57)	2.12 (1.02, 4.39)	2.22 (1.05, 4.69)
	Current	3.16 (1.90, 5.25)	2.61 (1.52, 4.50)	2.46 (1.36, 4.43)	2.10 (1.13, 3.91)
Incarceration history	Never	-ref-	-ref-	-ref-	-ref-
	History only	1.02 (0.72, 1.47)	0.91 (0.62, 1.34)	0.93 (0.58, 1.51)	0.95 (0.57, 1.59)
	Recent	0.87 (0.56, 1.34)	0.85 (0.52, 1.38)	0.85 (0.47, 1.53)	1.16 (0.60, 2.22)
Recency of injecting	>12 months	-ref-	-ref-	-ref-	-ref-
	Within 1-12 months	0.56 (0.32, 0.96)	0.65 (0.36, 1.12)	0.31 (0.13, 0.75)	0.37 (0.15, 0.91)
	Within last month, <daily	0.64 (0.39, 1.07)	0.81 (0.48, 1.36)	0.39 (0.17, 0.91)	0.48 (0.20, 1.14)
	Within last month, ≥daily	0.37 (0.22, 0.61)	0.52 (0.30, 0.88)	0.22 (0.10, 0.51)	0.29 (0.12, 0.69)
Main drug injected in last month	None	-ref-	omitted	-ref-	omitted
	Heroin	0.96 (0.64, 1.44)		0.62 (0.37, 1.04)	
	Other opioids	0.48 (0.29, 0.80)		1.13 (0.51, 2.51)	
	Methamphetamine	0.64 (0.44, 0.94)		0.56 (0.34, 0.91)	
	Other	0.48 (0.16, 1.46)		1.24 (0.15, 10.7)	

Main drug injected in last month was not included in adjusted analyses due to collinearity with recency and frequency of injecting

Supplementary Table 7: HCV treatment uptake among ETHOS Engage participants who had evidence of recent injection and valid point-of-care HCV RNA results, by recruitment wave

Characteristics		**Wave 1**		**Wave 2**	
		Previous or current HCV infection, n (row%)*	Treated, n (row%)	Previous or current HCV infection, n (row%)*	Treated, n (row%)
Total (N)		512 (56%)	324 (63%)	413 (53%)	312 (76%)
Age at enrolment	<45	276 (52%)	157 (57%)	198 (47%)	141 (71%)
	≥45	236 (60%)	167 (71%)	215 (60%)	171 (80%)
Gender	Male	352 (59%)	232 (66%)	307 (57%)	231 (75%)
	Female	158 (48%)	91 (58%)	101 (45%)	77 (76%)
	Other	2 (100%)	1 (50%)	5 (38%)	4 (80%)
Aboriginal or Torres Strait Islander	No	410 (57%)	267 (65%)	316 (53%)	242 (77%)
	Yes	102 (49%)	57 (56%)	97 (53%)	70 (72%)
Homeless	No	449 (57%)	297 (66%)	356 (52%)	275 (77%)
	Yes	63 (49%)	27 (43%)	57 (59%)	37 (65%)
OAT status	Never	63 (39%)	27 (43%)	47 (35%)	29 (62%)
	Past	72 (57%)	41 (57%)	83 (61%)	63 (76%)
	Current	377 (60%)	256 (68%)	283 (56%)	220 (78%)
Incarceration history‡	Never	118 (41%)	75 (64%)	93 (72%)	69 (74%)
	History only	287 (63%)	186 (64%)	233 (57%)	176 (76%)
	Recent	107 (61%)	63 (59%)	87 (58%)	67 (77%)
Frequency of injecting	<Daily	273 (55%)	189 (69%)	207 (51%)	167 (81%)
	≥Daily	439 (56%)	135 (57%)	206 (55%)	145 (70%)
Main drug injected in last month	Heroin	188 (60%)	132 (70%)	160 (57%)	120 (75%)
	Other opioids	83 (63%)	45 (54%)	58 (68%)	49 (84
	Methamphetamine	227 (51%)	139 (61%)	188 (47%)	137 (73%)
	Other	14 (50%)	8 (57%)	7 (50%)	6 (86%)

Supplementary Table 8: Unadjusted and adjusted analysis of factors associated with HCV treatment uptake ETHOS Engage participants who had evidence of recent injection and valid point-of-care HCV RNA results, by recruitment wave

Characteristic		**Wave 1**		**Wave 2**	
		OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Age at enrolment	<45	-ref-	-ref-	-ref-	-ref-
	≥45	1.83 (1.27, 2.65)	1.71 (1.15, 2.55)	1.57 (1.00, 2.47)	1.57 (0.95, 2.54)
Gender	Male	-ref-	-ref-	-ref-	-ref-
	Female	0.70 (0.48, 1.03)	0.65 (0.42, 1.00)	1.06 (0.62, 1.79)	1.10 (0.62, 1.94)
	Other	0.52 (0.03, 8.34)	0.44 (0.03, 7.38)	1.32 (0.14, 12.0)	0.92 (0.10, 8.98)
Aboriginal or Torres Strait Islander	No	-ref-	-ref-	-ref-	-ref-
	Yes	0.68 (0.43, 1.05)	0.72 (0.45, 1.16)	0.79 (0.47, 1.32)	0.78 (0.45, 1.34)
Homeless	No	-ref-	-ref-	-ref-	-ref-
	Yes	0.38 (0.22, 0.66)	0.51 (0.29, 0.91)	0.54 (0.30, 0.99)	0.58 (0.31, 1.10)
OAT status	Never	-ref-	-ref-	-ref-	-ref-
	Past	1.76 (0.89, 3.49)	1.70 (0.83, 3.48)	1.96 (0.90, 4.24)	1.84 (0.82, 4.14)
	Current	2.82 (1.63, 4.85)	2.40 (1.32, 4.37)	2.17 (1.13, 4.16)	1.95 (0.97, 3.92)
Incarceration history	Never	-ref-	-ref-	-ref-	-ref-
	>1 year ago	1.05 (0.68, 1.64)	0.89 (0.54, 1.47)	1.07 (0.62, 1.87)	1.13 (0.62, 2.06)
	Within last year	0.82 (0.48, 1.40)	0.77 (0.42, 1.39)	1.16 (0.59, 2.30)	1.66 (0.77, 3.56)
Frequency of injecting	<Daily	-ref-	-ref-	-ref-	-ref-
	≥Daily	0.58 (0.40, 0.83)	0.65 (0.44, 0.96)	0.57 (0.63, 0.90)	0.58 (0.35, 0.95)
Main drug injected in last month	Heroin	-ref-	-ref-	-ref-	-ref-
	Other opioids	0.50 (0.29, 0.85)	0.58 (0.33, 1.03)	1.81 (0.82, 4.02)	1.99 (0.88, 4.51)
	Methamphetamine	0.67 (0.44, 1.01)	0.80 (0.51, 1.26)	0.90 (0.55, 1.44)	0.96 (0.57, 1.64)
	Other	0.57 (0.19, 1.70)	0.37 (0.11, 1.19)	2.00 (0.23, 17.1)	1.72 (0.19, 15.7)

Chapter 6: Discussion

6.1 Chapter Introduction

The broad aim of this research was to evaluate progress towards eliminating HCV among PWID in Australia through evaluating the prevalence of current infection and treatment uptake in this group. The four specific aims and hypotheses corresponding to this broader aim are discussed below. This thesis has implications for the public health approach to HCV elimination and the directions of future research. These, along with the limitations and strengths of this work, are discussed in this chapter.

Key Findings:

6.2 Aim 1: To evaluate the prevalence of current HCV and treatment uptake among PWID attending drug treatment clinics and NSPs in Australia

Hypothesis: Factors relating to increased marginalisation (homelessness, recent incarceration, and injecting drug use frequency) will be associated with higher prevalence of current HCV infection and lower treatment uptake, while factors relating to increased engagement with health services (e.g. current receipt of OAT) will be associated with lower prevalence of current HCV prevalence and higher treatment uptake.

This aim is addressed in Chapter Two. Data regarding the prevalence of HCV infection and treatment uptake in an era of unrestricted DAA therapy are limited. Understanding the populations who require enhanced clinical support is essential in the pursuit of HCV elimination. Chapter Two evaluated progress towards HCV elimination by assessing the extent of current HCV infection and HCV treatment among PWID. Chapter Two uses data from an observational cohort study of people with a history of injection drug use

(either in the last six months or currently receiving OAT), recruited from drug treatment clinics and NSPs throughout Australia between May 2018 and September 2019. Current HCV status was determined by point-of-care HCV RNA testing and was obtained for over 95% of participants. All participants completed a questionnaire regarding behavioural and demographic information, HCV infection, testing, and treatment history. Of those with a valid test, around a quarter (24%) were currently infected with HCV (HCV RNA positive). Demographic and behavioural factors associated with current HCV infection included homelessness in the previous six months, history of incarceration, and frequent (≥ daily) injection drug use. Previous treatment was high (66%) among those with evidence of past or current infection. Participants who were homeless and those who were frequently injecting were less likely to have reported HCV treatment; participants who were older and who were currently receiving OAT were more likely to have reported a history of HCV treatment. This chapter has highlighted groups who must receive enhanced interventions to increase treatment uptake, reduce current infection, and achieve elimination across all populations of PWID.

6.3 Aim 2: To evaluate HCV treatment uptake and associated factors in a population-level cohort in the DAA era in New South Wales, Australia

Hypothesis: People with evidence of drug dependence in the DAA era will have slightly lower, but comparable DAA treatment uptake compared to those with distant history and no history of drug dependence. Among those with evidence of recent drug dependence, factors which contribute to increased marginalisation (recent incarceration, history of alcohol use disorder) will be associated with less DAA treatment.

This aim is addressed in Chapter Three. HCV treatment was historically withheld based on concurrent drug and alcohol use. Chapter Three uses data from a longitudinal cohort, including all HCV notifications made in NSW between 1995 and 2017 linked to administrative datasets. Such population-level DAA uptake data among people with evidence of drug dependence in an era of unrestricted DAA therapy are limited. Drug dependence was defined as hospitalisation due to injectable drugs or receipt of OAT, categorised as recent (occurring in 2016-2018), distant (pre-2016 only), and no evidence of drug dependence. DAA uptake was highest among those with recent (47%), compared to those with distant (38%), and no (33%) evidence of drug dependence in the DAA era. Among those with evidence of drug dependence in the DAA era, treatment was less likely among women, Indigenous Australian peoples, those born overseas, those with HBV co-infection, those who were notified of HCV in an outer-metropolitan region, and those with >1 hospitalisation in the DAA era. Treatment was more likely among those with HIV co-infection, a history of incarceration in the DAA era, and a history of alcohol use disorder (ever). Interestingly, those with increased interface with the health service (i.e. those with >1 hospitalisation in the DAA era) were less likely to have received treatment; this result yielded a subsequent analysis, presented in Chapter Four.

6.4 Aim 3: To evaluate the potential of inpatient hospitalisation to serve as a juncture for HCV care among a population-level cohort of DAA treatment-naïve in New South Wales, Australia

Hypothesis: People with evidence of recent drug dependence will incur a higher incidence of hospitalisation than people with a distant history and no history of drug dependence. Among the DAA treatment naïve people with evidence of recent drug dependence, incidence of drug-related hospitalisation will be highest and this will serve as a potential setting for enhance DAA treatment.

This aim was addressed in Chapter Four. Systems which regularly interface with PWID have been shown to be successful in increasing HCV education, testing, and treatment uptake, yet results from Chapter Three indicated that those with increased healthcare interaction via hospitalisation (>1 in the DAA era) were less likely to have initiated treatment. Using the longitudinal cohort as described in Chapter Three, Chapter Four uses hospital data to evaluate the potential for inpatient hospitalisation to be used as an opportunity to engage people with drug dependence with HCV care. People with evidence of recent drug dependence were more likely to have multiple hospital visits, longer hospital stays, and a higher incidence of hospitalisations relating to mental health disorders, injectable and non-injectable drug use, injection-related infectious diseases, alcohol use disorder, and liver complications. Survival analysis estimates indicated treatment uptake is lower among people with drug dependence who were hospitalised $\geq$2 times in the DAA era, who were hospitalised for $\geq$7 days in the DAA era, and who had a hospitalisation due to injection-related infectious diseases, injectable and non-injectable drugs, and mental health disorders.

6.5 Aim 4: To evaluate the change in HCV prevalence and treatment between 2018-2019 and 2019-2021 among PWID attending drug treatment clinics and NSPs in Australia

Hypothesis: The prevalence of current HCV infection will have reduced and the proportion of participants who have received treatment will have increased. Time will be significantly associated with both current HCV infection and HCV treatment. Other factors associated with HCV infection and HCV treatment will be similar to those found in Chapter Two (Aim 1).

This Aim was addressed in Chapter Five. Temporal data regarding changes in prevalence of HCV infection and treatment uptake in an era of unrestricted DAA therapy are limited. Temporal data add a greater understanding of the populations who may be falling behind in HCV elimination effort and therefore require enhanced clinical support. Chapter Five evaluated these changes using data collected from an observational cohort study of people with a history of injection drug use (either in the last six months or currently receiving OAT), recruited from drug treatment clinics and NSPs throughout Australia. These data were collected between two recruitment waves: Wave 1 (May 2018-September 2019) and Wave 2 (November 2019-June 2021) at OAT clinics and NSP sites (21 sites participating in both; 25 in Wave 1, 21 in Wave 2) visited 12-36 months apart. Between Wave 1 and Wave 2, prevalence of current HCV infection decreased (24% to 15%, respectively) and reported treatment increased (66% to 78%, respectively). In adjusted analyses, participants who were recruited during 2019-2021 were less likely to have current HCV infection. Those who were homeless, who had been incarcerated, and who had injected drugs in the last year were more likely to have current HCV infection. Participants who were recruited during 2019-2021 were more likely to have reported receiving HCV treatment. HCV treatment was also greater

among those who had received OAT, those aged ≥45. Women, participants who were homeless, and those who had injected drugs 1-12 months ago and ≥daily were less likely to have received HCV treatment. These results have highlighted groups in which to focus efforts in order to achieve HCV elimination.

6.6 Implications for achieving HCV Elimination among PWID

Australia is one of few settings internationally to provide a comprehensive national strategy to enhance testing, diagnosis, and treatment among PWID. This, along with the removal of prescriber-based and patient-based restrictions for the provision of DAA therapy, has placed Australia at the forefront of HCV elimination among PWID. The HCV treatment and current infection prevalence results found in Chapter Two are encouraging and highlight the importance of targeted interventions to engage more marginalised groups of PWID with HCV testing and treatment, including those who identified as women, those who were homeless, people who have been incarcerated, and those who had injected drugs $\geq$ daily. This may necessitate evolving from the traditional standard of HCV care to include tailored treatment interventions and the coupling of community-based clinics and HCV care. Overall, the findings in Chapter Two are supportive of the Australian approach to DAA therapy, with reduced prevalence of current HCV infection and higher treatment uptake observed in this study when compared to previous, similar Australian cohort studies from the interferon treatment era [26, 166] and the early DAA treatment era [166].

Indeed, from the initial listing of DAA therapy on PBS in March 2016, the characteristics of people initiating therapy has shifted and more people with recent drug dependence have initiated treatment. Encouragingly, in the context of HCV elimination efforts, findings in Chapter Three indicate that by the end of 2018, treatment uptake was higher among those with evidence of drug dependence in the DAA era compared to those with distant and no evidence of drug dependence. Despite this positive step towards health equity in this population, disparities persist within those with recent drug dependence. Whilst several factors related to marginalisation were associated with

higher treatment uptake—including HIV co-infection, recent incarceration, and history of alcohol use disorder, other marginalisation factors—including Indigenous Australian ethnicity and female sex were associated with less treatment uptake. These results highlight the importance of strategies to engage these populations, including addressing the compounding stigma, vulnerability, and discrimination incurred in these groups.

There is a clear need for innovative interventions to revolutionise the standard of HCV care. One such opportunity is to expand HCV clinical care into the inpatient setting, particularly among those hospitalised for long periods of time. There is a justification for increased HCV-related education amongst all medical specialities, particularly psychiatry, given the high incidence of psychiatric admissions and low treatment uptake in this group. Findings in Chapter Four should facilitate the develop and implementation of public health interventions and campaigns to enhance inpatient HCV care, an area of growing interest [199] and promise.

Although previous studies have observed a decline in current HCV infection associated with DAA treatment [151, 221-223], they are limited. Encouragingly, results in Chapter Five observed a reduction in the prevalence of current HCV infection and an increase in reported HCV treatment across all sub-populations of PWID half a decade into an era of unrestricted DAA therapy. These results underscore the continued success of unrestricted therapy in reaching PWID; however, the widening gaps observed in current HCV infection are worrying as we strive towards HCV elimination that is equitable across all groups of PWID. Increased coverage of harm reduction and simplified HCV testing among those with characteristics which are associated with current HCV

infection, particularly among those with a history of incarceration, are of paramount importance in curtailing further transmission. These interventions, particularly the implementation of simplified HCV testing, will have a profound impact on achieving HCV elimination globally [68]. Furthermore, overcoming persistent system, provider, and patient-level barriers to HCV care may require a broader understanding of stigma among people with HCV, particularly among those who with higher prevalence of current infection and those were less likely to have reported HCV treatment.

6.7 Directions for further research

Future public health intervention to accelerate HCV elimination among PWID will need to focus on several systems and mechanisms. First, and crucially, there is a clear need for the development of disease surveillance systems in Australia which can monitor elimination efforts on a national scale. While modelling has been employed to estimate the progress toward HCV elimination [95], the benefit of a population-level national surveillance system to epidemiologically categorise HCV infection among PWID cannot be overstated. Second, test-and-treat paradigms, where point-of-care testing platforms are used to test PWID for HCV infection and initiate treatment on the same day need to be further evaluated in community-based settings and inpatient hospitals. This intervention has the potential to greatly reduce the attrition between HCV test and treatment, particularly among marginalised PWID who have been found to have lesser treatment uptake, thus further facilitating elimination and simplifying HCV clinical care. Third, studies to evaluate the expansion of HCV-related education and care into a diverse range of medical specialities, including psychiatry, should be further explored. Evidence-based interventions to enhance the HCV cascade of care, including medical chart reminders, provider education, care integration, and patient navigation should be

optimised in settings which deliver HCV care [234]. Finally, efforts to enhance harm reduction among PWID will be required, particularly in the prison setting as this thesis has identified incarceration as a factor associated with current HCV infection.

Furthermore, the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and subsequent coronavirus disease 2019 (COVID-19) pandemic has dramatically changed the public health landscape over the past 18 months. There is no doubt that the effects of COVID-19 have been felt in every corner of the world. Indeed, this disease has changed the typical way of life, globally, in all communities across all nations. Both the disease's and its required physical distancing measures impact on the health and wellbeing of PWID and HCV elimination efforts in this population needs to be acknowledged. The pandemic's exacerbation of limited health literacy, stigma, discrimination, and health inequity already present in PWID make this population especially vulnerable to both COVID-19, physical distancing requirements, and increased policing of public health orders [244]. For example, physical distancing, as a measure to inhibit the spread of COVID-19, has increased disruptions in health settings, including those which interface with PWID: OAT clinics [245] and NSP sites [246], likely making these settings less able to opportunistically engage PWID in HCV testing and treatment.

Furthermore, due to its overwhelming demand on the healthcare system, COVID-19 has caused many HCV elimination programs to stall or come to a stop in many settings internationally [247]. Modelling has projected the potential impact of delaying HCV elimination strategies between 2020-2021 due to COVID-19, resulting in an estimated 44,800 (UI: 43,800-49,300) excess cases of HCC and 72,300 (UI:70,600-79,400) excess

liver deaths [247]. The true extent of the impact of COVID-19 on the health and wellbeing of PWID is yet to be fully realised; however, early data are emerging. The Australian Needle and Syringe Program survey reported a reduction in recent HCV testing from 54% to 48% and recent HCV treatment from 44% to 32% between 2019 and 2020, respectively [61]. Worryingly, this disruption in HCV elimination efforts, likely associated with the COVID-19 pandemic, has been documented in high-income [248, 249] and low-middle-income [250] countries alike, although these studies did not account for current injecting status. Further research will be needed to assess this impact on PWID specifically and identify the groups of PWID who have been disproportionately impacted by COVID-19 and associated public health ordinances. These populations of PWID may require concerted and innovative efforts to enhance HCV care in a time where HCV infection may no longer be a priority.

Indeed, PWID are often combatting intersecting health and social injustices including blood borne viruses, mental health disorders, COVID-19, homelessness, overdose, and criminalisation of drug use [207, 251]. The ultimate public health goal of achieving HCV elimination is to improve the health and wellbeing of people living with HCV. Alarmingly, an estimated 42% of PWID experience an overdose event at some point in their lifetime, with 21% experiencing an overdose event in the last year [252]. Whilst recent data has demonstrated the potential of DAA therapy in reducing drug-related deaths [101], the increasing incidence of fatal overdose should be a concern to those providing HCV care to PWID. Drug-related deaths have been increasing in Australia since 2006 [253], a trend that has been echoed more severely in other settings globally [254-256]. Addressing the syndemic of HCV and overdose in PWID requires multi-stakeholder buy-in and engagement to increase the safe supply of drugs used for

consumption, increase in the coverage of harm reduction, and ultimately the decriminalisation of drugs [251, 257]. Clearly, to improve morbidity and mortality among PWID, rethinking the narrow lens of "HCV elimination" may be necessary going forward.

6.9 Thesis limitations and strengths

This thesis utilises two different cohort studies to investigate the progress toward HCV elimination among PWID, including an observational cohort and longitudinal cohort. The strengths and limitations of both study designs have been discussed in each chapter.

Chapters Two and Five utilise data from the ETHOS Engage Study, a national observational cohort of PWID with a high proportion of valid point-of-care HCV RNA test results, married to a robust survey collecting data on a range of health and behavioural-related exposures and outcomes. The limitations of self-administered questionnaires used in Chapters Two and Five include social desirability and recall bias, although the risk of these biases have been shown to be minimal [183]. Chapters Three and Four utilise data from a population-based administrative data linkage study, which includes all notifications of HCV reported in NSW, Australia. While there are clear strengths in this study design with regard to power, there are several limitations to linkage studies. For example, administrative datasets including more robust behavioural and demographic data, (e.g. homelessness and outpatient mental health care) could have enriched the findings Chapters Three and Four. Linkage studies can be prone to misclassification bias. This limitation has been discussed in Chapters Three and Four.

A final limitation of this thesis is the lack of data on HCV-related and all-cause mortality among PWID. Conclusions regarding the progress toward achieving the HCV elimination goal of reducing mortality by 65% by 2030 could not be assessed in this work. While this needs to be further investigated, given the high treatment uptake, high efficacy of DAA therapy, and the emerging evidence of the association between successful DAA treatment and the reduction of mortality [99, 101], we can surmise that an increase in treatment uptake may be indicative of a reduction in mortality.

6.10 Conclusion

The results found in this thesis are clearly indicative of a "good news story" and the successes of the Australian public health approach to the provision of HCV therapy: treatment among PWID is high and current HCV infection among PWID is low. Nevertheless, these results have highlighted the urgent need for innovative public health action to equalise elimination progress, particularly among those with demographic and behavioural factors which are associated with a higher prevalence of current HCV infection and lower treatment uptake. Ultimately, these focused interventions have the potential to improve HCV treatment uptake, reduce the burden of HCV infection, and improve the health and wellbeing of PWID.

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