Barriers to the Assessment and Treatment of Hepatitis C Virus Infection in People Who Inject Drugs

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Background: Hepatitis C virus (HCV)-related morbidity and mortality are rising. Despite recent therapeutic advances, HCV assessment and treatment uptake remains suboptimal, particularly among people who inject drugs (PWID).

Aims: The broad aim of this research was to inform barriers to the assessment and treatment of HCV infection among PWID. Specific aims included evaluation of mortality and life expectancy among people with chronic HCV infection; evaluation of HCV treatment uptake and associated factors among inner city residents; evaluation of HCV assessment and treatment uptake among PWID in opioid substitution setting; evaluation of willingness to receive HCV treatment among PWID; and evaluation of the impact of treatment for HCV infection on depression and mental health parameters.

Methods: In Chapter Two, data from a population-based linkage study were analysed, using a competing risk methodology for calculation of mortality rates and life expectancy. In Chapter Three, data from the Community Health and Safety Evaluation (CHASE) cohort were analysed, using person-time and logistic regression methods. In Chapters Four and Five, data from the Enhancing Treatment for Hepatitis C in Opioid Substitution Settings (ETHOS) study were analysed, using logistic regression. In Chapter Six, data from the Australian Trial in Acute Hepatitis C (ATAHC) study were analysed, using logistic regression.

Key Findings: Among people with an HCV notification, liver-related mortality is increasing. Life expectancy in this population is considerably lower, compared to the general population. Over the last decade, HCV treatment uptake has slightly increased yet remained suboptimal. Integration of HCV care within existing infrastructures for addiction care is successful in increasing HCV assessment and treatment uptake among PWID. Despite low HCV treatment uptake, treatment willingness is high among PWID and predicts subsequent assessment and treatment. PWID with poor social functioning may be most at risk of developing depression during HCV therapy. However, depression prior to or during treatment does not have an impact on sustained virological response.

Conclusion: Strategic public health planning is needed to lower the rising HCV disease burden. Barriers to HCV assessment and treatment among PWID are complex and require a multidimensional approach. Multidisciplinary partnerships are needed to expand access to HCV services.

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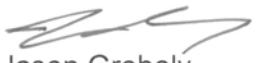

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Acknowledgments

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List of Publications

A list of peer-reviewed publications, accepted, or published during candidature is presented below:

1- Alavi M, Law MG, Grebely J, Thein HH, Walter S, Amin J, Dore GJ. Lower life expectancy among people with an HCV notification: a population-based linkage study. Journal of Viral Hepatitis 2013 (Accepted, JVH-00479-2013).
2- Alavi M, Raffa JD, Deans GD, Lai C, Krajden, M, Dore GJ, Tyndall MW, Grebely J. Continued low uptake of treatment for hepatitis C virus infection in a large community-based cohort of inner city residents. Liver International 2013; In Press.
3- Alavi M, Grebely J, Micallef M, Dunlop AJ, Balcomb AC, Day CA, Treloar C, Bath N, Haber PS, Dore GJ. Assessment and treatment of hepatitis C virus infection among people who inject drugs in the opioid substitution setting: ETHOS study. Clinical Infectious Diseases 2013; 57 (Suppl 2), S62-S69.
4- Alavi M, Micallef M, Dunlop AJ, Balcomb AC, Day CA, Treloar C, Bath N, Haber PS, Dore GJ, Grebely J. Effect of treatment willingness on specialist assessment and treatment uptake for hepatitis C virus infection among people who use drugs: The ETHOS study. Journal of Viral Hepatitis 2014 (Accepted, JVH-00022-2014).
5- Alavi M, Grebely J, Matthews GV, Petoumenos K, Yeung B, Day C, Lloyd AR,Van Beek I, Kaldor JM, Hellard M, Dore GJ and Haber PS on behalf of the ATAHC Study Group. Impact of pegylated interferon alfa-2a treatment on mental health during recent hepatitis C virus infection. Journal of Gastroenterology and Hepatology 2012; 27(5):957-65

Abbreviations

DAA	direct-acting-antiviral
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
IFNL3	interferon-lambda-3 gene
MSM	Men who have sex with men
NSP	Needle and syringe programs
OST	Opioid substitution therapy
PEG-IFN	Pegylated interferon
PWID	People who inject drugs
RBV	Ribavirin
SVR	Sustained virological response

Chapter one

Introduction and Literature Review

This chapter provides a background and rationale for the program of research presented in this thesis. It begins with the epidemiology and natural history of hepatitis C virus (HCV) infection. Further, it outlines suboptimal HCV assessment and treatment uptake, barriers to HCV assessment and treatment, current and future therapeutic regimens for HCV infection, and different strategies to enhance HCV assessment and treatment uptake. Finally, it presents an overview of the thesis, including the thesis rationale, aims and key hypotheses.

1.1. Hepatitis C Virus Infection

HCV is a major global health issue and a significant cause of mortality (1-3). People who inject drugs (PWID) represent the core of HCV epidemics in many countries (1, 3, 4). The majority of people exposed to HCV infection develop persistent, chronic HCV infection and are at risk of progressive liver disease, cirrhosis, liver failure or hepatocellular carcinoma (HCC) (4). Without therapeutic intervention, a significant proportion of people with chronic HCV infection are likely to have shortened life expectancy through HCV-related mortality (5). Over the past two decades, HCV treatment regimens have evolved to achieve higher rates of sustained virological response (SVR). The recent development of direct-acting antiviral (DAA) therapy for chronic HCV infection has brought further optimism to the HCV sector (6, 7). However, despite advances in antiviral therapy for HCV infection, HCV assessment and treatment uptake remains suboptimal, particularly among PWID (8-10). In the absence of enhanced HCV treatment uptake, the disease burden of HCV has been rising among ageing populations of PWID. Effective interventions to increase HCV assessment and treatment uptake are needed to reduce the rising burden of HCV-related liver disease.

1.2. Global Epidemiology

Previous global burden of disease estimates published by the World Health Organization, indicated that worldwide, 54,000 deaths and 950,000 disability adjusted life-years were associated with acute HCV infection (11). However, the major burden from HCV infection is attributed to liver disease complications from chronic infection. An estimated 2-3% of the world population (130-170 million people) live with chronic HCV infection (4, 12). In 2006, globally, 366,000 deaths were estimated to be attributed to chronic HCV infection, including 211,000 deaths from cirrhosis and 155,000 deaths from liver cancer (13). HCV prevalence varies markedly by geographic region, ranging from less than 1% to more than 10% in individual countries (3, 4, 14). The highest prevalence has been reported in low- and middle-income countries in Africa and the Middle East (>3.5%), whereas high-income countries in

the Americas, Australia and Northern and Western Europe have a low HCV prevalence (<2%) (3, 4, 14).

HCV is transmitted by percutaneous exposure to contaminated blood. Modes of HCV transmission include injecting drug use (sharing of syringes and/or other drug preparation equipment) (15), medical transmission through contaminated blood-products (16), occupational exposure to contaminated blood among healthcare workers (17), tattooing, piercing (18), and sexual transmission (19). Mother-to-child transmission occurs, with a 5% vertical transmission rate from mothers with detectable HCV RNA (20). In high-income countries, injecting drug use is the dominant mode of transmission, whereas medical and occupational transmissions of HCV are uncommon (4, 21). In most low- and middle-income countries, historically, iatrogenic transmission through blood transfusion and unsafe medical procedures has driven HCV epidemics (4). However, the recent emergence of injecting drug use is an additional risk in many low- and middle-income settings (4, 21). Sexual transmission of HCV mainly occurs among men who have sex with men (MSM), who have HIV infection and engage in high-risk sexual behaviour involving anal mucosal damage (19). Tattooing and piercing are not common risk factors for HCV transmission in the general population; however, tattoos applied by friends or in prison settings are risk factors for HCV acquisition (18).

In 2007, 16 million people were estimated to have injected drugs worldwide (range 11-21 million) (1). The majority of new and existing cases of HCV infection are attributed to injecting drug use in many countries (1, 4). The risk of HCV infection is highest among younger individuals and recent initiates into injecting drug use (22-24). Given that risk-taking and injecting behaviours change during an individuals' life time (25, 26), injecting-related problems, including the risk of HCV infection are also subject to change over time. For example, most PWID in high-income countries have periods of opioid substitution treatment (OST) and may inject drugs at a lower frequency during OST or temporarily cease injecting

drug use at least once during adulthood (25, 27). Despite potential differences in natural history and demographics between active and former PWID, the two definitions of PWID vary across studies. Former PWID has been defined as at least four (28), six (29) or twelve months (30) of abstinence from injecting drug use or six months on OST, with at least three months of no concurrent use of other drugs (31). In Australia, the illicit Drug Reporting System defines active PWID as injecting drug use at least monthly over the last six months (32). However, given the scarcity of data among PWID populations, many studies combine data from active and former PWID populations (1, 8), or do not define the active or former PWID status (33, 34).

The geographic prevalence of HCV among PWID populations is extremely diverse. In 2010, HCV prevalence was estimated to be 67%, ranging between 60-80% in PWID in 25 countries, and 80% or higher in a further 12 (1) . It is estimated that 10 million PWID were HCV antibody positive (range 6-15 million) in 2010 (1). The largest populations of PWID with HCV infection live in eastern Europe (2 million, range 1–4) and east and southeast Asia (3 million, range 2–4) (1).

As reviewed elsewhere (3, 4), the patterns of HCV epidemiology are highly heterogeneous across different settings (3, 4). Past HCV incidence, current HCV prevalence and the disease progression of HCV determine the HCV epidemiology and disease burden in various countries (3, 4). Consistent with temporal patterns of HCV epidemics, there are three distinct patterns of HCV transmission worldwide (3, 4). The first pattern is characteristic of countries in which HCV is endemic; high HCV incidence in the past and present means a relatively high prevalence among all age groups (e.g. Egypt). The second pattern exists in countries where prevalence is low among younger people, but increases dramatically and is sustained in older populations. This pattern is a reflection of high HCV incidence in the distant past that is no longer present (e.g. Japan and Italy). The third pattern is characteristic of the HCV epidemic in countries such as the United States, Australia and several other high-income

countries in Western Europe. In these countries, prevalence is low among younger people and rises steadily or sharply through middle age. After the peak HCV prevalence is reached, it declines in older ages. The peak HCV prevalence seen in this pattern of transmission is commonly referred to as a "cohort effect" and countries with this third HCV transmission pattern are anticipated to be following the second pattern, but with a later time interval of 20-30 years (3, 4).

HCV is classified virologically as seven genotypes (1-7) and 67 subtypes (1a, 1b, etc.) (35). Reflecting differences in epidemiology of HCV, the global distribution of HCV genotypes is diverse. HCV genotypes 1, 2, and 3 have a fairly broad geographical distribution, whereas other HCV genotypes are limited to specific geographical regions (4). Genotype 1 has the broadest geographical distribution, being the most common genotype in most of North America, Northern and Western Europe, South America, Asia and Australia (4). HCV genotypes 1b and 2a are associated with transfusion of blood products (36, 37), whereas HCV genotypes 1a and 3a are more common among PWID (37-39). Following the implementation of more effective blood product screening, there has been a decrease in prevalence of genotypes 1b and 2a and an increase in the prevalence of genotypes 1a and 3a, particularly among PWID (37, 38, 40).

1.3. Epidemiology of HCV in Australia

Approximately, 230,000 people in Australia live with chronic HCV infection (41). HCV prevalence (based on detection of HCV antibody) is estimated to be 1.4% among the general population (41), 0.01% among blood donors (41) and 55% among active and former PWID (1). Recently, sexual transmission of HCV among MSM with HIV infection has also been reported (~0.5% per year) (42).

The pattern of HCV transmission in Australia is consistent with the third pattern described earlier, with the highest rate of HCV notifications occurring among those aged 30-39 years

(3, 4, 41). In Australia, HCV incidence increased from 1960s, peaked in late 1990s and has been decreasing since early 2000s (43, 44). HCV incidence is estimated to have been mainly driven by heroin injecting, which decreased in prevalence in Australia in 2000s (43-45). Consistent with this pattern, notifications of newly diagnosed HCV decreased by 50% from 1997-2006 (46). In Australia, notification of HCV diagnosis is required by law (47) and rates of HCV diagnosis are relatively high (43), compared to other high-income countries (14). However, HCV may still remain underdiagnosed. Similar to the general population of Australia, there is evidence that HCV incidence has been gradually decreasing among PWID populations (41, 48). Among people attending Needle and Syringe Programs (NSPs) in 2008 and 2012, HCV prevalence dropped from 63% to 52% among males and from 61% to 54% among females, respectively (41).

HCV genotypes 1 and 3 are most common in Australia; however, genotypes 2, 4, and 6 have also been reported (49). The most common subtype in Australia is 3a (49).

1.4. Summary

Globally, HCV infection is a major health problem. In many countries, active and former PWID are the group most at risk of HCV acquisition, particularly in high-income settings, including Australia. The risk of HCV infection is highest among younger individuals and recent initiates into injecting drug use. In Australia, HCV incidence is estimated to have peaked in the late 1990s, and decreased through the 2000s.

1.5. Natural History of HCV Infection

Following exposure to HCV, the initial 6 months of infection marks the acute phase of infection, with asymptomatic disease in the majority of cases (70-85%). Symptomatic acute HCV infection generally occurs within 5-12 weeks of HCV exposure and lasts 2-12 weeks (50). Symptomatic acute HCV is often mild, involving nonspecific symptoms such as lethargy and myalgia, but jaundice might also be observed (50).

Approximately 25% of people with acute HCV spontaneously clear the virus within the initial six months of infection, whereas the remaining 75% progress to chronic HCV infection (51). Whether acute HCV infection spontaneously clears or persists is probably affected by a complex interplay between the host and the virus (4). The strongest host factor associated with HCV clearance is polymorphisms in the *interferon-lambda-3 gene (IFNL3, formerly known as IL28B)* (52). Following chronic HCV infection, there is a risk of progressive hepatic fibrosis culminating in cirrhosis, and liver failure or hepatocellular carcinoma (53). Among those with spontaneous HCV clearance, re-infection in the setting of ongoing HCV exposure is possible (54). Many people with re-infection clear repeatedly; however, others develop persistent infection (54).

Liver fibrosis is staged in five categories, F0-F4, where F0 indicates no fibrosis and F4 indicates cirrhosis (55). Among people with chronic HCV infection, factors associated with an increased risk of fibrosis progression include male gender (56), ethnicity (57), age >40 years at infection (56, 58), immunosuppression (for example, HIV co-infection) (59), chronic hepatitis B virus co-infection (60), diabetes (61), insulin resistance (62), obesity (63), and hepatic steatosis (64). Behavioural factors such as heavy alcohol intake (65) and daily cannabis smoking (66) are also associated with an increased risk of fibrosis progression. The progressive nature of chronic HCV infection is generally slow, with limited advanced liver disease in the initial 10-15 years of infection (even in those individuals with co-factors for fibrosis development). Therefore, the duration of HCV infection and its surrogate, age,

are key determinants of risk of liver-related morbidity and mortality (53). Without therapeutic intervention, an estimated 7-18% of people with chronic HCV mono-infection will develop cirrhosis over a 20 year infection period (53, 55) and be at risk of HCC (1-6% per annum) or liver failure (2-3% per annum) (53).

1.6. Natural History of HCV Infection in Australia

In 2012, approximately, 310,000 people living in Australia had been infected with HCV (41). Of these, 80,000 people were estimated to have cleared their infection, and of the 230,000 with chronic HCV infection 173,500 had early liver disease (fibrosis stage F0-1), 51,500 had moderate to severe liver fibrosis (fibrosis stage F2-3), and 6,500 were living with HCV-related cirrhosis (41).

1.7. Mortality Among People with HCV Infection

Compared to the general population, people with chronic HCV infection are at excess risk of mortality (2, 5, 67-71). The overall risk of mortality and causes of death in this population are influenced by several factors including the presence of risk factors for cause-specific mortality and access to effective therapeutic intervention that alters the natural history of chronic HCV infection.

As reviewed elsewhere (5), liver disease (including decompensated cirrhosis and HCC) is a major cause of death among people with chronic HCV infection (5). Further, drug-related causes (including overdose and suicide) and HIV co-infection contribute to excess risk of mortality in this population (5). In Australia (68), Sweden (72), Scotland (73) and Denmark (74), estimates from population-based linkage studies suggested that liver disease contributes to approximately 20% of all deaths among people with an HCV notification, with an additional 20-30% of mortality being attributed to drug-related causes, and 0-10% being attributed to HCV/HIV co-infection. A high percentage of drug-related deaths is consistent with injecting drug use being the major mode of HCV acquisition in all four settings. The

proportion of HIV-related deaths among people with an HCV notification was highest in Scotland (8%) (73) (4% had HCV/HIV co-infection) and lowest in Australia (0.4%) (68) (0.5% of the population had HCV/HIV co-infection). In Australia, the early introduction of HIV prevention programs in the mid-1980s has contributed to low HIV prevalence in the subsequent decades (75, 76). However, settings in which the HCV/HIV co-infection rate is even higher than Scotland (e.g. North America and some European countries), would be expected to have larger proportions of deaths attributed to HIV-related causes (5, 77). There is also recent evidence that HCV infection is associated with an increase in both hepatic and extra-hepatic disease, including circulatory diseases, renal diseases, and neuropsychiatric disorders (78).

Among people with chronic HCV infection, mortality rates and distribution are subject to various temporal trends. In New South Wales, Australia, the number of deaths from drug-related causes increased rapidly during the 1990s but has considerably declined in 2000s (68). This decline is thought to be due to a number of factors. Firstly, it has been largely due to a nation-wide heroin shortage, in which both supply and purity decreased while the price increased markedly in late 2000 and early 2001 (79, 80). Although the heroin market has stabilised after the shortage, the supply, price and purity have not returned to the pre-2001 levels (79). Secondly, a wider implementation of interventions such as NSPs and other harm reduction strategies since mid to late 1990s may have contributed to the maintenance of reduced drug-related mortality in 2000s (81). Lastly, there is evidence that following the heroin shortage in early 2000s, the number of young PWID and initiates to injecting drug use have declined (48, 82-85), and many older PWID have changed to injecting non-opioid drugs which are less likely to result in a fatal overdose (80, 86-88).

In contrast, over the 1992-2006 period, there has been a steady increase in the number of people with an HCV notification dying from liver-related causes (68). Interestingly, over the 1997-2006 decade, age-adjusted liver disease mortality rate has been stable (around 15

deaths per 10,000 person years), indicating no impact of improved HCV treatment (68). The generally low treatment uptake rate and sub-optimal efficacy of antiviral therapy (particularly among those with advanced liver disease) are suggested to have contributed to the lack of a population level effect of HCV treatment (5). Consistent with increasing numbers of liver-related deaths among people with HCV infection, the proportion of all liver disease deaths with underlying HCV is increasing in many settings (5, 13, 89, 90).

Despite extensive research on rates and causes of mortality among people with HCV infection, uncertainty remains on estimates of life expectancy in this population. A recent analysis of mortality in Australia among people receiving OST between 1985 and 2005, demonstrated an average of 44 years of potential life lost for each fatality in the cohort (85). Almost half of the years of potential life lost were due to drug-related deaths (85). Similar results have been demonstrated among people with heroin-dependency in the United States (91), indicating the significant contribution of drug-related causes of death to mortality among young PWID (85, 91). Further, life-style related factors, such as drug use and excessive alcohol intake have been suggested to contribute to a low mean age at death among people with HCV infection, compared to the general population (71, 92). Finally, rates of survival among untreated people with HCV infection (93) or dialysis patients with HCV infection (94) have been shown to be lower, compared to those undergone antiviral therapy or dialysis patients without HCV infection, respectively. Nonetheless, years of potential life lost, lower age at death and lower rates of survival may not be accurate estimates of life expectancy among people with HCV infection. Given the heterogeneity of causes and rates of mortality, any estimate of mortality incidence rates and life expectancy in this population will have to be adjusted for the presence of competing risks of mortality. An accurate understanding of parameters associated with HCV disease progression and estimates of life expectancy is essential in developing strategies to lower the rising rates of HCV-related mortality.

1.8. Mortality Among PWID with HCV Infection

The prevalence of HCV infection among active and former PWID and people receiving OST is 50-80% (1). Therefore, mortality studies among people receiving OST are likely to reflect mortality among PWID populations with HCV infection. All-cause mortality rates among PWID and people receiving OST are 1-2% (95, 96), although previous findings have shown that OST reduces drug-related mortality (97, 98). In the absence of enhanced HCV treatment uptake in Australia, high HCV incidence among PWID, particularly during the 1990s, means there will inevitably be greater incidence of liver disease and liver-related mortality over the next one to two decades (5). Recent findings have demonstrated an increased contribution of liver disease (99, 100) and cancer (101) to mortality among opioid-dependent cohorts in Australian settings. Comparable trends in mortality rates have been observed in other high-income countries with similar temporal patterns of HCV epidemiology and low HCV treatment uptake (67, 69, 70, 102). In Canada, a community-based cohort study has evaluated mortality in a large population, in which 81% and 42% reported recent drug use and injecting drug, respectively (67, 69). HCV prevalence was 64% in this population. Between 2003 and 2007, the all-cause annual mortality rate was 2%, with causes of death being 7% liver-, 20% drug-, 21% HIV- and 52% other cause-related. However, drug-related mortality tended to peak among people aged less than 40 years, while those aged over 50 years were at significant risk of liver-related mortality (67). Similarly, other findings suggest that death from chronic diseases increasingly dominate mortality in opioid users over 40 years of age (102) and PWID over 50 years of age (70).

1.9. Summary

After HCV infection, the majority of people progress to chronic HCV infection, with associated risk of progressive liver disease, cirrhosis, liver failure or HCC. Compared to the general population, people with chronic HCV infection are at excess risk of mortality. Three major causes of death in this population are liver-, drug-, and HIV-related. Among people with chronic HCV infection, causes and rates of mortality are subject to presence of risk factors for cause-specific mortality, access to effective therapeutic intervention, and age/duration of infection. Overall, the slowly progressive nature of HCV-related liver disease means that younger people with chronic HCV infection are at lower risk of HCV-related mortality. However, drug-related mortality is higher among younger PWID. In the absence of enhanced HCV treatment uptake, liver-related mortality and disease burden of HCV infection have been rising in ageing populations of PWID with chronic HCV infection. Despite an enhanced understanding of the causes and rates of mortality among PWID with chronic HCV infection, accurate estimates of life expectancy in this population require further research.

1.10. Suboptimal HCV Assessment and Treatment Uptake

HCV care comprises of testing, diagnosis, liver disease assessment (including suitability for treatment), management of lifestyle factors associated with disease progression (including alcohol intake and weight), and HCV treatment (if required). Proportions of HCV testing and diagnosis varies across different countries. In Australia, approximately 80-85% of people with HCV infection is estimated to have been diagnosed and are aware of their infection (43). This is similar to rates of HCV diagnosis in some high-income countries in Europe (e.g. Sweden) (14). However, HCV diagnosis rates are lower in many other high-income settings such as Canada (67%), France (57%), Germany (38%), and Italy (12%) (14). In the United States, only half of the population with HCV are aware of their infection (103, 104).

Given differences in recruitment strategies and definitions of HCV assessment, the proportion of diagnosed individuals having received HCV assessment varies across studies. Data from community-based studies have demonstrated that approximately half of those diagnosed with HCV infection receive assessment (105-108). However, in one community-based study from the United Kingdom, only 20% of people with chronic HCV infection attended their assessment appointment (109). Compared to the community-based studies, data from PWID cohorts have shown lower rates of HCV assessment. It is estimated that approximately 14-30% of PWID receive HCV assessment (110-114). Recent findings from an observational study among clients of four OST clinics and a medically supervised injecting centre in Australia indicated that 75% of participants had received HCV assessment by a nurse or a doctor (self-reported) (115). However, two of the OST clinics in this study were involved in a specific initiative to enhance assessment and treatment delivery.

Despite the heterogeneous nature of populations with HCV infection and various study designs, over the past decade, several studies have indicated that HCV treatment uptake is gradually increasing. Nonetheless, the number of people undergoing HCV antiviral therapy has remained suboptimal. In the United States, a national study was conducted to assess

uptake of antiviral therapy among veterans who received a diagnosis of chronic HCV infection, between 2003 and 2004 (116). Among 29,695 veterans with HCV infection, the vast majority (77%) were seen by an HCV specialist. However, only 14% received antiviral therapy within two years after diagnosis (116). In a recent surveillance study in the United Kingdom, over 250,000 HCV RNA test results (representing 100,809 individuals) were analysed to assess HCV treatment trends between 2002 and 2011 (117). Between 2002 and 2008, the number of individuals who received antiviral therapy annually increased from under 500 to over 3000, respectively. In 2009, the number receiving treatment increased to 3,295. Despite the annual increase in HCV treatment uptake, only 20% of individuals had received antiviral therapy between 2002 and 2011 (117). Similarly, in Australia, surveillance data indicate that HCV treatment uptake has been slowly increasing since early 2000s; however, less than 3,500 people with chronic HCV infection are estimated to receive antiviral therapy each year (41). In 2001, 930 people (0.6% of 157,000 living with chronic HCV infection in Australia) were treated for HCV infection (118). In 2012, 2,360 people (1% of the 230,000 living with chronic HCV infection in Australia) received HCV treatment (41). Data from population-based studies in most European countries (119, 120), and the United States (103) have shown comparable trends in HCV treatment uptake. However, HCV treatment uptake per annum has been shown to be higher in some European settings; 6.7% in France, 4.3% in Sweden and Germany, 3.5% in Netherlands and 3.4% in the United Kingdom (120). Compared to population-based studies, some community-based studies in high-income settings have shown higher proportions of HCV treatment uptake (15-24%) (105-107). However, most participants in these studies were people attending tertiary care centres and the majority of those who received antiviral therapy where people with medically acquired HCV infection (107), former, or non-PWID (compared to active/recent PWID) (106), and those who had an HCV diagnosis by a gastrointestinal specialist (compared to a general practitioner) (105).

Similar to the patterns of HCV treatment uptake in the general population, antiviral therapy has been slowly increasing among PWID. In a community-based study in the United States, between 1989 and 1998, only 1 of 1,667 PWID (0.06%) with HCV infection reported having received antiviral therapy (121). In the 2000s, data from cohorts of PWID have demonstrated HCV treatment uptake rates ranging from 1-6% per year (10, 110, 111, 113, 122). In Canada, data from a large community-based study among inner city residents have shown that between 2000 and 2004, 1.1% of the 1,360 HCV antibody-positive individuals received HCV treatment (10). The majority (87%) of HCV antibody-positive people in this study had self-reported drug use over the six months prior to study enrolment (10). In 2005, another community-based study in the United States assessed HCV treatment uptake among 597 PWID (110). Overall, 6% reported having received antiviral therapy for HCV infection (110). More recently, a large study of PWID attending Australian Needle and Syringe Programs (NSPs) has shown a modest increase in HCV treatment uptake per annum, from 0.5% in 1999 to 2% in 2011 (122). The proportion of NSP participants reporting a lifetime history of HCV treatment increased from 3.4% in 1999 to 8.6% in 2011 (122).

Compared to population-based studies and those among PWID cohorts, some clinic-based studies (123-141) have shown higher proportions of HCV treatment uptake (3-38%). However, these results may not be generalizable to other populations of people with HCV infection. Given that clinic-based studies are predominantly conducted at tertiary care settings, participants might have had a higher level of engagement with the healthcare system and practitioners might have been more likely to treat people with HCV infection, particularly PWID. Recruiting small study populations is another limitation of many clinic-based studies.

The majority of studies on HCV assessment and treatment uptake have been performed during early- to mid-2000s. Given the changing patterns of HCV treatment uptake and scarcity of recent data, further research is needed to monitor annual HCV treatment uptake

at the population and community levels. Strategies to increase HCV assessment and treatment uptake rely on identifying populations with impaired access to HCV care, and factors contributing to suboptimal HCV assessment and treatment in these populations. Overall, low HCV assessment and treatment uptake are suggested to result from the combination of multiple barriers to antiviral therapy present at the levels of the systems, provider, and patient (142-144).

1.11. Systems-level Barriers to HCV Treatment

At the systems level, a lack of consensus about screening and treatment guidelines has resulted in low HCV testing and evaluation (143) . Furthermore, the setting of HCV clinics (in highly structured secondary or tertiary care centres) is generally not adapted to the specific needs of PWID populations (142, 143, 145). There is limited infrastructure for provision of HCV care in substance use treatment and primary care services catering to marginalized populations (143). Limited knowledge about HCV testing and treatment, limited accessibility of testing locations, and long waiting lists for accessing HCV care are cited as barriers to care among patients (146, 147). In some countries, the cost of antiviral therapy and private health insurance can be a relevant system barrier to HCV treatment (142, 148). A recent population-based study have demonstrated that only a third of people with HCV infection in the United States can potentially benefit from and have access to antiviral treatment; the remaining individuals are either uninsured or have potential contraindications to antiviral treatment (148).

Given the prospect of improved interferon-free DAA-based therapeutic strategies in the near future, the importance of liver disease staging and treatment recommendations based on degree of fibrosis has further increased. Historically, liver biopsy has been considered the best test for liver fibrosis assessment; however, the procedure is costly, invasive and in a small minority of cases can result in complications such as significant bleeding, organ puncture, or death (149). Hepatic elastography (e.g. FibroScan®) is a non-invasive

alternative; however, it is still not licensed in many countries, thus opportunities to assess disease severity and target therapy to patients with more advanced fibrosis are limited (143).

1.12. Provider-level Barriers to HCV Treatment

Having a specialist consultant has been shown to be a predictor of HCV treatment uptake (105, 116). However, many physicians are reluctant to treat active PWID, driven by concerns of adherence, drug and alcohol use, medical co-morbidities and the risk of re-infection (106, 107, 138, 141, 146, 150-155). In a study of Canadian HCV specialists, only 20% would consider providing treatment to active PWID (154). An Australian community-based study found that people currently receiving treatment for drug dependency were five times less likely to receive HCV treatment (107). In a national study of addiction medicine physicians in the United States, 61% reported screening most PWID for HCV antibodies (152). However, only 9% reported providing HCV treatment and only 30% were willing to provide HCV treatment, even if given the appropriate training and resources (152). Among physicians, lack of confidence in initiating HCV treatment because of low number of patients and inadequate HCV knowledge are among factors contributing to low HCV screening, evaluation, and treatment uptake (156). Given regional variations in HCV epidemiology and structure of healthcare systems, there might be differences in providers' view of barriers to access HCV care. Recently, an international survey study of HCV treatment providers was conducted among 697 physicians across eight global regions, representing 29 individual countries (157). Physicians from Northern and Western European countries had remarkably low perceptions of treatment barriers. In contrast, Middle Eastern and African physicians perceived all barrier categories as problematic (157). Interestingly, despite regional differences in the magnitude of perceived barriers, across all global regions, patient-level factors were viewed as the greatest obstacles to treatment. Particularly, fear of treatment side effects was the most frequently cited barrier (157). Further, the doctor–patient relationship has been shown to play an important role for patients whether or not they discuss HCV treatment with general practitioner (147, 158). PWID are likely to be

stigmatized by healthcare professionals without specific training in addiction medicine (159, 160).

These findings demonstrate that, lack of knowledge about HCV and its treatment often leads to the perception that PWID cannot be treated because of pre-existing notions about substance use or psychiatric co-morbid conditions that will have a negative impact on treatment outcomes (143). However, recent data across substance use, primary, and outpatient mental health settings have demonstrated that the possibility of initiating antiviral therapy can be a motivating factor for decreasing alcohol use in people with HCV infection (161). Finally, some providers might be deferring HCV treatment, given that interferon-free regimens with increased simplicity, improved tolerability and efficacy will soon be available (143).

1.13. Patient-level Barriers to HCV Treatment

Among PWID, willingness to receive interferon-based treatment for HCV infection lies between 53% and 86% (112, 113, 162-167). In late 1990s, a study among 306 OST clients assessed patients HCV treatment willingness under four scenarios of interferon-based therapy (163). Despite requiring weekly injections, 97% of participants would definitely or probably use therapy. If therapy only worked in 20% of cases, 84% of people would undergo treatment. With a 30% chance of nausea during treatment, 71% would use therapy. Despite the requirement of liver biopsy, 71% would still use therapy. The majority (53%) responded that they would definitely or probably take therapy under all four scenarios (163). Another early study among people with HCV/HIV co-infection demonstrated that 64% of participants were not willing to receive HCV treatment (135). However, the low treatment willingness might have been due to concomitant burden of HIV medications. More recently, a survey among 284 people with self-reported HCV infection assessed patients' willingness to receive an antiviral regimen with the treatment profile of PEG-INF/RBV combined with telaprevir or boceprevir. Interestingly, likelihood of an SVR was the most important treatment outcome to

participants, followed by severe side effects, therapy type (a combination of total duration of treatment and weeks on the third medicine), and dosing of the third medicine (168). These results are consistent with previous findings on patients' perception of cost and benefit of HCV treatment. Side effects of interferon-based treatment, particularly fatigue, depression, and flu-like symptoms may affect patients decision to adhere to antiviral therapy (169, 170). However, patients who perceive higher benefits of treatment (higher SVR, lower risk of liver disease) have been shown to be more willing to accept side effects of interferon-base therapy (169, 170).

Despite the high HCV treatment willingness among patients, several modifiable barriers to access HCV care at individual patient level remain, including poor knowledge and inaccurate notions about HCV infection and its treatment (115, 146, 166, 171, 172). Poor knowledge, combined with asymptomatic disease and perceptions about HCV infection being a benign disease, results in a low perceived need for therapy (146, 147, 158, 173). Other important barriers to HCV care include lack of social support, unemployment or employment responsibilities, unstable housing, transportation, parental responsibilities, poverty, incarceration, stigma and inadequate access to healthcare (146, 155, 158, 174, 175).

Further, racial and ethnic inequalities in access to healthcare may also complicate HCV care (143, 176, 177). People may intentionally avoid HCV assessment and treatment because of the "horror stories" about liver biopsies and HCV treatment circulated within peer networks (147). Other medical co-morbidities, particularly among people with HCV/HIV co-infection, may require more immediate attention and differ initiation of HCV treatment (143). Finally, cognitive-affective factors may lead to poor adherence to the HCV assessment and treatment process (147). These findings contribute to a better understanding of factors associated with patient-level barriers to access HCV care, and developing strategies to remove modifiable barriers. However, another key step toward enhanced HCV care is to

understand the impact of patients' treatment willingness on subsequent HCV assessment and treatment uptake, which remains unclear.

1.14. Treatment of HCV Infection

The goal of HCV treatment is viral eradication as represented by SVR [HCV RNA undetectable in the blood 12 weeks (SVR12) or 24 weeks (SVR24) following treatment]. SVR is associated with improved quality of life, regression of fibrosis, and reduced risk of complications in patients with cirrhosis (178-181). During 1990s, antiviral therapy for HCV infection consisted of treatment with interferon alfa-2b for 48 weeks (182, 183). SVR rates of this regimen were approximately 15-20% (182, 183). In late 1990s, ribavirin (RBV) was added to interferon alfa-2b to achieve higher rates of SVR among those treated for 24 weeks (31%) or 48 weeks (38%) (184). In early 2000s, large randomised studies demonstrated higher SVR rates among people who received pegylated interferon alfa-2b and ribavirin, compared to those treated with interferon alfa-2b and ribavirin (54% vs. 47%) (185), which was followed by development of pegylated interferon alfa-2a (186). Until 2011, dual therapy with peginterferon plus ribavirin (PEG-IFN/RBV) has been the standard of care for treatment of HCV infection (9). Dual therapy with PEG-IFN/RBV has a success rates of approximately 40% for genotype 1 and 4 and 70% for genotypes 2 and 3 in people who use drugs (9).

Despite improved pharmacokinetics of PEG-IFN/RBV, numerous side effects have been associated with this antiviral regimen (187, 188). The most frequently experienced side effects include fatigue (54%), headache (47%), pyrexia (43%), myalgia (42%), insomnia (37%), anorexia/weight loss (32%), nausea (29%), irritability (24%), and depression (22%) (187). Further, suicidal thoughts have been reported in about 10% of patients undergoing PEG-IFN/RBV therapy; however, case reports of suicide or suicidal attempts remain only anecdotal (189). The side effects of PEG-IFN/RBV treatment (particularly the psychiatric side effects) are mostly attributed to the interferon component of the regimen (188, 190).

Earlier HCV treatment guidelines excluded people with psychiatric co-morbidities or active drug use, based on concerns of poor adherence, exacerbation of pre-existing drug use and psychiatric co- morbidities, and risk of re-infection (191-193). However, these concerns were not supported by prospective and controlled clinical studies including PWID or patients with psychiatric comorbidities (194). Over the last decade, extensive research on HCV treatment among PWID has demonstrated efficacy and safety of antiviral therapy in this population (8, 9, 195). Consequently, recent HCV treatment guidelines have been revised to consider antiviral therapy among PWID, following an individualised assessment (196-198).

1.15. Efficacy of HCV Treatment among PWID

In response to concerns about HCV treatment among PWID, in 2009, a review of the published literature was undertaken to evaluate HCV treatment outcomes in this population (195). Given the heterogeneity in study designs, study samples, and treatment regimens, there were considerable variations in the SVR rates among PWID; ranging from 18% to 94% (median 54%) for chronic HCV infection treated with pegylated interferon and ribavirin (195). Studies on treatment of acute HCV infection among PWID were scarce; overall, only 200 PWID with acute HCV infection were treated in eight studies and within individual studies, SVR ranged from 50% to 100% (median 69%) (195). Despite the discrepancy in SVR rates, there was a small difference in HCV treatment outcomes between PWID and non-PWID within studies that included a non-PWID group (195). These data suggest that PWID can be successfully treated for HCV infection.

More recently, a meta-analysis evaluated the completion rates and efficacy of HCV treatment (with PEG-INF/RBV) among people with a history of injecting drug use (8). Thirty six studies were included in this analysis; however, definitions of active or former injecting drug use varied between studies (8). Former drug use was defined as 4, 6, 12, or 24 months of abstinence prior to HCV treatment. The pooled treatment completion rate was 83% (8). Co-infection with HIV (vs. HCV mono-infection), HCV genotypes 1 or 4 (vs. HCV genotypes

2 or 3) and no addiction treatment during antiviral therapy were found to be associated with lower HCV treatment completion rates (8). Further, results of a multivariable meta-regression analysis indicated a significant positive correlation between treatment completion and availability of support services (8). The pooled SVR rate was 56% among all PWID and 53% among those who received addiction treatment during antiviral therapy (8). Results of a multivariable meta-regression analysis indicated a significant positive correlation between SVR and involvement of a multidisciplinary team (8). HCV treatment completion and SVR rates in this meta-analysis are comparable to results obtained in PEG-IFN/RBV registration trials (185, 186).

Given the heterogeneity in the definition of active or former injecting drug use, in 2013, a systematic review was conducted to evaluate HCV treatment outcomes (with PEG-INF/RBV) only among those who reported active drug use (9). Six studies were included in the analysis of SVR and five in the analysis of re-infection (9). Pooled SVR rates were 37% for HCV genotypes 1 and 4, and 67% for HCV genotypes 2 and 3 (9). Although lower than SVR rates obtained in the PEG-IFN/RBV registration trials, similar SVR rates have been observed in studies other than clinical trials (199, 200). Further, small study samples might have contributed to the low SVR rate in this systematic review. Pooled estimates of treatment adherence and discontinuation were 82% and 22%, respectively (9). Finally, the pooled estimate of HCV re-infection was low (2.4 per 100 person-years) (9).

A history of injecting drug use does not generally compromise adherence (201-203), treatment completion (29, 195, 201, 204), or SVR (204-213). Recent injecting drug use at treatment initiation has limited impact on adherence (30, 109, 201, 202, 214, 215), treatment completion (30, 201, 216), or SVR (29, 30, 217-223). Some studies have reported lower treatment completion in those with recent injecting drug use at treatment initiation (206, 213). Further, the reported rates of re-infection following successful HCV treatment among PWID

are low (1-5% per year) (224-226). Occasional injecting drug use during treatment does not impact adherence (29, 30, 201, 215), treatment completion (30, 201, 206), or SVR (29, 30, 218). However, lower adherence (172, 201, 202) or SVR (219, 220, 227) has been observed in people with frequent injecting drug use during treatment (daily or every other day). Other than concerns about efficacy of HCV treatment for PWID, toxicity of interferon-based therapy has added further concerns about safety of HCV treatment in this population.

1.16. Safety of HCV Treatment among PWID

Early stages of interferon-based therapy (first few weeks of treatment) are associated with "flu-like" symptoms. These symptoms appear in a majority of patients and remain persistent during the duration of treatment (190, 228) . However, mood and cognitive symptoms, develop at later stages of treatment, with intensified depressive symptoms after week eight (190, 228). Consequently, PWID or patients with psychiatric comorbidities should be monitored frequently, particularly during the first months of HCV treatment (229). Most of the neuropsychiatric side effects of interferon-based therapy resolve with treatment cessation (190); however, in some cases persistent, recurring, or new developing symptoms have been described (230). Nonetheless, pre-existing psychiatric symptoms of OST are not associated with long term worsening of psychiatric symptoms post HCV treatment (231).

Compared to the general population, cognitive disturbances and psychiatric comorbidities are more prevalent in people with chronic HCV infection (229, 232-234), particularly among PWID (235-237). Given that interferon-based therapy has been shown to be associated with neuropsychiatric side effects (187, 188), several studies have investigated psychiatric symptoms during HCV treatment (208, 210, 231, 238-243). Interferon-induced depression, particularly among people with previous or ongoing depressive symptoms can be reduced by use of antidepressants during HCV treatment (190, 208, 242, 244). However, preventative antidepressant use prior to treatment initiation is not associated with lower incidence of interferon-induced depression during antiviral therapy (245-248). Further, antidepressant use

during HCV treatment is not associated with low SVR or high treatment discontinuation (208, 245, 246, 249). Nonetheless, psychiatric comorbidities have not shown to be associated with lower adherence, treatment completion, SVR, or depression during PEG-IFN/RBV treatment (208, 210, 231, 238-243, 250).

Despite extensive research on psychiatric symptoms during HCV treatment, inconsistencies remain on incidence and severity of neuropsychiatric side effects during antiviral therapy, psychiatrist comorbidities prior to initiation of treatment, and factors associated with development of psychiatric comorbidities during HCV treatment. These inconsistencies might be attributed to several factors including different socio-demographic characteristics between studies, varying doses and durations of therapy, differences in study designs, and variations in the methodological approaches for assessment and classifications of psychiatric comorbidities (251). It has been suggested that some people with a history of drug or alcohol use, or people receiving opioid substitution treatment, may confound flu-like symptoms and somatic side effects of PEG-IFN/RBV with drug or alcohol withdrawal symptoms, possibly followed by a relapse of substance use (190). Cravings may also occur secondary to PEG-IFN/RBV-induced mood changes or be related to needles that are used for therapy (190). Nevertheless, HCV treatment does not have an impact on drug dependency treatment or increase drug use (205, 209).

Despite the safety and efficacy of PEG-IFN/RBV therapy for PWID (9, 195, 252), and international guidelines recommending HCV treatment for PWID following individualised assessment (196-198), HCV assessment and treatment uptake have remained suboptimal in this population. Further research is needed to understand treatment outcomes and response to antiviral therapy among PWIDs. In particular, developing a pre-treatment risk profile would facilitate identifying and implementing interventions for people who might be at higher risk of developing psychiatric symptoms during treatment.

1.17. Future HCV Treatment Regimens

The recent approval of two DAA agents (NS3-4A protease inhibitors, telaprevir and boceprevir) have increased SVR rate up to 70% (6, 7). The two DAA agents specifically inhibit viral replication and have been approved for treatment of genotype 1 infection in combination with PEG-IFN/ribavirin. Given the rapid development of additional potent agents, more effective, interferon-free antiviral regimens are likely to dominate the HCV therapeutic landscape within the next 5 years. These regimens will offer enhanced efficacy (>90%), lowered toxicity, shortened durations of treatment (8-12 weeks), simplified dosing (all oral, once-daily regimens) and monitoring schedules (6, 7).

1.18. Broad Expansion of HCV Assessment and Treatment Uptake

Recent development of DAA-based treatments, particularly IFN-free regimens, provide the potential to cure HCV infection in the vast majority of treated individuals (6, 7). However, unless the proportion of individuals screened, assessed and treated for HCV is substantially increased, these anticipated therapeutic advances will have limited impact at the population level (5). In recognition that HCV is a major public health issue, HCV Action Plans have been launched in some settings (253, 254). Evaluation of England and Scotland HCV Action Plans has shown an increase in testing, diagnosis, assessment and treatment uptake in these countries (253, 254). In Australia, national hepatitis C strategies (255) and state HCV Action Plans (256) have been launched. However, insufficient government investment has limited the impact of these plans at the population level.

Within clinics with large populations of PWID where systematic programs are established for comprehensive HCV screening, uptake of HCV testing and assessment of more than 85% can be achieved (123, 221, 257). In the primary care setting, interventions based on targeted case-finding (258, 259), risk-based assessment (260, 261), birth-cohort screening (261), and motivational interviewing with case management (262) have been effective in increasing HCV screening. Furthermore, enhanced HCV screening could also be achieved through

targeted testing initiatives including rapid finger-prick testing (259, 263, 264), oral saliva testing (263-266), and dried blood spot testing (267-270).

Following HCV screening, newly diagnosed individuals should engage with services offering HCV assessment and treatment. However, assessment of HCV-related liver disease has been complicated by the invasive nature of liver biopsy. Recently, development of non-invasive fibrosis assessment methods such as transient elastography (e.g. Fibroscan) has improved the ease of liver disease assessment. Recent studies have shown that transient elastography is a useful tool for enhancing liver disease screening among PWID attending addiction clinics (271, 272). Increased community-based liver disease assessment might be one strategy for enhanced engagement of PWID in HCV care and identifying those with advanced liver disease who might be in need of immediate treatment.

Following HCV assessment, barriers at the level of the system, provider and patient need to be overcome to increase HCV treatment uptake among PWID. Recently, various strategies to improve engagement with HCV services and enhance treatment uptake have been explored (273). Strategies that have been successful in enhancing HCV assessment, treatment adherence, or treatment response include hospital-, primary-, and specialty care-based integrated care (109, 257, 274-283), community-based telehealth (284), nurse-led education (285), directly observed therapy (31, 219, 286), and peer-support groups and workers (215, 287-289). Given that each of these models of care constitutes of different measures and disciplines, their effectiveness cannot be fully compared with other models of HCV care. Further, most evidence about these different strategies are from observational studies with low numbers of patients. Therefore, it has not been possible to assess the impact of the individual factors on assessment, treatment uptake, adherence, and treatment outcome at the population level (273). Given the heterogeneity of PWID populations and differences in healthcare systems in various settings, not all of the described models of HCV care are feasible for any setting (273). A recent meta-analysis of studies examining

treatment outcome of at least 10 PWID identified “treatment of addiction during HCV therapy” as a parameter leading to higher treatment completion (8). However, this meta-analysis did not further differentiate between various models of care. Despite different structures of strategies to increase HCV assessment and treatment uptake, a multidisciplinary approach to HCV treatment has been the common component among all these models of care. Multidisciplinary teams often include clinicians and nursing staff for clinical assessment and monitoring, drug and alcohol support services, psychiatric services, social work, and other social support services (including peer support, if available) (273). As reviewed elsewhere, successful implementation of multidisciplinary models of HCV care requires a nonjudgmental attitude toward PWID among all involved health providers, and a high level of acceptance of the individual life circumstances of PWID (273).

At the provider and patient levels, improved patient-practitioner interactions are needed to increase HCV assessment and treatment. At the provider-level, promotion of national HCV testing guidelines, enhanced education and training of general and drug and alcohol practitioners about HCV and its treatment, and an improved awareness of programs offering comprehensive multidisciplinary HCV care are among the strategies that may remove provider-level barriers to access HCV care. The recent development of the first international recommendations for the management of HCV among PWID is a key step toward providing practitioners with an evidence-base guideline for appropriate HCV assessment and treatment (198). Given appropriate training and education, healthcare providers in drug and alcohol clinics have shown to be willing to develop skills required to provide on-site HCV treatment and support their patients during the course of antiviral therapy (158, 290). Further, if required, healthcare providers should receive education toward reducing stigma and discrimination related to HCV and drug use (291). At the patient-level, programs offering HCV education (e.g. peer support programs) may be one strategy to improve HCV

knowledge and enhance engagement in HCV assessment and treatment programs (292-294).

Further research is needed to better understand why PWID are not being assessed for and receiving treatment so that future strategies can be designed to enhance HCV assessment and treatment uptake. Moreover, research is needed to evaluate the effects of different models of HCV care on improved access to HCV assessment and treatment, and to provide further recommendations on the most efficient methods to provide HCV care to PWID in different settings.

1.19. Cost-effectiveness of HCV Assessment and Treatment

The sequelae of HCV infection impose a high economic burden in many countries. It has been estimated that in the United States, in 2012, the healthcare cost of HCV infection was $6.5 billion, and the cost has been predicted to peak at $9.1 billion in 2024 (295). The health burden of HCV is mainly attributed to the development of advanced liver disease, which can lead to liver transplant. In the United States, HCV is the leading cause of hepatocellular carcinoma (296). The medical cost of hepatocellular carcinoma has been estimated to be $23,755 to $44,200 per year per person, and the cost of liver transplant has been estimated to be as high as $201,110 per year per person (297). Further, HCV-related extra-hepatic diseases (e.g. renal disease) are thought to generate additional disease burden and cost (298).

Despite the high economic burden of HCV infection, implementation of strategies to increase HCV assessment and treatment uptake will depend on issues related to cost-effectiveness and government subsidization, particularly for future IFN-free regimens. Several studies from the United States have demonstrated cost-effectiveness of birth-cohort screening for all people born in 1945-1965 or 1946-1970, compared to risk-based screening (299-301). Despite cost-effectiveness, the birth-cohort approach is likely to identify HCV infection

among ex-, or non-injecting populations, which has a small impact on HCV transmission prevention. HCV case-finding in addiction services, using cheap and widely available dried blood spot testing might be another strategy to enhance HCV assessment, which is cost-effective and will have a more significant impact on HCV transmission prevention (270). In many settings, current HCV treatment has been demonstrated to be cost-effective among non-PWID or those without risk of re-infection (302-304). There is also considerable evidence from Australia, Europe, New Zealand and the United States demonstrating that HCV treatment (either PEG-IFN/RBV or PEG-IFN/RBV and a protease inhibitor for those with genotype 1) for active and former PWID is cost-effective (305-310). Recent mathematical modelling (305) has demonstrated that treating chronic HCV infection among both active PWID and ex- or non-PWID populations is cost-effective; however, the treatment of active PWID may be more cost-effective in settings with lower prevalence of chronic HCV infection (below 60%) (305). These findings suggest that HCV treatment among PWID should be prioritised, given the potential prevention and cost-effectiveness benefits. However, new and more effective HCV treatment regimens will be associated with increased cost. Price reform and enhanced access to therapy for those with HCV will require considerable public health advocacy from all sectors in the HCV community, including community organizations representing PWID.

1.20. Summary

Proportions of HCV assessment and treatment uptake are suboptimal, particularly among PWID. Low HCV assessment and treatment often results from the combination of multiple barriers to antiviral therapy present at the levels of the systems, provider, and patient. The goal of HCV therapy is viral eradication as represented by SVR. Interferon-based antiviral regimens have evolved to achieve higher rates of SVR; from 15-20% SVR rates in 1990s to the current overall 56% SVR rate among PWID. Current antiviral treatment for HCV infection is safe and effective among PWID, and international guidelines recommend treatment for PWID following individualised assessment. More effective, interferon-free treatment regimens are anticipated to dominate the HCV therapeutic landscape within the next 5 years. Interferon-based treatment is associated with several side effects, including development of psychiatric symptoms. Recently, various models of HCV care have evolved to remove barriers to access HCV assessment and treatment. A multidisciplinary approach has been the foundation of all these models; however, not all models of HCV care are feasible in any setting. Further research is needed to, a) monitor trends in HCV treatment uptake; b) better understand factors associated with suboptimal HCV assessment and treatment and to evaluate the effects of different models of HCV care on improved access to HCV care; c) evaluate the impact of patients treatment willingness on subsequent HCV assessment and treatment uptake, and; d) evaluate PWIDs response to antiviral therapy.

1.21. Thesis Rationale

PWID are the group most at risk for HCV transmission, particularly in high-income countries such as Australia. Compared to the general population, PWID are at higher risk of mortality. Concurrent with the ageing cohort effect in many PWID populations, HCV-related liver disease and liver-related mortality have been rising. Despite advances in antiviral therapy, safety and efficacy of HCV treatment for PWID and international guidelines recommending treatment for PWID following individualised assessment, there remain several barriers to accessing HCV assessment and treatment in this group. Enhanced HCV assessment and treatment uptake is a key step toward reducing the rising disease burden of HCV at the population level. To develop strategies to enhance HCV assessment and treatment uptake, research is needed to better understand the long term impact of chronic HCV infection on risk of mortality and estimates of life expectancy, factors associated with HCV assessment and treatment uptake among PWID and predictors of response to therapy in this population. This project aims to address these issues as main barriers to the assessment and treatment of HCV infection among PWID.

This thesis consists of a literature review (in this chapter) and five manuscripts that have been published, or submitted for publication, in peer-reviewed scientific journals. The specific aims of the research described in this thesis and relevant hypotheses are:

1. To evaluate mortality and life expectancy among people with chronic HCV infection

Hypothesis: Without therapeutic intervention, people with chronic HCV infection are at higher risk of liver-related mortality and reduction in life expectancy.

2. To evaluate HCV treatment uptake and associated factors among inner city residents

Hypothesis: Despite advances in antiviral therapy, HCV treatment uptake has remained suboptimal. Several clinical (including HCV/HIV co-infection) and socio-demographic factors

(including age, ethnicity, employment status, housing status and recent drug use) are associated with low HCV treatment uptake.

3. To evaluate HCV assessment and treatment uptake among PWID in opioid substitution setting

Hypothesis: Integration of HCV care within the existing infrastructure of opioid substitution treatment clinics is a successful strategy to increase HCV assessment and treatment uptake among PWID.

4. To evaluate willingness to receive HCV treatment among PWID

Hypothesis: Despite self-reported barriers to HCV treatment, PWID have a high willingness to receive antiviral therapy. High willingness to receive HCV treatment is associated with subsequent HCV assessment and treatment uptake.

5. To evaluate the impact of treatment for HCV infection on depression and mental health parameters

Hypothesis: PWID have a higher risk of mental health disorders (including depression). However, HCV treatment does not increase the risk of mental health issues in this group of patients.

Chapter 2

Cause-specific mortality and life expectancy among people with an HCV notification

2.1. Chapter Introduction

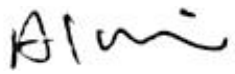
Despite two decades of research on the natural history of HCV infection, uncertainty remains on the individual mortality risk and estimates of life expectancy among people with HCV infection. The absence of large cohorts with long-term follow-up of people with chronic HCV infection in different settings, together with suboptimal HCV screening in most countries, has limited the characterisation of HCV disease progression and representative mortality distribution. This paper is one the first population-based studies utilising data linkage techniques to estimate life expectancy among people with an HCV infection notification. These findings significantly contribute to development of future strategies to lower the rising burden of HCV-related disease in Australia and internationally. The manuscript has been accepted for publication in the Journal of Viral Hepatitis:

Publication I

Alavi M, Law MG, Grebely J, Thein HH, Walter S, Amin J, Dore GJ. Lower life expectancy among people with an HCV notification: a population-based linkage study. Journal of Viral Hepatitis 2013 (Accepted, JVH-00479-2013)

2.2. 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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2.3. Co-authorship Acknowledgemnet

In the case of Chapter Two, the nature and extent of my contribution to the work was the following:

Name	Contribution (%)	Nature of contribution*
Maryam Alavi	50	Conducted the data analysis and led the development, writing and critical revision of the manuscript.
Matthew Law	15	Contributed to study design, collection, statistical analysis and interpretation of data.
Jason Grebely	5	Contributed to writing and critical revision of the manuscript.
Hla Hla Thein	5	Contributed to study design and data collection.
Scott Walter	5	Contributed to study design and statistical analysis of data.
Janaki Amin	5	Contributed to study design, collection and statistical analysis of data.
Gregory Dore	15	Contributed to study design, data collection and critical revision of the manuscript.

2.4. Lower life expectancy among people with an HCV notification: a population-based linkage study

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2.5. Abbreviations

HCV, Hepatitis C virus; HBV, Hepatitis B virus; NSW, New South Wales; NDD, Notifiable Diseases Database; PWID, people who inject drugs; RBDM, the NSW Registry of Births, Deaths and Marriages; ABS, Australian Bureau of Statistics; ICD, International Classification of Diseases; NHR, National HIV Registry; HCC, hepatocellular carcinoma; IQR, interquartile range.

2.6. Abstract

Background: Among people with hepatitis C virus (HCV) infection, liver disease-related deaths have risen over the last 20 years. Life expectancy has not been estimated in this population. **Methods:** HCV notifications (mandatory notification of anti-HCV positive serology since 1991) reported to the New South Wales Health Department from 1992-2006 were linked to cause of death data. Abridged life tables were constructed from age-specific mortality rates. Life expectancy from ages 18-70 years for non drug-related mortality causes was estimated using competing risk methods and compared to the general population of Australia. **Results:** The cohort comprised 81,644 individuals with an HCV notification, with median follow-up of 7.6 years. Median age at notification was 34 years [interquartile range (IQR) 28-42], 63% were male. Between 1992-2006, 4,607 deaths occurred. Median age at liver- and drug-related deaths among males was 51 (IQR 45-66) and 36 (IQR 31-42) years, respectively; and among females was 63 (IQR 49-74) and 36 (IQR 30-41) years, respectively. In each year of follow-up before 2000, 15-21% of deaths were liver- and 30-39% were drug-related. After 2000, liver-related deaths increased to 20-26% of deaths in each year and drug-related deaths decreased to 13-19%. Excluding drug-related causes of death, life expectancy was lowered by an average of 4.2 (SD ±1.0) and 5.4 (SD ± 0.7) years for males and females, respectively. **Conclusions:** Among people with an HCV notification, an increasing proportion of deaths are liver-related. Following removal of drug-related mortality, life expectancy in this population remained considerably lower, compared to the general population.

Keywords: drug-related mortality; HCV treatment; liver-related mortality; people who inject drugs

2.7. Introduction

Despite two decades of research on the natural history of hepatitis C virus (HCV) infection, uncertainty remains on the individual mortality risk and estimates of life expectancy among people with HCV infection. HCV-related liver disease is generally progressive, accelerated by co-factors including heavy alcohol intake (311), HIV or hepatitis B virus (HBV) co-infection (60, 146) obesity and diabetes (312).

At individual and population levels, risk of HCV mortality from end-stage liver disease, depends on a number of factors, such as duration of chronic HCV infection (55) age at HCV acquisition (56) and co-factors for disease progression. Competing causes of death also impact HCV liver disease mortality risk (313), particularly for people who have acquired infection via contaminated blood products and people who inject drugs (5).

The absence of large cohorts with long-term follow-up of people with chronic HCV infection in different settings, together with suboptimal HCV screening in most countries, has limited characterisation of HCV disease progression and representative mortality distribution (5). The mandatory notification of anti-HCV positive serology since 1991 in Australia (47), alongside high rates of screening of individuals with prior or current HCV risk behaviour (314), have enabled characterisation of disease-specific mortality rates and trends (2, 315). Our objectives in this study were to further characterise the distribution and rates of mortality across age groups and notification periods and to estimate life expectancy among people with an HCV notification.

2.8. Methods

Data sources

The study population consisted of all people recorded in the New South Wales (NSW) Notifiable Diseases Database (NDD) with a notification of positive anti-HCV serology between 1 January 1992 and 31 December 2006. Since 1991, state government legislation has mandated reporting of all notifications of hepatitis B virus (HBV) and HCV to the NSW Department of Health (NSW Public Health Act 1991) (47). Notifications of HCV are made to local health authorities and de-identified information including age, gender, postcode of residence and year of serology test results are forwarded to the NDD in each state. The vast majority of HCV notifications are received from laboratories where serological screening tests for HCV have been available since 1990. A notifiable HBV case requires detection of HBV surface antigen or HBV DNA. A notifiable HCV case requires detection of anti-HCV antibody or HCV RNA. Personal identifiers were first recorded in the NDD in 1992.

The NSW Registry of Births, Deaths, and Marriages (RBDM) records the date of death for all deaths occurring in NSW. The RBDM supplies the Australian Bureau of Statistics (ABS) with the Medical Certificate of Cause of Death. ABS codes the underlying cause of death according to the International Classification of Diseases (ICD) (316).

In Australia, national surveillance for HIV is coordinated by The Kirby Institute. Notified cases of HIV infection are reported to the National HIV Registry (NHR) on the first occasion of diagnosis. Reporting of HIV has been mandatory in NSW since 1985 and has been nationally administered since 1989 (317). NHR data sources uses a four letter name code consisting of the first two letters of the first and last name, and records gender and date of birth information.

Linkage

Data linkage occurred in two stages. In the first stage, HBV and HCV notifications in the NDD were matched internally to allow identification of cases with an HCV/HBV notification. All notifications were then matched to RBDM death records. In these steps, linkage was done probabilistically using full name, gender, date of birth and address by means of ChoiceMaker software (318). ABS cause of death records were linked deterministically to RBDM death records. In the second stage, to identify individuals with an HCV/HIV notification, data were matched deterministically to notifications from NHR using name code, gender, and date of birth. All linkage was performed by the NSW Centre for Health Record Linkage (72).

People with an HBV notification, HCV/HBV, HCV/HIV, and HCV/HBV/HIV notification were excluded from analysis. Thus, all analyses are based on people with a notification of anti-HCV positive serology.

Statistical methods

People who died within six months of an HCV notification were not included in any analyses because of the potential for bias towards higher rates of notifications in people with symptomatic advanced liver disease. Consistent with this exclusion, all other people remaining in the study group had their time at risk shortened by six months. Underlying causes of death in the ABS mortality data were defined using ICD-9 codes prior to 1 January 1997, and thereafter ICD-10 codes were used. Drug-related deaths were defined according to methods set out by the ABS (319). This refers to deaths involving dependence disorders due to psychoactive substances, abuse of non-dependence producing substance (chapters: ICD-10 mental and behavioural disorders, ICD-9 mental disorders), and poisoning or overdose by exposure to legal or illegal drugs (chapters: ICD-10 external-causes, ICD-9 injury and poisoning). Liver-related deaths consisted of deaths by underlying cause of viral hepatitis, sequelae of viral hepatitis (chapters: ICD-10 certain infectious and parasitic

diseases, ICD-9 infectious and parasitic diseases), hepatocellular carcinoma (HCC), other causes of primary liver cancer (chapters: ICD-10 and ICD-9 neoplasms) and alcoholic and non-alcoholic liver disease (chapters: ICD-10 and ICD-9 diseases of the digestive system (320). Among people with HCV mono-infection, comparability ratios between ICD-9 and ICD-10 coding of drug- and liver-related mortality are very close to 1.0 (321).

The distribution of age at death (all-cause and cause-specific) was described and stratified by gender. Temporal trends in the distribution of liver-, drug- and other-cause related deaths were described over the 1992-1995 follow-up period and thereafter for each calendar year of follow-up up to 2006. Small numbers of death over the 1992-1995 follow-up period were combined to allow meaningful comparison with the rest of the follow-up period. Mortality rates after an HCV notification were estimated using person time methodology, for individuals aged 0 up to 20 years, and thereafter for 5-year-age-groups up to 70 years. Confidence intervals for mortality rates were estimated by use of a quadratic approximation, on the assumption that recorded deaths follow a Poisson distribution. Person-years at risk were calculated for each person as time from NDD notification date to either date of death or December 31, 2006, if there was no death recorded. The cumulative incidences of liver-, drug-, and other-cause related mortality were calculated within a competing risk framework (322). Competing risks were defined as competing events (drug- and other-cause related deaths) whose occurrence prevent or alter the probability of occurrence of the main event under examination (liver-related deaths).

Abridged life tables were constructed from age-specific mortality probabilities to estimate life expectancy from 18 to 70 years of age. These tables describe the mortality experience that hypothetical cohorts of people with an HCV notification would have had if they were subjected to the mortality in the observed period. Life expectancy at an exact age is the average additional years that will be lived by a person after that age, according to the cross sectional age-specific mortality rates for all causes during the study period. To estimate the

potential association of HCV with life expectancy, only non drug-related deaths were included in the abridged life tables, using a competing risk methodology (322). Competing risks were defined as competing events (drug-related deaths) whose occurrence prevent or alter the probability of occurrence of the main event under examination (non drug-related deaths). Cause-specific mortality probabilities (for non drug-related deaths) in each age stratum were calculated, taking into account the effect of competing risk and assuming no individual died later than 100 years of age. Mortality probabilities for the open age grouping (≥70 years) could not be meaningfully estimated as the sample size was too small to allow further stratification by age. Therefore the mortality probabilities in those aged ≥70 years were adjusted by using the average relative risk of mortality in the NSW population with an HCV notification to that of the Australian population (hereafter referred to as the general population). Among the NSW study cohort aged <70 years, smoothed mortality probabilities (by including a nonlinear regression line) were used to calculate relative risks of mortality. The average relative risk of mortality was then extrapolated from the 50-70 year age group to the open age group; 1.81 for males and 2.40 for females. We investigated the sensitivity of these estimates by varying the calculation of average relative risk from 60-80 to 70-80 year age groups. We assumed mortality probabilities in the open age group were the same as the average mortality probabilities calculated from extrapolated average relative risks in NSW cohort and mortality probabilities in the general population aged ≥70 years.

Ethics approval for the study was granted by NSW Health, NSW Cancer Council, the Australian Institute of Health and Welfare, and the University of New South Wales.

2.9. Results

The initial NSW cohort consisted of 128,726 people who had an HCV or HBV notification between 1992 and 2006. Data on 42,480 people with an HBV notification, 3,285 people with an HCV/HBV notification, 620 people with an HCV/HIV notification, 269 people with an HBV/HIV notification, and 38 people with an HBV/HCV/HIV notification were excluded. Moreover, 390 people with an HCV notification whose gender was unknown were excluded. Overall, 81,644 people with an HCV notification were included in this analysis (Figure 1). The median year of birth among males and females was 1963 [interquartile range (IQR) 1956-1970] and 1964 (IQR 1957-1972), respectively. The median age at HCV notification among males and females was 35 years (IQR28-42) and 34 years (IQR 27-41), respectively.

A total of 4,607 (6%) people with an HCV notification died during a median follow-up of 7.6 years, comprising 20% (n=939) liver-related deaths, 24% (n=1,109) drug-related deaths, and 56% (n=2,559) deaths from other causes. Median age at death among males and females was 46 years (IQR 37-59) and 51 years (IQR 40-74), respectively. Among males, median age at all-cause-, liver-, drug- and other cause-related death was 46 years (IQR 37-59), 51 years (IQR 45-66), 36 years (IQR 31-42) and 50 years (IQR 40-70), respectively (Table 1). Among females, median age at all-cause-, liver-, drug- and other cause-related deaths was 51 years (IQR 40-74), 63 years (IQR 49-74), 36 years (IQR 30-41) and 60 years (IQR 44-78), respectively (Table 1).

Over the 1992-1995 period and thereafter in each calendar year up until 2000, liver-, drug- and other cause-related deaths comprised less than 21%, 30%-39% and 44%-51% of the total number of deaths, respectively (Figure 2). After 2000, the number of liver- and other cause-related deaths increased to reach 26% and 63% in 2006, respectively. After 2000, the number of drug-related deaths decreased to 13% of all deaths in 2006 (Figure 2). Over the 1992-1995 period and thereafter in each calendar year up until 2001, median age at liver-related death was between 53 years and 60 years, with the exception of 1998 (median age

at death 46 years). After 2001, the median age at liver-related death lowered to 52 years in 2006 (IQR 48-61) (Table 1, Figure 2). Between 1992 and 1995, the median age at drug- and other-cause related deaths were 33 years (IQR 28-39) and 52 years (IQR 35-73), respectively. The median age at drug- and other-cause related deaths remained between 35 to 40 years and 45 to 54 years from 1997 to 2006, respectively (Table 1, Figure 2).

The study population were followed for a median of 7.6 years (range 0.7-15.0), for a total of 627,821 person-years at risk. Cumulative incidence of drug-related mortality was initially higher than liver-related mortality (Figure 3). At 12 years following HCV notification, cumulative incidence of liver-related mortality surpassed the cumulative incidence of drug-related mortality (Figure 3).

For both genders, age-specific rates of all-cause, liver- and other cause-related mortality increased by age, from 30 years onwards (Figure 4). However, there were lower numbers of HCV notifications in older age groups among both genders. The crude numbers of liver-related deaths were highest in the 35-39 (n=133), 40-44 (n=190) and 45-49 year (n=104) age groups. Compared to other age-specific mortality rates, rates of drug-related mortality were higher among relatively younger ages for both genders. The rates were elevated from early 20s into early to mid 40s, after which they decreased gradually (Figure 4). Estimates of life expectancy were undertaken following removal of drug-related mortality.

Among the NSW study cohort, males had consistently shorter life expectancy compared to females (Figure 5). The life expectancy (after excluding drug-related causes of death) at the median age at HCV notification among NSW males and females (35 and 34 years, respectively) was 39 and 44 years, compared to 45 and 51 years among males and females of the general population, respectively. The life expectancy at a notification age of 50 years among NSW males and females was 27 and 29 years, compared to 31 and 35 years among males and females of the general population, respectively. Compared to males of the

general population, life expectancy for males in the NSW study cohort was lowered by an average of 4.2 years (SD± 1.0). Compared to females of the general population, life expectancy for females in the NSW study cohort was lowered by an average of 5.4 years (SD± 0.7).

2.10. Discussion

In this large population-based linkage study, once drug-related deaths were excluded, life expectancy among people with an HCV notification was 4-5 years lower compared to the general population. This study also demonstrates the changing distribution of cause of death among people with an HCV notification in NSW, Australia. Since 2000, concurrent with the HCV cohort ageing and the decreasing number of drug-related deaths, liver-related deaths have steadily increased. These findings build on those from previous NSW linkage studies (2, 315) in providing additional data on mortality among people with an HCV notification.

Our analysis demonstrated drug-related death as a major cause of mortality in people with an HCV notification in 1990s. During this decade, heroin was the most commonly injected drug among people who injected drugs regularly in NSW, resulting in an increase in associated harms, including fatal overdoses (314). Following a wider implementation of harm reduction policies in the late 1990s (81) and the nation-wide reduced availability of heroin from 2001 (45, 323), indicators of injecting drug use decreased across the country (43). Subsequently, there has been a decline in the number of drug-related deaths (81) and young adults initiating injecting drug use (82). The initial reduction in injecting drug use has been further enhanced within the population of people with HCV mono-infection through the ageing cohort nature of the population and the resultant impact on drug use patterns.

Declining drug-related mortality among people with an HCV notification in NSW is contrasted by increasing liver-related deaths. Although age-specific liver-related mortality is not increasing (315), expanding HCV prevalence and the ageing cohort nature of the population are leading to a rising burden of liver-related deaths. Low HCV treatment uptake remains another major contributor (5). It has been suggested that achieving sustained virological response is associated with reduced risk of all-cause mortality, including mortality from non liver-related causes (180). High proportions of other cause-related deaths in this analysis

may further reflect on suboptimal HCV treatment uptake and development of liver and non liver-related conditions that contribute to high mortality among people with an HCV notification.

There are several limitations in our study. First, HCV notification registries do not collect treatment information; therefore, we could not assess the impact of HCV therapy on liver disease mortality. However, HCV treatment uptake has been low throughout the study period, with only 1-2% of people with chronic infection receiving interferon-based treatment annually (107). Second, while confirmed HCV notifications are entered to NDD within a short period of time, it is not possible to precisely distinguish between diagnosed and notified cases in each calendar year. Third, as HCV notifications are generally based on positive anti-HCV serology, many HCV notifications will not have chronic infection, as an estimated 25% of infections spontaneously clear (51) and remain HCV antibody positive. However, inclusion of all anti-HCV antibody positive notifications should underestimate the liver disease mortality related to chronic HCV infection. Fourth, there may be some uncertainty with respect to the duration of HCV infection, given this data is based on the date of notification (the time of infection among many cases may be unknown).

Fifth, given the absence of lifestyle information in this study, we were also not able to evaluate the potential impact of specific exposures (e.g. alcohol consumption, smoking, drug use) on increased mortality. As such, the direct impact of HCV infection on mortality and decline in life expectancy could not be quantified. Sixth, although an estimated 80-85% of all HCV infections in Australia have been notified (43), lower screening rates in some sub-populations (particularly non-PWID), could affect representativeness. The exclusion of individual cases with death within six months of notification should, however, have reduced potential symptomatic-base selection bias. Seventh, the current analysis is among people with an HCV notification until December 2006 which may limit our understanding of more recent changes in mortality trends. However, given the ageing cohort effect and low levels of

HCV treatment uptake (324), overall mortality trends in this population are not expected to have changed markedly since 2006. Lastly, the accuracy of data linkage relies upon the accuracy of identified personal information, which may be poorly recorded. Alias identities may lead to inaccuracies in linkage. However, another Australian study in prisons, where aliases are very common, has estimated that the linkage accuracy for NSW prisoners and the National Death Index has a sensitivity of 88.4% and specificity of 99.7% (325). There is no reason to believe the accuracy of linkage was lower in the present study.

Successful HCV treatment with viral eradication is associated with improved quality of life, liver disease regression, and reduction in liver- and all cause-related mortality (180). The HCV therapeutic landscape will change markedly over the next decade (6). Preliminary evidence indicates that interferon-free combination direct acting antiviral regimens should reduce toxicity, shorten treatment durations (from 24-48 weeks to 12-24 weeks), improve dosing schedules, and enhance cure rates (6). These therapeutic developments will be associated with considerable additional expense, at least during the initial decade of their implementation. Cost-effectiveness analyses will therefore need to incorporate parameters associated with disease progression and lowered life expectancy based on representative population-based cohorts. Often, these parameters have been derived from liver clinic-based studies, which contain selection bias (326).

In summary, among people with an HCV notification, mortality is higher and life expectancy is lower, compared with the general population. As individuals age, major causes of death shift from drug- to liver-related causes. Liver-related deaths are expected to further increase as the cohort is ageing and duration of infection increases. Our findings should facilitate public health strategic planning in response to increasing disease burden among people with HCV infection.

2.11. Acknowledgments

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Authors Contributions

M Alavi contributed to the statistical analysis, interpretation of data, and drafting the article. M Law and G Dore contributed to the study conception, design, and the interpretation of data; J Grebely contributed to interpretation of data and drafting the article; J Amin contributed to the study design, the acquisition, and interpretation of data; S Walter contributed to the acquisition and interpretation of data; HH Thein contributed to the study conception, design and interpretation of data. All authors revised and approved the final version for publication.

Conflict of interest

None of the authors has commercial relationships that might pose a conflict of interest in connection with this manuscript.

Ethics committee approval

Ethics approval for the study was granted by NSW Health, NSW Cancer Council, the Australian Institute of Health and Welfare, and the University of New South Wales.

Financial disclosure

J Grebely is a consultant/advisor for Merck. GJ Dore is a consultant/advisor and has received research grants from Roche, Merck, Janssen, Gilead, Bristol Myers Squibb and AbbVie. The other authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Role of the funding source

The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

2.12. Tables

Table 1. Distribution of age at death among NSW people with an HCV notification, n= 81,644

	Number of Deaths	Median Age at Death	Interquartile Range (IQR)
All-cause mortality	4607	47	38 to 66
male*	3220	46	37 to 59
female	1387	51	40 to 74
Liver-related mortality†	939	53	46 to 70
male	665	51	45 to 66
female	274	62	49 to 74
Drug-related mortality‡	1109	36	31 to 42
male	845	36	31 to 42
female	264	36	30 to 41
Other-cause mortality	2559	51	41 to 73
male	1710	50	40 t0 70
female	849	60	44 to 78

* unknown/ other gender is not included in analysis.

† defined as any death caused by; viral hepatitis, sequelae of viral hepatitis, HCC, non-HCC liver cancer, alcoholic and non-alcoholic liver disease.

‡ defined by ABS definition of drug-related deaths.

2.13. Figures

Figure 1. Distribution of HCV and HBV notifications in NSW, 1992-2006

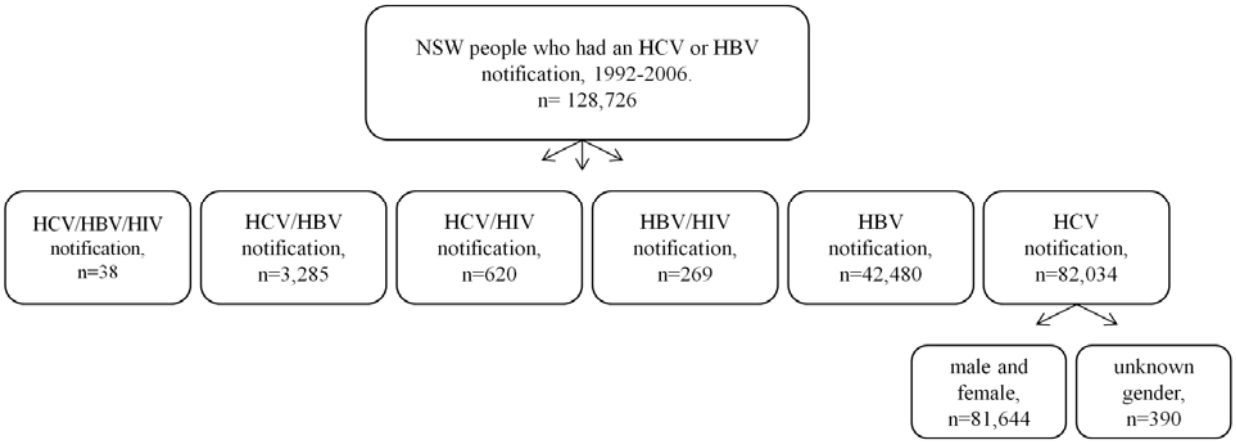


Figure 2. Temporal trends in the distribution of mortality among NSW people with an HCV notification, by year of follow-up. (A) cause-specific mortality; (B) median age at cause-specific mortality

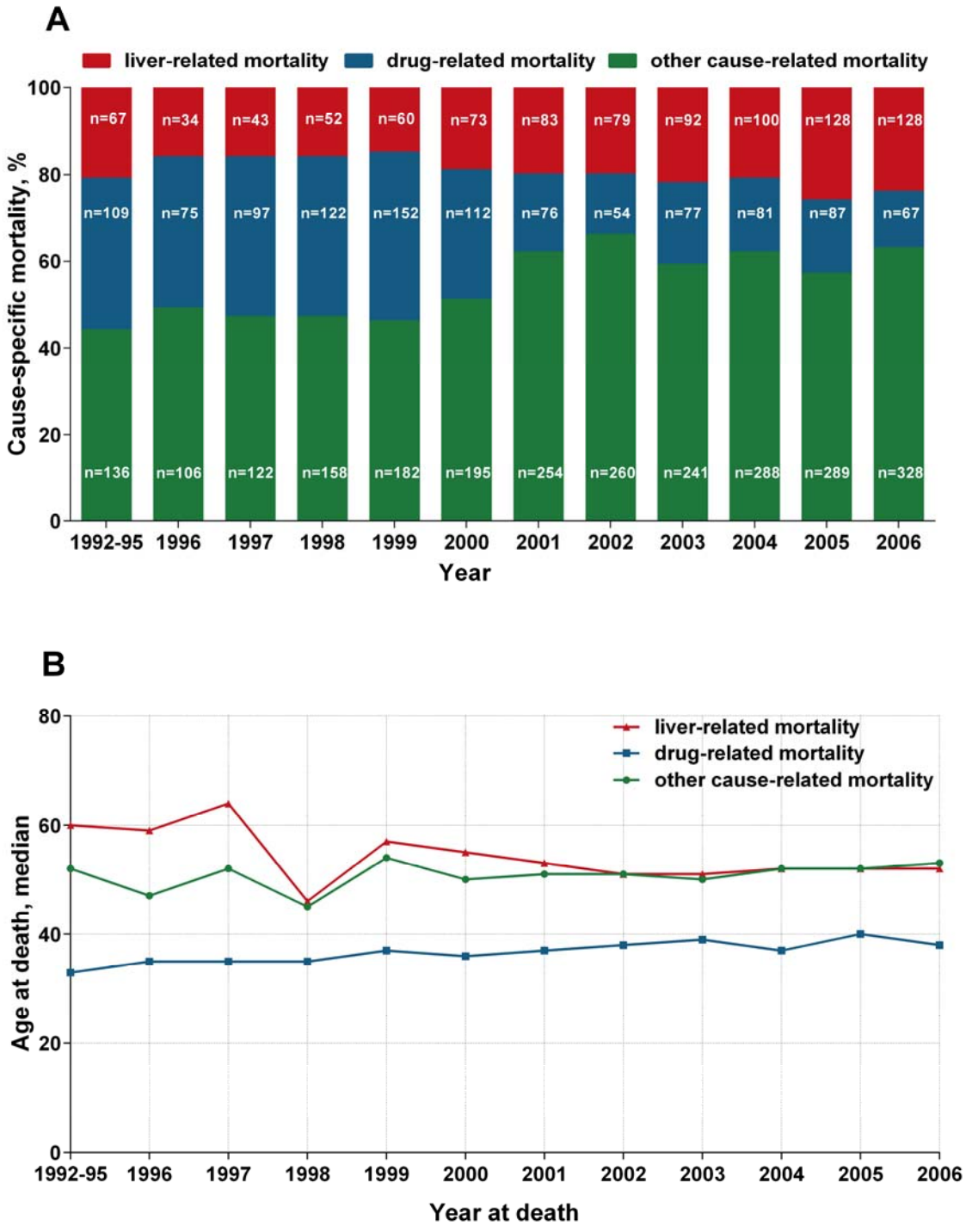


Figure 3. Cumulative incidence for cause-specific mortality among NSW people with an HCV notification

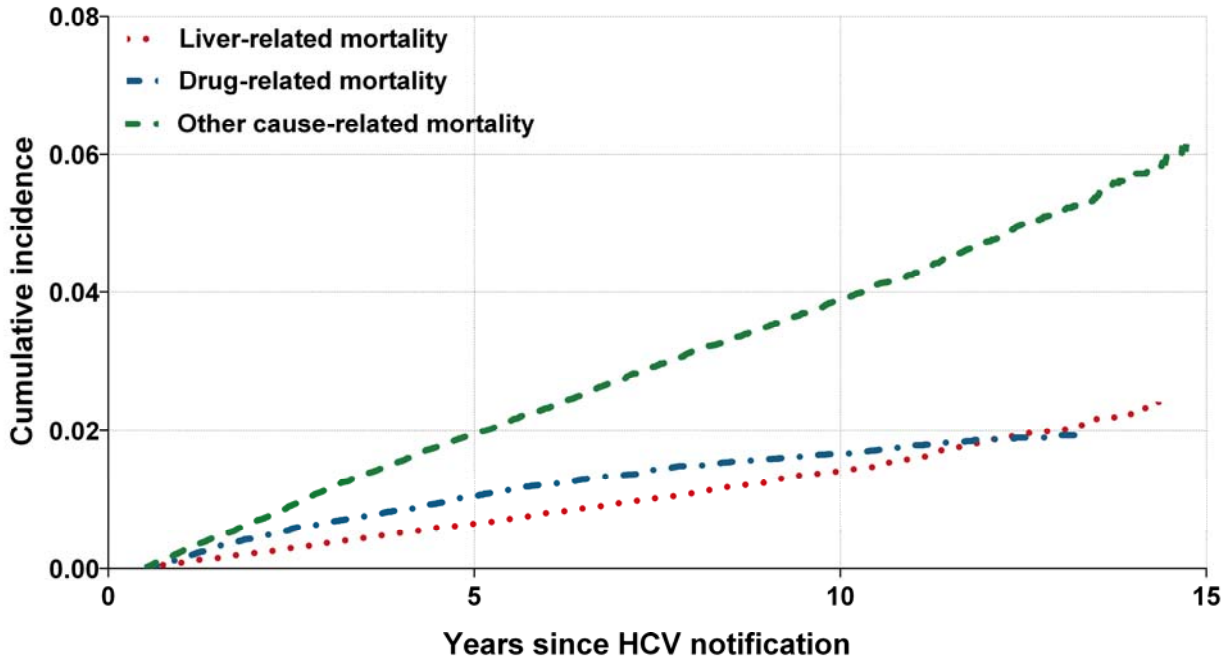


Figure 4. Incidence of all-cause, other cause-, liver-, and drug-related mortality, by age group. (A) males; (B) females

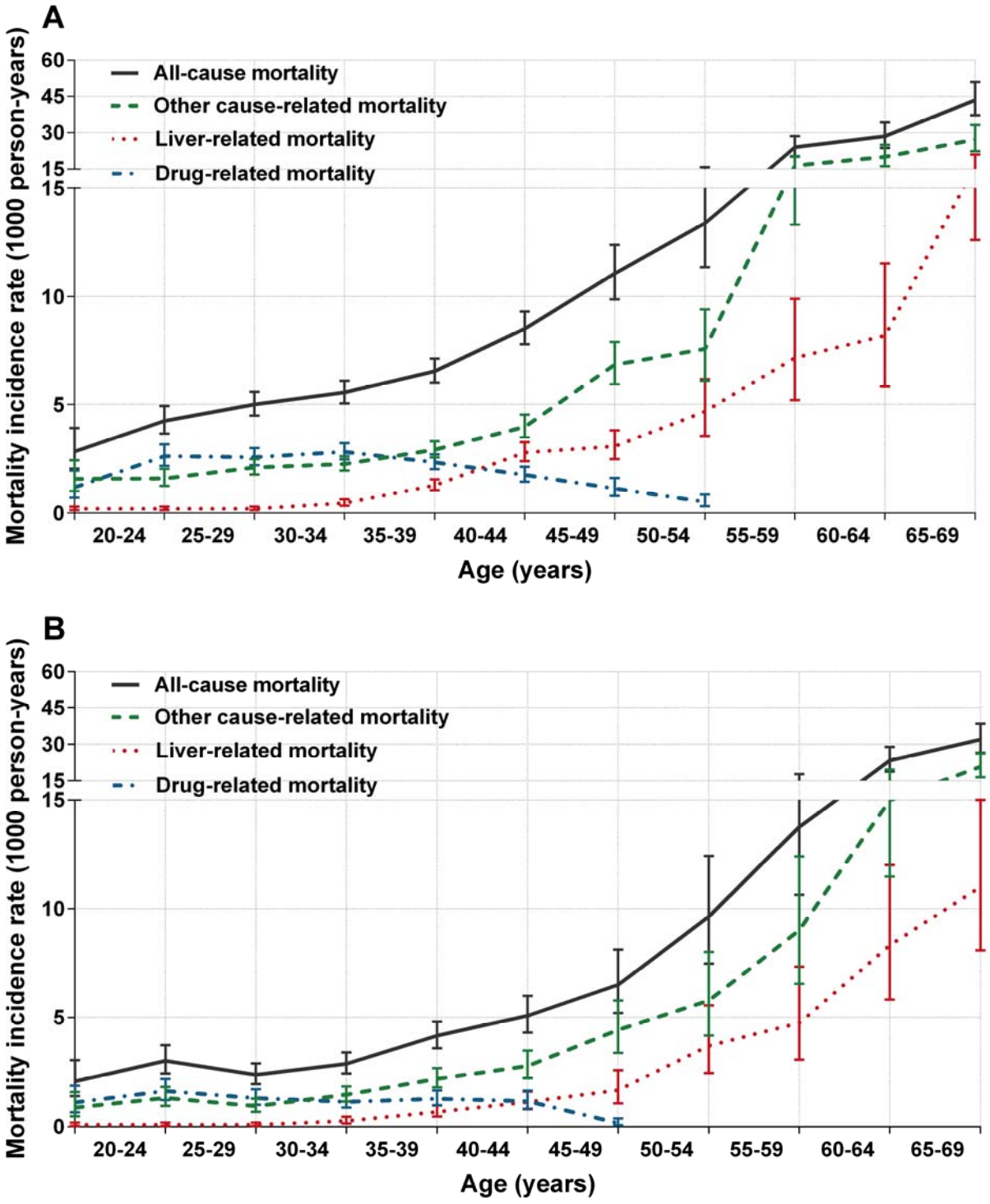
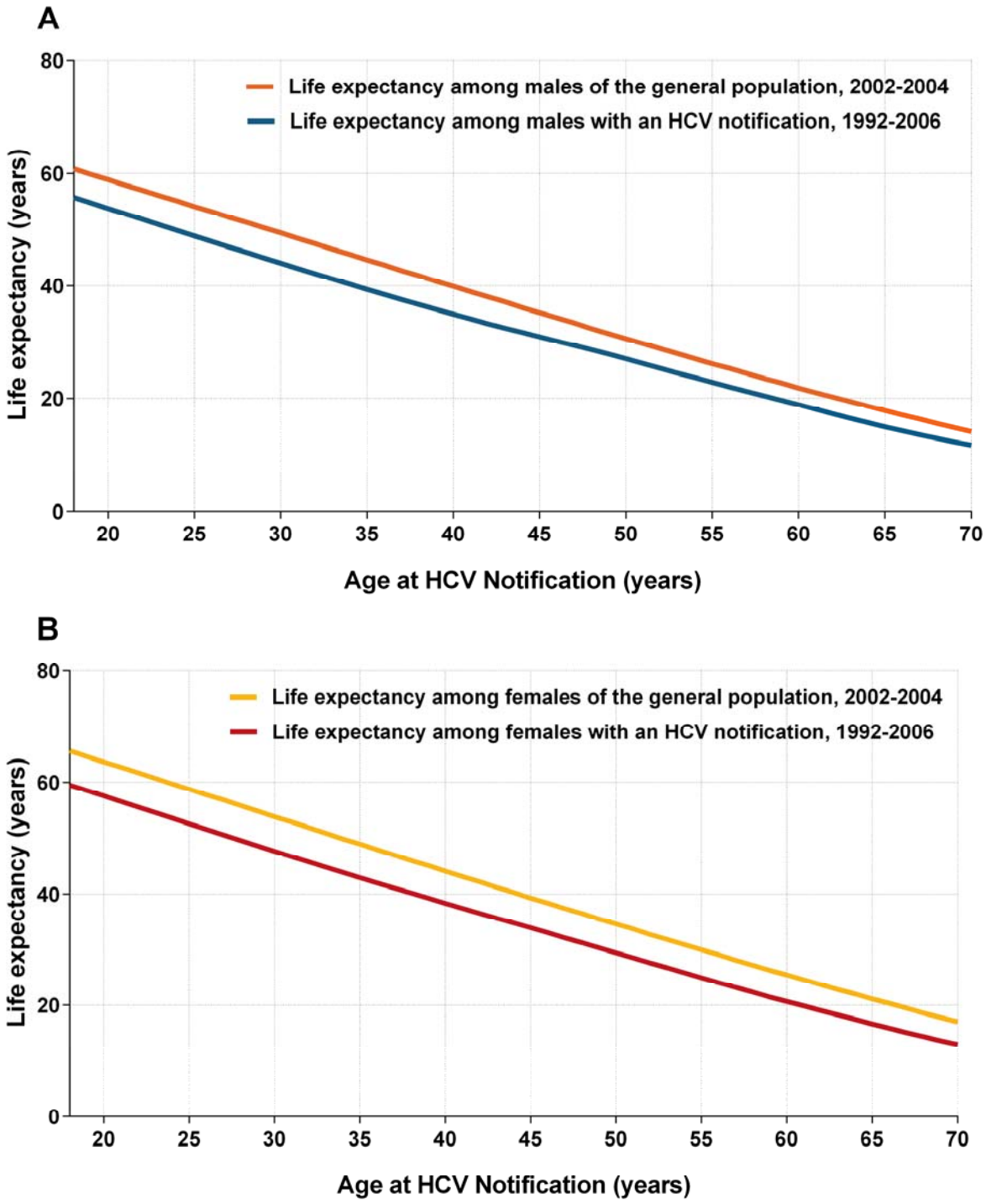


Figure 5. Life expectancy in NSW cohort compared to general population, excluding drug-related mortality. (A) males; (B) females



Chapter 3

Factors associated with HCV assessment and treatment uptake among inner city residents

3.1. Chapter Introduction

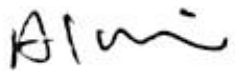
Despite high HCV treatment willingness among PWID and safety and efficacy of HCV treatment for this population, treatment uptake remains suboptimal among PWID. There are few recent data on the surveillance of HCV treatment uptake, particularly among people who use drugs, including recent trends and factors associated with HCV treatment. This large cohort of inner city residents with chronic HCV infection is unique, given the ability to retrospectively and prospectively link participant survey data from a large community-based cohort to pharmacy records for HCV treatment. Findings from this study identified many clinical and demographic factors associated with HCV treatment and underscored the importance of ongoing surveillance of HCV treatment uptake. A major shift in the public health approach to HCV care will be required to expand access to treatment among PWID. The manuscript is in press in Liver International:

Publication II

Alavi M, Raffa JD, Deans GD, Lai C, Krajden, M, Dore GJ, Tyndall MW, Grebely J. Continued low uptake of treatment for hepatitis C virus infection in a large community-based cohort of inner city residents. Liver International 2013; In Press.

3.2. 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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3.3. Co-authorship Acknowledgemnet

In the case of Chapter Three, the nature and extent of my contribution to the work was the following:

Name	Contribution (%)	Nature of contribution
Maryam Alavi	50	Conducted the data analysis and led the development, writing and critical revision of the manuscript.
Jesse Raffa	5	Contributed to study design, statistical analysis and interpretation of data.
Gregory Deans	5	Contributed to writing and critical revision of the manuscript.
Calvin Lai	5	Contributed to study design and data collection.
Mel Krajden	5	Contributed to study design, data collection and revision of the manuscript.
Gregory Dore	5	Contributed to interpretation of data, writing and critical revision of the manuscript.
Mark Tyndall	10	Contributed to study design, data collection and critical revision of the manuscript.
Jason Grebely	15	Contributed to study design, data collection and interpretation, writing and critical revision of the manuscript.

3.4. Continued low uptake of treatment for hepatitis C virus infection in a large community-based cohort of inner city residents

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Running title: HCV treatment uptake among inner city residents

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3.5. Abbreviations

AOR, adjusted odds ratio; CHASE, Community Health and Safety Evaluation; PWID, people who inject drugs; HCV, hepatitis C virus.

3.6. Abstract

Background: Despite advances in HCV treatment, recent data on treatment uptake is sparse. **Aims:** HCV treatment uptake and associated factors were evaluated in a community-based cohort in Vancouver, Canada. **Methods:** The CHASE study is a cohort of inner city residents recruited from January 2003-June 2004. HCV status and treatment were retrospectively and prospectively determined through data linkages with provincial virology and pharmacy databases. Logistic regression analyses were used to identify factors associated with HCV treatment uptake. **Results:** Among 2,913, HCV antibody testing was performed in 2,405, 64% were HCV antibody-positive (n=1,533). Individuals with spontaneous clearance (18%, n=276) were excluded. Among the remaining 1,257 HCV antibody-positive participants (mean age 42, 71% male), 29% were Aboriginal. At enrolment, the majority reported recent injecting (60%) and non-injecting drug use (87%). Between January 1998 and March 2010, 6% (77 of 1,257) initiated HCV treatment. In adjusted analyses, Aboriginal ethnicity [adjusted odds ratio (AOR) 0.23; 95% CI 0.10, 0.51] and crack cocaine use (AOR 0.61; 95% CI 0.37, 0.99) were associated with a decreased odds of receiving HCV treatment, while methamphetamine injecting (AOR 0.16; 95% CI 0.02, 1.18) trended towards a lower odds of receiving treatment. HCV treatment uptake ranged from 0.2 (95% CI 0.0, 0.7) per 100 person-years (PYs) in 2003 to 1.6 (95% CI 0.9, 2.6) per 100 PYs in 2009. **Conclusion:** HCV treatment uptake remains low in this large community-based cohort of inner city residents with a high HCV prevalence and access to universal healthcare.

Keywords: hepatitis C virus; drug use; people who inject drugs; treatment uptake

3.7. Introduction

In most developed countries, people who inject drugs (PWID) account for the majority of new (80%) and existing (60%) cases of hepatitis C virus (HCV) infection (4). Chronic HCV infection is associated with a significant disease burden, including major morbidities (55), excess risk of mortality (146) and health care costs (327). Data suggest that HCV-related morbidity and mortality are increasing, particularly among the ageing population of PWID (5, 55, 70, 146, 327). HCV treatment is associated with reductions in HCV-related morbidity and mortality (5, 181). However, despite recent therapeutic advances (6) and high sustained virological response among PWID (8, 195) HCV treatment uptake remains low in this population (142). There are few recent data on the surveillance of HCV treatment uptake, particularly among people who use drugs, including recent trends and factors associated with HCV treatment.

In 2005, estimates from Europe (119), and the United States (103, 126) suggested that 3-4% of people with chronic HCV infection had ever received antiviral therapy, with treatment uptake increasing by only 0.5% per year (103, 119, 126). Among populations of PWID, studies from Australia (328), Canada (10) and the United States (110) during the same period demonstrated that HCV treatment uptake ranged from 1-6%. However, drug use has been associated with reduced uptake of HCV treatment (10, 107, 116, 153). A more recent study among 22 European countries, suggested HCV treatment uptake ranged from 0.3% to 6.7% in 2010 (120). Over the past decade, guidelines have advocated for a broadened HCV assessment and treatment among PWID (197, 329-332) and programs for HCV treatment among PWID have produced encouraging outcomes (215, 221, 277, 284, 287). However, there are little recent data on HCV treatment uptake among PWID to assess whether a corresponding increase in HCV treatment uptake has been observed among this group.

Previous data from a large cohort of inner city residents consisting mainly of drug users from Vancouver, Canada (CHASE cohort), demonstrated that between 2000 and 2004 the uptake of HCV treatment was only 1% overall and 0.3% per year (10). The aim of this study was to further examine the CHASE cohort with respect to HCV treatment uptake, factors associated with HCV treatment and trends in HCV treatment between 2003 and 2009. This study is unique, given the ability to retrospectively and prospectively link participant survey data from a large community-based cohort to pharmacy records for HCV treatment.

3.8. Methods

Study population

The Community Health and Safety Evaluation (CHASE) cohort was designed to evaluate the uptake of health services and health outcomes in the Downtown Eastside of Vancouver, Canada. In an effort to collect a representative sample of residents in this community, facility-based sampling was used (333) and venues for recruitment were selected based on census tract data from a total population of approximately 16,000 people. Individuals were informed of the project through community-based agency staff, postings in local agencies, door-to-door initiatives and through word of mouth. Surveys were administered in a variety of settings, including 10 community-based agencies, two community health clinics, 117 single room occupancy hotels and social housing buildings and a large space that operates as a needle exchange site. All those included in the study had to have their names and personal health numbers verified through the British Columbia Ministry of Health database, ensuring that the participants all had the potential to be linked successfully to virology test results and health indicator databases.

Between January 2003 and June 2004, 2,913 participants completed a one-time interviewer administered survey (collecting information on demographics, health service utilization, self-reported HIV and HCV testing and recent drug use) and consented to have specific laboratory, treatment records and health-related information accessed through data linkages using their names, date of birth and/or personal health card numbers. Participants were followed retrospectively and prospectively through health-related database linkages. Study participants received CDN$10 to complete the survey. The University of British Columbia/Providence Health Care Research Ethics Board approved this study.

For the current study, individuals with a history of HCV antibody testing were included. Individuals with spontaneous HCV clearance were subsequently excluded from analyses of HCV treatment uptake. Spontaneous clearance was defined by a positive HCV antibody test

followed by ≥1 negative qualitative HCV RNA test among those who had never received HCV treatment.

Laboratory testing

Linked serologic and RNA testing results for HIV and HCV infections were available from January 1991 to December 2009through database linkages with the British Columbia Centre for Disease Control and the University of British Columbia Virology Department (the two laboratories responsible for all HCV and HIV testing in the province). HCV antibody testing was performed using second- or third-generation enzyme-linked immunosorbent assays including Organon Teknika (UBI) v2.0, v2.1, v4.0 (Organon Teknika, Durham, NC, USA), Ortho Ecl (Ortho, Toronto, ON, Canada) and Abbott AxSYM HCV 3.0 (Abbott Diagnostics, Chicago, IL, USA). HCV RNA testing was performed by the qualitative COBAS AMPLICOR HCV Test v2.0 (limit of detection <50 IU/mL, Roche Diagnostic Systems, Mississauga, ON, Canada).

HCV treatment

HCV treatment prescription data was obtained from the British Columbia Ministry of Health PharmaCare database from January 1998 to March 2010. This database captures all HCV treatment administered through publicly funded sources in the province. HCV treatment uptake was defined by linkage to prescriptions for ribavirin with either interferon or peginterferon alpha-2a or 2b.

Mortality

The underlying causes of mortality from 2003 to 2009 were obtained from the British Columbia Vital Statistics database that captures information on all deaths in the Province.

Statistical analysis

The proportion of HCV antibody-positive individuals with chronic infection receiving HCV treatment between January 1998 and March 2010 was evaluated. Factors associated with HCV treatment uptake were evaluated. Unadjusted analyses were performed using Chi-squared test or Fisher's exact test, as appropriate. Potential factors associated with HCV treatment uptake were determined *a priori* and included age (107, 116), sex (10, 116), ethnicity (10, 107, 116), housing status (107, 277), employment status (107), recent methadone maintenance treatment (107, 153), recent access to needle-exchange programs (154), recent access to nursing care (124, 275), having a regular doctor (107, 124), recent self-reported antidepressant medication (116), recent self-reported injecting (cocaine, heroin, methamphetamine) and non-injecting (crack, cannabis, opioids, methamphetamine and benzodiazepines) drug use (10, 107, 116, 153), recent alcohol use (116), recent poly-drug use (injecting and non-injecting) and HCV/HIV co-infection status (116). Recent drug and alcohol use, access to health services and antidepressant use were defined over the six months prior to study enrolment date. Unstable housing was defined as homeless, staying in a temporary shelter, residing in single room occupancy hotel. Unstable income was defined as not having full- or part-time employment. Recent injecting and non-injecting drug use (in the previous 6 months) were evaluated as any drug use *vs* none. Recent poly-drug use (injecting and non-injecting) was defined as injecting or using more than one type of drug *vs* only one type or none. HCV/HIV co-infection status was determined by a composite of HIV serology (HIV antibody and RNA testing) and HIV antiretroviral medication usage. Following unadjusted analyses, multivariable logistic regression was performed using a backwards elimination approach subject to a likelihood ratio test at each step, beginning with only those factors that were significant at the 0.20 level in unadjusted analyses.

The incidence of HCV treatment uptake from the time of enrolment of the first participant (January 1, 2003) to the end of the last full year of follow-up (December 31, 2009) was also assessed. Incidence of HCV treatment uptake was evaluated using person-years of

observation. Person-years at risk were calculated for each person as the time from date of either (i) January 1, 2003 (date of study recruitment), for individuals who were HCV antibody-positive at this time or; (ii) the date of the first antibody-positive test for individuals with HCV seroconversion. Follow-up was calculated from index date to either the date of HCV treatment initiation or death or December 31, 2009, whichever occurred first. Confidence intervals for incidence rates were calculated using the exact method. The cumulative proportion of individuals who received HCV treatment was calculated between 2003 and 2009. The total number of individuals treated for HCV in each calendar year (and previous years for calendar years after 2003) was divided by the overall number of HCV antibody positive individuals without evidence of spontaneous clearance. Statistically significant differences were assessed at $P<0.05$; *P*-values are two-sided. All analyses were performed using the statistical package Stata v12.0 (College Station, TX, United States).

3.9. Results

A total of 2,913 residents of inner city Vancouver were recruited into the CHASE cohort in 2003 and 2004. HCV antibody testing results were available for 83% (n=2,405) and of the tested, 64% (n=1,533) tested positive.

The characteristics of participants stratified by HCV antibody status are shown in Table 1. Compared to those who were HCV antibody negative (n=872), HCV antibody positive participants were more often female (33% *vs*. 26%, *P*=0.001); reported having a regular doctor (70% *vs*. 62%, *P*<0.001); reported recent (6 months prior to study enrolment) episodes of overdose (10% *vs*. 5%, *P*<0.001) and imprisonment (25% *vs.* 17%, *P*<0.001); reported using mental health services (84% *vs*. 76%, *P*<0.001); reported recent injecting (58% *vs*. 12%, *P*<0.001) and non-injecting drug use (87% *vs.* 68%, *P*<0.001); and were HIV positive (30% *vs*. 4%, *P*<0.001). Compared to those who were HCV antibody negative, HCV antibody positive participants were less educated (16% *vs*. 20%, *P*=0.011); had unstable income (94% *vs.* 91%, *P* <0.001); and had not recently used needle-exchange (31% *vs*. 76%, *P*<0.001), methadone maintenance treatment (63% *vs*. 92%, *P*<0.001) and nursing care (63% *vs*. 68%, *P*=0.009) services. There were no statistically significant differences in age (mean 41.8 *vs*. 42.2, *P*=0.368), Aboriginal ethnicity (33% *vs*. 30%, *P*=0.082), unstable housing (23% *vs*. 24%, *P*=0.795), always or usual access to health care (84% *vs*. 83%, *P*=0.800) and alcohol use (12% *vs*.14%, *P*=0.422)

Among HCV antibody positive individuals (n=1,533), 18% (n=276) demonstrated spontaneous HCV clearance and were excluded from further analyses resulting in an analysis population of 1,257 HCV antibody participants without clearance. Among those with available HCV genotype testing (n=564), 61% were genotype 1 (n=343), 9% were HCV genotype 2 (n=48), 30% were HCV genotype 3 (n=170) and 0.2% had genotype 4 (n=1). Overall, 6% (77 of 1,257) received HCV treatment between January 1998 and March 2010. A further 17% (n=212) died over the follow-up period.

Factors associated with a decreased odds of receiving HCV treatment in unadjusted analyses included Aboriginal ethnicity and recent non-injecting crack cocaine use (Table 2). In adjusted logistic regression analysis (Table 2), Aboriginal ethnicity [adjusted odds ratio (AOR) 0.23, 95% CI, 0.10, 0.51, $P<0.001$] and recent non-injecting crack cocaine use (AOR 0.61, 95% CI 0.37, 0.99, $P = 0.045$) were associated with a decreased odds of receiving HCV treatment, while recent methamphetamine injecting (AOR 0.16; 95% CI 0.02, 1.18, $P = 0.073$) trended towards a lower odds of receiving HCV treatment, but was not statistically significant at the 0.05 significance level.

Between 2003 (enrolment) and 2009, the study population was followed for a median of 7.0 years (range 0.5-7.3), for a total of 7,402 person-years at risk. During this period, 60 individuals initiated HCV treatment. The overall rate of HCV treatment uptake between 2003 and 2009 was 0.81 cases per 100 person-years (95% CI 0.62, 1.04). There was a statistically significant ($P=0.046$) increase in the incidence of HCV treatment uptake from 0.2 (95% CI 0.0, 0.7) per 100 person-years in 2003 to 1.6 (95% CI 0.9, 2.6) per 100 person-years in 2009 (Figure 1). However, there was no statistically significant difference between the incidence of HCV treatment uptake over the 2003-2006 period (0.65, 95% CI 0.42, 0.93 per 100 person-years), compared with the 2007-2009 period (1.04, 95% CI 0.71, 1.47 per 100 person-years) ($P=0.792$).The cumulative proportion of HCV antibody positive individuals without evidence of spontaneous clearance who received HCV treatment increased from 0.9% in 2003 to 5.7% in 2009 (Figure 2).

3.10. Discussion

Based on this large community-based study among people who use drugs, demographic and behavioural factors were associated with impaired access to HCV treatment. While treatment uptake remains low in this population, there has been a modest increase in HCV treatment uptake between 2003 and 2009. However, barriers to care at the patient-, provider- and systems-levels continue to limit the proportions engaged in care for HCV (142, 146). Given the considerable burden of HCV-related morbidity and mortality among an ageing population of people with chronic HCV (146) these results highlight the need for continuing efforts to expand HCV assessment and treatment among people who use drugs.

Between 1998 and March 2010, six percent of individuals received HCV treatment overall. This figure represents a modest increase in HCV treatment uptake compared with previous analyses from the CHASE cohort covering the period 2000 to 2004 that indicated treatment uptake of 1% overall, with only 0.3% receiving treatment per year (10). The low overall HCV treatment uptake in this study is consistent with previous findings among drug users in Australia (328), Canada (10) and United States (110). However, this study is novel and adds to the body of literature in this area, given a scarcity of accurate data on recent trends of HCV treatment uptake among people who use drugs. Although the difference between HCV treatment uptake between 2003-2006 and 2007-2009 was not significant, there was a significant increase in HCV treatment uptake between the years 2003 and 2009. Despite these encouraging results, the small proportion of treated individuals demonstrates the large gap between evidence-based guidelines and clinical practice (197, 198, 329-332).

Aboriginal ethnicity was found to be associated with lower HCV treatment uptake. Minority ethnicity has previously been shown to be associated with impaired access to HCV treatment among individuals of black (116, 126) and Hispanic (126) ethnicities. Given a higher prevalence and incidence of HCV among Aboriginal (334, 335), black (336) and Hispanic (337) people, it is important to develop targeted strategies to address this disparity

in access to HCV treatment. Among Aboriginal people, injecting drug use (334, 338), impaired access to harm reduction and addiction treatment programs (338) and low income and unstable housing (339) are associated with a high prevalence of HCV and HCV/HIV co-infection (340). Subsequently, these socio-economic and clinical factors further contribute to lower HCV treatment uptake in this population. Despite data showing similar treatment outcomes among Aboriginal people as compared to non-Aboriginals (341), Aboriginal people remain greatly under-represented in HCV treatment programs (341). In the Vancouver context this is occurring despite programs that specifically fast-track government approval of medication for HCV treatment. Further efforts to deliver culturally appropriate programs developed by and for the Aboriginal community will be important to expand HCV assessment and treatment and address the burden of disease in this important population.

Crack cocaine and methamphetamine injecting were associated with a lower uptake of HCV treatment. Drug use is a well-documented barrier to accessing HCV treatment (10, 107, 116, 124, 153, 275). This result is not surprising, given the low proportions of active PWID evaluated for HCV treatment (110) and high proportion of practitioners that are only willing to treat PWIDs who are stable on opiate substitution therapy (90%) (154). While HCV treatment among active or recent drug users has been successful in the context of addiction treatment programs (8), more marginalised populations of drug users may not be represented in these settings (277). There is no analogous pharmacological treatment for use of crack cocaine, an increasingly prevalent illicit substance in Canada associated with HCV infection and significant social marginalisation (277, 342). Methamphetamine injecting is also associated with poverty, insecure income and other indicators of social marginalisation (343). These findings highlight variations in the characteristics of populations of drug users, illustrating the complex social barriers to accessing HCV care.

In addition to patient-level barriers to HCV treatment uptake that were identified in this study, it is possible that other unmeasured barriers at the provider and system levels further

contribute to low HCV treatment uptake. At the provider level, many physicians are unwilling to treat PWID and many addiction physicians do not consider HCV treatment as a part of their “core” business. Further, patient-provider relationship has an important influence on whether people with HCV infection discuss HCV and treatment options with their physicians (142, 143). The majority of participants in this study (84%) has usual or always access to a doctor. However, in adjusted analysis this factor was not associated with HCV treatment uptake. At the system level, lack of consensus about screening/treatment guidelines, limited infrastructure for HCV assessment and treatment and limited accessibility of HCV testing, results and treatment contribute to suboptimal HCV treatment uptake (143). In many countries including Canada, antiviral therapy is freely available for people with low income. Therefore it is unlikely that cost of HCV treatment has restricted treatment uptake.

There are a number of limitations to this study. Because the marginalized, hard-to-reach population under study did not allow for randomized sampling, the sample cannot be considered representative (333) as in other studies with similar populations (344). However, the sampling measures used ensured a broad reach and inclusion of participants and provided the highest possible degree of representativeness under real-life circumstances. Participation bias related to illicit activities or status in the study population may also be an issue (333) although this bias is also found in general population surveys (345). Testing for HCV antibodies was not completed on a systematic basis, with assays being ordered as clinically indicated. Missing HCV antibody testing information may have led to an underestimation of the number of HCV antibody-positive individuals, thereby overestimating HCV treatment uptake. It was assumed that no individuals received treatment through private coverage or other settings not covered by our data. We have no reason to believe that this would be occurring among this cohort. Further, socio-demographic and select behavioural risk data were self-reported and only collected at study enrolment. Thus, we were unable to determine the impact of changing behavioural characteristics on HCV treatment uptake. Moreover, self-reported data may be prone to socially desirable

responses. Clinical information was limited through the survey instrument and some participants may have had other contra-indications to treatment that were not collected**.** Finally, while the linked mortality records capture all deaths reported within the province of British Columbia, any deaths that went unreported or occurred in other jurisdictions would lead to an overestimation of person-years of follow-up.

Over the next decade, the HCV therapeutic landscape will change markedly. Future interferon-free regimens should be less toxic, with shortened treatment durations, improved dosing schedules and enhanced cure rates (6). These anticipated developments will simplify HCV management for a broad range of patients, including PWID. However, new therapies will not have a significant impact on lowering the HCV epidemic unless programs for HCV assessment and treatment are expanded. A variety of different models of care have been successful in expanding access to HCV care among PWID including community-based and primary care practices, opiate pharmacotherapy clinics, and treatment in prisons (146, 346). Continued expansion of these programs, with specific consideration to barriers that may limit access to treatment, will be important moving forward.

Our findings underscore the importance of ongoing surveillance of HCV treatment uptake. Over the past decade, in this large cohort of inner city residents with chronic HCV infection, uptake of HCV treatment has been increasing, but only incrementally. Aboriginal ethnicity, crack cocaine use and methamphetamine injecting were associated with lower treatment uptake. A major shift in the public health approach to HCV care and treatment will be required to expand access and reduce the future burden of HCV-related disease among PWID.

3.11. Acknowledgements

All authors revised and approved the final version for publication**.** The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

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3.12. Tables

Table 1. Characteristics of participants among those with HCV antibody testing results in a large, community-based cohort in the inner city of Vancouver (n= 2,405)

	Overall	HCV antibody positive	HCV antibody negative	*P*
	n=2,405	n=1,533	n=872	
Age, mean (±SD)	42.0 (±9.3)	41.8 (±8.4)	42.2 (±10.7)	0.368
Male gender, n (%)[μ]	1,668 (69%)	1,026 (67%)	642 (74%)	0.001
Aboriginal ethnicity, n (%)	767 (32%)	508 (33%)	259 (30%)	0.082
Tertiary education, n (%)*	398 (17%)	230 (16%)	168 (20%)	0.011
Unstable housing, n (%)	561 (23%)	355 (23%)	206 (24%)	0.795
Unstable income, n (%)	2,237 (93%)	1,447 (94%)	790 (91%)	<0.001
Usual or always access to health care, n (%)*	2,004 (84%)	1,283 (84%)	721 (83%)	0.800
Have a regular doctor, n (%)	1,617 (67%)	1,080 (70%)	537 (62%)	<0.001
Methadone maintenance therapy, n (%)[¥]	1,778 (74%)	972 (63%)	806 (92%)	<0.001
Needle-exchange program, n (%)*[¥]	1,111 (48%)	469 (31%)	642 (76%)	<0.001
Nursing care services, n (%)[¥]	1,563 (65%)	967 (63%)	596 (68%)	0.009
Mental health services, n (%)[¥]	1,946 (81%)	1,285 (84%)	661 (76%)	<0.001
Overdose, n (%)[¥]	188 (8%)	148 (10%)	40 (5%)	<0.001
Imprisonment, n (%)[¥]	529 (22%)	385 (25%)	144 (17%)	<0.001
Injecting drug use, n (%)[¥]	1,000 (42%)	894 (58%)	106 (12%)	<0.001
Cocaine[¶]	804 (80%)	726 (81%)	78 (74%)	0.062
Heroin[¶]	578 (58%)	514 (57%)	64 (60%)	0.570
Methamphetamine[¶]	119 (12%)	99 (11%)	20 (19%)	0.019
Poly-drug use (injecting), n (%)	459 (46%)	409 (45%)	50 (47%)	<0.001
Non-injecting drug use, n (%)[¥]	1,932 (80%)	1,336 (87%)	596 (68%)	<0.001
Crack cocaine[¶]	1,482 (77%)	1,095 (82%)	387 (65%)	<0.001
Marijuana[¶]	1,203 (62%)	779 (58%)	424 (71%)	<0.001
Methadone[¶]	222 (11%)	209 (16%)	13 (2%)	<0.001
Benzodiazepine[¶]	156 (8%)	133 (10%)	23 (4%)	<0.001
Heroin[¶]	138 (7%)	92 (7%)	46 (8%)	0.512
Methamphetamine[¶]	117 (6%)	62 (5%)	55 (9%)	<0.001
Poly-drug use (non-injecting), n (%)	511 (26%)	417 (31%)	94 (16%)	<0.001
Daily alcohol use, n (%)[¥]	308 (13%)	190 (12%)	118 (14%)	0.422
HIV antibody positive, n (%)	501 (21%)	465 (30%)	36 (4%)	<0.001

[μ]among males and females only, *among participants with available data, [¥] self-reported, in the six months prior to study enrolment, [¶] among participants who self-reported injecting and non-injecting drug use, respectively

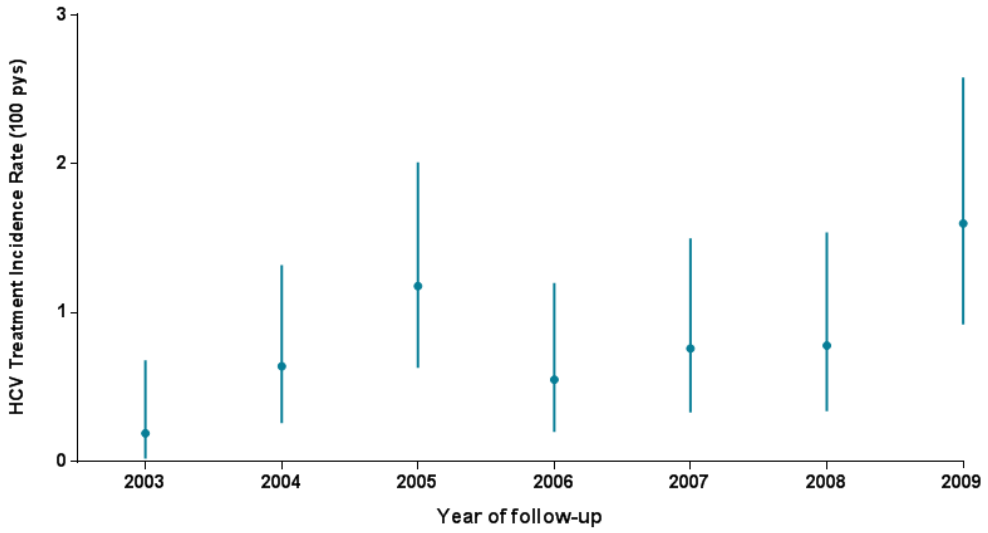
Table 2. Characteristics associated with HCV treatment uptake in a large, community-based cohort in the inner city of Vancouver (n=1,257)

Characteristic	Treated for HCV*	OR	95% CI	*P*	*P*-overall	AOR[¶]	95% CI	*P*
Age								
39-45 (vs. 19-38), n (%)	29 (7%)	1.24	0.71-2.15	0.446	-	-	-	-
46-79 (vs. 19-38), n (%)	23 (6%)	0.94	0.53-1.69	0.851	0.600	-	-	-
Female sex (vs. male), n (%)	16 (4%)	0.63	0.36-1.11	0.113	-	-	-	-
Aboriginal ethnicity (vs. non-Aboriginal), n (%)	8 (2%)	0.26	0.12-0.55	<0.001	-	0.23	0.10-0.51	<0.001
Tertiary education (vs. sub-tertiary), n (%)	16 (8%)	1.41	0.80-2.51	0.236	-	-	-	-
Unstable housing (vs. stable), n (%)	21 (7%)	1.18	0.70-1.99	0.525	-	-	-	-
Unstable income (vs. stable), n (%)	72 (6%)	0.84	0.33-2.15	0.715	-	-	-	-
Usual or always access to health care (vs. sometimes or rare)[¥], n (%)	66 (6%)	1.31	0.66-2.59	0.441	-	-	-	-
Have regular doctor (vs. no regular), n (%)	61 (7%)	1.66	0.94-2.92	0.078	-	-	-	-
Methadone maintenance therapy (vs. no use of this service)[¥], n (%)	45 (6%)	0.83	0.52-1.33	0.445	-	-	-	-
Needle-exchange program (vs. no use of this service)[¥], n (%)	29 (8%)	1.44	0.89-2.33	0.132	-	-	-	-
Nursing care services (vs. no use of this service)[¥], n (%)	54 (7%)	1.37	0.83-2.26	0.218	-	-	-	-
Mental health services (vs. no use of this service)[¥], n (%)	63 (6%)	0.90	0.49-1.64	0.735	-	-	-	-
Injecting cocaine use (vs. no injecting or injecting other)[¥], n (%)	32 (5%)	0.72	0.45-1.15	0.165	-	-	-	-
Injecting heroin use (vs. no injecting or injecting other)[¥], n (%)	30 (7%)	1.21	0.75-1.95	0.426	-	-	-	-
Injecting methamphetamine use (vs. no injecting or injecting other)[¥], n (%)	2 (2%)	0.36	0.09-1.48	0.156	-	0.16	0.02-1.18	0.073
Non-injecting crack cocaine use (vs. no drug use or using other)[¥], n (%)	45 (5%)	0.55	0.34-0.88	0.012	-	0.61	0.37-0.99	0.045
Non-injecting methadone use (vs. no drug use or using other)[¥], n (%)	14 (8%)	1.40	0.76-2.55	0.277	-	-	-	-
Non-injecting heroin use (vs. no drug use or using other)[¥], n (%)	2 (3%)	0.39	0.09-1.63	0.198	-	-	-	-
Non-injecting methamphetamine use (vs. no drug use or using other)[¥], n (%)	3 (6%)	1.00	0.30-3.29	0.999	-	-	-	-
Daily alcohol use (vs. no alcohol use or not daily)[¥], n (%)	4 (3%)	0.41	0.15-1.13	0.085	-	-	-	-
HIV antibody positive (vs. antibody negative), n (%)	21 (5%)	0.81	0.49-1.36	0.436	-	-	-	-

*n=77, [¶]adjusted odds ratio from the multivariable analysis, [¥]self-reported, over the six months prior to study enrolment

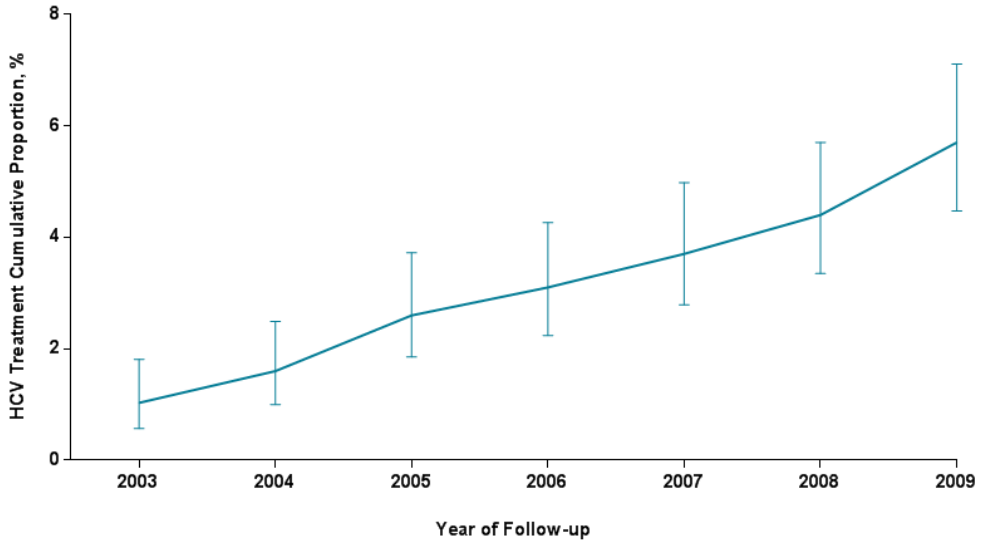
3.13. Figures

Figure 1. Incidence rate of HCV treatment in a large, community-based cohort in the inner city of Vancouver (*n*= 1,257), bars represent 95% confidence intervals



								Total
HCV treatment, n	2	7	13	6	8	8	16	60
Follow-up (pys)	1054	1087	1104	1087	1053	1024	993	7402
Incidence of treatment uptake (100 pys)	0.19	0.64	1.18	0.55	0.76	0.78	1.61	0.81
95% CI	0.02 - 0.68	0.26 - 1.32	0.63 - 2.01	0.20 - 1.20	0.33 - 1.49	0.34 - 1.53	0.92 - 2.60	0.62 - 1.04

Figure 2. Cumulative proportion of HCV treatment in a large, community-based cohort in the inner city of Vancouver (n= 1,257), bars represent 95% confidence intervals



HCV treatment, %	1.0	1.6	2.6	3.1	3.7	4.4	5.7
95% CI	0.6 - 1.8	1.0 - 2.5	1.9 - 3.7	2.2 - 4.3	2.8 – 5.0	3.4 - 5.7	4.5 - 7.1

Chapter 4

Factors associated with HCV assessment and treatment uptake among PWID

4.1. Chapter Introduction

The traditional management of HCV infection via referral to secondary or tertiary healthcare centres has not been successful in expanding HCV care services among PWID, resulting in low HCV assessment and treatment uptake in this population. However, the implementation of different integrated models across various settings has been effective at addressing barriers to care to enhance HCV assessment and treatment among PWID. Integration of HCV care within existing infrastructures for addiction care in the ETHOS study was successful in increasing the number of PWID assessed and treated for HCV infection. Future strategies should be focused on educating patients and providers about HCV and HCV treatment and developing culturally appropriate care services that are adapted for the needs of PWID and other marginalised populations. The manuscript has been published in Clinical Infectious Diseases:

Publication III

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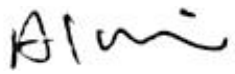
4.2. Declaration

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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4.3. Co-authorship Acknowledgemnet

In the case of Chapter Four, the nature and extent of my contribution to the work was the following:

Name	Contribution (%)	Nature of contribution
Maryam Alavi	50	Conducted data analysis and led the development, writing and critical revisions of the manuscript.
Jason Grebely	15	Supervised data analysis and contributed to data interpretation. Contributed to writing and critical revision of the manuscript.
Michelle Micallef	8	Coordinated implementation of the study and data collection. Contributed to writing and revision of the manuscript.
Adrian Dunlop	2	Contributed to study design, implementation of the study and data collection.
Annie Balcomb	2	Contributed to study design, implementation of the study and data collection.
Carolyn Day	2	Contributed to study design, implementation of the study and data collection.
Carla Treloar	2	Contributed to study design, implementation of the study and data collection.
Nicky Bath	2	Contributed to study design, implementation of the study and data collection.
Paul Haber	2	Contributed to study design, implementation of the study and data collection.
Gregory Dore	15	Contributed to study design, implementation and interpretation of findings and writing and critical revision of the manuscript.

4.4. Assessment and treatment of hepatitis C virus infection among people who inject drugs in the opioid substitution setting: the ETHOS study

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Running title: Assessment and treatment of HCV among PWID

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4.5. Abbreviations

HCV, hepatitis C virus; PWID, people who inject drugs; OST, opioid substitution therapy; ETHOS, Enhancing Treatment for Hepatitis C Opioid Substitution Settings; NSW, New South Wales; DASS; depression, anxiety and stress scale; AUDIT-C, Alcohol Use Disorders Identification Test-Consumption; AOR, adjusted odds ratio.

4.6. Abstract

Background: Access to hepatitis C virus (HCV) treatment remains extremely limited among people who inject drugs (PWID). HCV assessment and treatment was evaluated through an innovative model for the provision of HCV care among PWID with chronic HCV infection. **Methods:** Enhancing Treatment for Hepatitis C in Opioid Substitution Settings (ETHOS) was a prospective observational cohort. Recruitment was through five opioid substitution treatment (OST) clinics and three community health centres in NSW, Australia. **Results:** Among 387 enrolled participants, mean age was 41 years, 71% were male and 15% of Aboriginal ethnicity. Specialist assessment was undertaken in 191 (49%), and 84 (22%) participants commenced interferon-based treatment. In adjusted analysis, HCV specialist assessment was associated with non-Aboriginal ethnicity [adjusted odds ratio (AOR) 4.02, 95% CI 2.05, 7.90], no recent benzodiazepine use (AOR 2.06, 95% CI 1.31, 3.24), and non-1 HCV genotype (AOR 2.13, 95% CI 1.32, 3.43). In adjusted analysis, HCV treatment was associated with non-Aboriginal ethnicity (AOR 4.59, 95% CI 1.49, 14.12), living with the support of family and/or friends (AOR 2.15, 95% CI 1.25, 3.71), never receiving OST (AOR 4.40, 95% CI 2.27,8.54), no recent methamphetamine use (AOR 2.26, 95% CI 1.12, 4.57) and non-1 HCV genotype (AOR 3.07, 95% CI 1.67,5.64). **Conclusion:** HCV treatment uptake was relatively high among this highly marginalised population of PWID. Potentially modifiable factors associated with treatment include drug use and social support.

Keywords: PWID; integrated care; HCV; opioid substitution; drug users

4.7. Introduction

Injecting drug use is the major risk factor driving the hepatitis C virus (HCV) epidemic in most developed countries (347). Chronic HCV infection is associated with excess risk of morbidity and mortality (5). Antiviral therapy is associated with reduction in HCV disease burden (5) and is effective among people who inject drugs (PWID) (8). The broadened inclusion of PWID in HCV treatment programs has been supported by international guidelines (197). However, the traditional management of HCV infection via referral to secondary or tertiary healthcare centres has not been successful in expanding HCV care services among PWID, resulting in low HCV assessment and treatment uptake in this population (10).

HCV treatment among PWID presents multiple challenges due to barriers of care at the patient-, provider- and systems-levels (5). However, the implementation of different integrated models across various settings has been effective at addressing barriers to care to enhance HCV assessment and treatment among PWID (273, 284, 287). A multidisciplinary approach has been the foundation of successful integrated models (273), including close collaboration between clinicians, nursing staff and other support services for delivery of HCV care (273). Opioid substitution treatment (OST) clinics and community health centres offer an opportunity for integration of HCV care within existing infrastructures for addiction care and such models have been demonstrated to increase HCV assessment and treatment (257, 283, 287). However, the majority of studies in the literature have consisted of small participant numbers, are often limited to one centre and rely on retrospective data collection. There is a need for larger, multi-centre and prospective studies to evaluate the effectiveness of HCV treatment models for enhancing HCV assessment and treatment uptake among PWID.

The Enhancing Treatment for Hepatitis C Opioid Substitution Settings (ETHOS) recruited participants between 2009 and 2012 within a network of eight clinics in New South Wales

(NSW), Australia. The aim of this study was to evaluate HCV specialist assessment, treatment uptake and associated factors among people with chronic HCV infection and a history of injecting drug use.

4.8. Methods

Study population and design

The ETHOS study is a prospective observational cohort, designed to evaluate an innovative model for the provision of HCV assessment and treatment among people with a history of injecting drug use in NSW, Australia. The core components of the ETHOS model include the provision of on-site HCV nursing and physician assessment and treatment in clinics with existing infrastructure for addiction care (the majority of services had limited previous experience in providing HCV care). Study recruitment was performed through a collaborative network of eight clinics (five OST clinics and three community health centres) undertaking HCV assessment, treatment and monitoring among people with a history of injecting drug use.

Inclusion criteria included age ≥18 years, a history of injecting drug use and chronic HCV infection (HCV antibody and RNA positive). Exclusion criteria included acute HCV infection, negative or unknown HCV antibody status and current HCV treatment.

People attending one of the study sites who satisfied these inclusion and exclusion study criteria were invited to participate in ETHOS and receive HCV assessment by a nurse. Study recruitment occurred between February 2009 and December 2012 (close of study enrolment). Ongoing follow-up is planned through mid-2014. All study participants provided written informed consent and were reimbursed for their time with a $20 voucher (or gift card) at the time of each study visits. The study was approved by the St. Vincent's Hospital (Sydney) Human Research Ethics Committee and the Aboriginal Health & Medical Research Council Ethics Committee.

Study sites

Recruitment was performed through a network of nine clinics in NSW, Australia (six OST clinics and three community health centres); including one rural, one regional and seven

urban clinics. One of the clinics (Gateway clinic) did not have available enrolment data and was excluded from analyses (Supplementary Figure 1 and Supplementary Table 1).

At study enrolment, participants were assessed for HCV infection by a clinical nurse or general practitioner. HCV nursing services were available at seven of eight clinics, with one clinic only providing general practitioner services (Aboriginal Medical Service Western Sydney). Following assessment by a nurse, all participants were considered for referral to a specialist (including Infectious Diseases Specialist, Hepatologist, Gastroenterologist or a general practitioner with HCV training and prescribing rights) for HCV assessment. HCV specialist services occurred on-site at five clinics, on-site/off-site at two clinics and off-site at one clinic. Two clinics offered HCV peer-support services (see Supplementary Table 1).

Data collection

All patients enrolled in the study were recommended to return for six-monthly follow-up. At enrolment and each six-monthly visit, forms were completed comprising of a practitioner-administered questionnaire, standard clinical assessment and structured case note review. The practitioner-administered questionnaires included demographics, injecting behaviours, addiction treatment, evaluation of social functioning and mental health and history of HCV treatment. The clinical assessment and case note review collected information on HCV testing, assessment for HCV treatment and medical and psychiatric history.

Study assessments

HCV treatment willingness, future treatment plans, specialist assessment and treatment uptake were assessed among all participants. Participants who were referred to a specialist and attended their appointment were considered assessed for HCV treatment. Participants with a defined date of HCV treatment initiation were considered treated.

Statistical analysis

Factors hypothesized to be associated with HCV specialist assessment and treatment were assessed. These were determined *a priori* and included age (107, 116), sex (10, 116), ethnicity (10, 107, 116), education level (115), housing status (107), current employment status (124), living alone (124), ever and/or recent imprisonment (348), alcohol consumption (126, 153), ever and/or current enrolment in OST programs (107, 153), mental health parameters (116, 126), social functioning (107), drug use (benzodiazepines, methamphetamine) and injecting drug use (benzodiazepines, cocaine, heroin, methadone, methamphetamine, morphine) (10, 107, 116, 153) and HCV genotype (116, 124).

Unadjusted analyses were performed using Chi-squared test or Fisher's exact test, as appropriate.

Mental health was evaluated by the Depression, Anxiety and Stress Scale (DASS-21), a 21 item self-administered survey assessing the severity of depression, anxiety and stress (349). Social functioning was evaluated by the shortened scale from the Opiate Treatment Index, addressing employment, residential stability, and inter-personal conflict as well as social support (higher scores indicate lower social functioning- measured over the previous three months) (350). Housing status, recent imprisonment and recent drug use behaviour were defined over the six months prior to study enrolment. Alcohol consumption was evaluated by AUDIT-Consumption (AUDIT-C, scores higher than three and four indicate high-risk consumption among women and men, respectively) (351).

Following unadjusted analyses, multivariable logistic regression was performed, considering factors significant at the 0.20 level in unadjusted analyses, excluding mental health parameters and social functioning. Model selection was performed according to a stepwise backwards elimination, subject to a likelihood ratio test. For all analyses, statistically

significant differences were assessed at $p<0.05$; *P*-values were two-sided. All analyses were performed using the statistical package Stata v12.0 (College Station, TX, United States).

4.9. Results

Study Participants

Between 2009 and 2012, 387 participants were recruited into the ETHOS study (Figure 1). Mean age was 41 years, 71% (n=275) were male, 15% (n=59) were of Aboriginal ethnicity and 64% (n=248) had recently used illicit drugs (Table 1). The majority were enrolled through OST clinics (72%, n=277) and 79% (n=307) were currently receiving OST. Compared to participants who had never received OST, those currently receiving OST were younger, had less full/part-time employment, had poorer social functioning, higher proportions of imprisonment, drug use and injecting drug use (see Supplementary Table 2).

HCV treatment willingness

Although the majority of enrolled participants (86%, 331 of 387) were definitely or somewhat willing to receive treatment, 59% (213 of 387) had never sought HCV treatment previously. The most common reasons for not having sought HCV treatment were lack of knowledge about HCV (23%, n=49), concerns about treatment side-effects (17%, n=36) and asymptomatic disease (14%, n=31).

When participants were asked whether they planned to initiate HCV treatment in the future, 74% (n=282) indicated they had plans to do so in the next 12 months, 13% (n=51) in the next 1-2 years and 8% (n=31) in the next 2-5 years. For those not planning to initiate HCV treatment over the next 12 months (n=101), the most common reasons were concerns about treatment side effects (26%, n=26), other medical priorities (14%, n=14), asymptomatic disease (9%, n=9) and lack of knowledge about HCV infection (8%, n=8).

HCV specialist assessment and treatment following nurse assessment

Among 387 participants enrolled and assessed by a clinic nurse or a general practitioner, 61% (n=236) were referred to see an HCV specialist. Eighty-one percent (n=191) of those referred to a specialist attended their specialist appointment (49% of enrolled participants,

Figure 1). Following HCV specialist assessment, HCV treatment was recommended and commenced by 22% (n=84) of the overall study population (44% of those who attended a specialist appointment, Figure 1). The median time between study enrolment and HCV treatment initiation was 0.2 years (range 0.0-2.0).

Factors associated with HCV specialist assessment

In unadjusted analysis, HCV specialist assessment was associated with older age, non-Aboriginal ethnicity, absence of moderate/extremely severe depression, better social functioning, no recent drug use, no recent injecting drug use, no recent benzodiazepine use, no recent methamphetamine use and non-1 HCV genotype. There were no differences with respect to other factors assessed (Table 2, Supplementary Table 3). In adjusted logistic regression analysis, non-Aboriginal ethnicity [adjusted odds ratio (AOR) 4.02, 95% CI 2.05, 7.90], no recent benzodiazepine use (AOR 2.06, 95% CI 1.31, 3.24), and non-1 HCV genotype (AOR 2.13, 95% CI 1.32, 3.43) were associated with HCV specialist assessment (Table 2).

Factors associated with HCV treatment

In unadjusted analysis, HCV treatment uptake was associated with older age, living with the support of family and/or friends, full- and/or part-time employment, absence of moderate/extremely severe stress, non-Aboriginal ethnicity, never receiving OST, no recent drug use, no recent injecting drug use, no recent benzodiazepine and methamphetamine use, no recent heroin and methamphetamine injecting use and non-1 HCV genotype. There were no differences with respect to other factors assessed (Table 3, Supplementary Table 3). In adjusted logistic regression analysis, non-Aboriginal ethnicity (AOR 4.59, 95% CI 1.49, 14.12), living with the support of family and/or friends (AOR 2.15, 95% CI 1.25, 3.71), never receiving OST (AOR 4.40, 95% CI 2.27,8.54), no recent methamphetamine use (AOR 2.26, 95% CI 1.12, 4.57) and non-1 HCV genotype (AOR 3.07, 95% CI 1.67,5.64) were associated with initiation of HCV treatment (Table 3).

4.10. Discussion

In this prospective study of people with chronic HCV infection and a history of injecting drug use assessed for HCV infection within existing OST clinics and community health centres in NSW, Australia, HCV specialist assessment and treatment were relatively high. Factors independently associated with HCV specialist assessment included non-Aboriginal ethnicity, no recent benzodiazepine use and non-1 HCV genotype. Factors independently associated with HCV treatment included non-Aboriginal ethnicity, living with the support of family and/or friends, never receiving OST, no recent methamphetamine use and non-1 HCV genotype. Participants who had never sought HCV treatment described lack of HCV-related knowledge as the major reason for not having ever sought treatment. These findings highlight the need for delivery of HCV care services in settings that are adapted for the needs of PWID.

More than half of participants had never sought treatment before, describing lack of HCV-related knowledge as the main reason for not seeking HCV treatment. This is not surprising, given that previous findings have shown an association between lack of HCV-related knowledge and no specialist assessment and treatment uptake (107). However, the majority of participants were willing to receive antiviral therapy in future and had plans to initiate treatment over the next 12 months. These proportions were higher than that observed in another study among OST clients using similar measures to evaluate willingness to receive therapy and plans to undergo treatment in near future (115). Following HCV assessment, those who were not planning to initiate HCV treatment over the next 12 months described concerns about treatment side effects as the major reason for their decision. Given the development of new therapeutic regimens with improved tolerability, these findings highlight the importance of continually educating and delivering information to achieve better health outcomes among people with HCV infection.

The majority of participants were referred to an HCV specialist following practitioner assessment and almost half (49%) were assessed by an HCV specialist, higher than levels

of assessment (14-21%) previously reported from drug-user cohorts (110, 111). Treatment uptake was 22%, which is higher than treatment uptake observed among drug-user cohorts in the community (1-6%) (10, 110, 111, 352). Treatment uptake in the ETHOS study is consistent with that observed in tertiary-based clinics (15-42%) (105, 107, 153) and community-based integrated models (22-52%) (123, 257, 283, 287). The proportions of HCV specialist assessment and treatment in ETHOS are encouraging, particularly as many non-treated participants plan to initiate HCV treatment over the next 12 months. Ongoing follow-up will assess HCV treatment outcomes, further uptake of HCV treatment, including the relationship between willingness to be treated and treatment uptake.

In adjusted analysis, several demographic, behavioural, and clinical factors were independently associated with HCV specialist assessment and treatment. Aboriginal participants were less likely to have HCV specialist assessment and treatment. Minority ethnicity has been shown to be associated with lower HCV treatment uptake (124, 126). Compared to the non-Aboriginal Australians, Aboriginal people have a higher prevalence of risk factors for acquisition of HCV infection, including high rates of imprisonment and injecting drug use (353). Despite similar access to HCV testing between the two populations (353), the socio-demographic and broader structural factors that put Aboriginal people at higher risk of HCV acquisition, may further contribute to low HCV specialist assessment and treatment in this population.

Living alone was found to be associated with no HCV treatment uptake. This is not surprising, given that living without the support of family and/or friends might be an indicator of poorer social support. It has been suggested that people with greater social support might be more readily equipped to engage with HCV treatment, hence more likely to be assessed for treatment 12 and to initiate therapy.

Benzodiazepine and methamphetamine use were found to be associated with no HCV specialist assessment and treatment, respectively. Benzodiazepine use is prevalent among people maintained on opioid agonists (354). Compared to opioid users, opioid and benzodiazepine users are more likely to use additional drugs, to inject more frequently and have higher rates of psychiatric co-morbidities including self-harm ideation (354). Frequent crystal methamphetamine use among regular drug users has been shown to be associated with earlier initiation to injecting, greater risk-taking injecting behaviour, psychotic symptoms and dependence (355). Compared to people who inject heroin or other types of drugs, methamphetamine injectors are less likely to engage in drug treatment and more likely to have lower levels of education and social functioning (356).

The majority of participants in ETHOS were currently receiving OST. However, current OST was associated with lower rates of HCV treatment. Eligibility criteria only required a history of injecting drug use and compared to participants currently receiving OST, those with no history of OST would appear to be less drug dependent (recent injecting drug use 19% vs. 56%, respectively) and less marginalised. Current drug use has been identified as a predictor of treatment deferral (153) and no treatment uptake (10, 105, 107, 110, 126). Likewise, previous findings have demonstrated receiving OST is associated with lower treatment deferral and treatment uptake (10, 153). Although OST is associated with a reduction in injecting risk behaviour and improved social functioning among individuals with drug dependence, there clearly remain socio-demographic characteristics that make current HCV treatment problematic for many in this population. Continuing attention to barriers at the provider and system levels (such as the availability of support for patients with complex needs) is required to enhance management of hepatitis C and move towards uptake of treatment in the longer term.

HCV genotype 1 was found to be associated with lower rates of HCV specialist assessment and treatment than other genotypes (predominantly genotypes 2/3). HCV genotype 1 is

associated with lower sustained virological response among patients receiving interferon-based therapy (8). During the study period, there was very limited access to HCV genotype 1 triple therapy (including telaprevir or boceprevir), therefore ongoing evaluation of the impact of HCV genotype on treatment uptake will be of great interest as direct-acting antiviral (DAA) therapy becomes more broadly available (telaprevir and boceprevir were approved for Australian government subsidization from April 2013).

There are a number of limitations in this study. Given the recruitment methodology and that all participants were assessed by a nurse or general practitioner at enrolment, the study population may represent a group that is more engaged in health services, leading to an overestimation of proportions receiving specialist assessment and treatment. Further, the low numbers of HCV specialist assessment and treatment among Aboriginal participants might be due to the external HCV specialist referral in the Aboriginal Medical Service Western Sydney clinic that recruited the majority of Aboriginal participants. Finally, these findings may not be generalisable to other populations of people with HCV infection, particularly those less engaged in health services.

A variety of clinical models using multidisciplinary approaches have been successful in delivering HCV care services to drug-using cohorts (273). Given that many clinics in the current study had limited prior expertise with specialised HCV care, provision of HCV nursing and specialist support within the existing infrastructure for addiction treatment has produced encouraging results. Expanding specialised care and expertise from secondary or tertiary clinics to primary care centres has been highly successful in accessing marginalised populations and increasing the numbers effectively treated for HCV infection (284). While new interferon-free DAA therapy regimens will facilitate the removal of many of the barriers to HCV assessment and treatment, developing evidence-based strategies will be crucial to enhance delivery of HCV care services. Future strategies should be focused on educating

patients and providers about HCV and HCV treatment and developing culturally appropriate care services that are adapted for the needs of PWID and other marginalised populations.

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Protocol Steering Committee – Paul Haber (Chair, University of Sydney), Nicky Bath (New South Wales Users and AIDS Association), Carolyn Day (University of Sydney), Gregory Dore (University of New South Wales), Jason Grebely (University of New South Wales), Claire Honey (NSW Health Department), Murray Krahn (University of Toronto), Mike Lodge (NSW Health Department), Stuart Loveday (Hepatitis C Council of New South Wales, Inc.), Michelle Micallef (University of New South Wales), Hla-Hla Thein (University of Toronto), Carla Treloar (University of New South Wales).

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Site Data Managers – Fiona D'Aquino (Clinic 96), Anna Doab (Kirketon Road Centre), Lucia Evangelista (Clinic 36 and Regent House), Sussan Hazelwood (Newcastle Pharmacotherapy Service), Jamieleigh Petersen and Emma Pollard (Gateway Clinic), Alison Sevehon (Rankin Court) and Julieanne Wrightson (Centre for Addiction Medicine)

Disclaimer

The findings and views expressed in this publication are those of the authors and do not represent the position of the Australian Government.

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Potential Conflicts of Interest

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

4.12. Tables

Table 1. Characteristics of participants with chronic HCV infection, a history of injecting drug use and assessed by a nurse in the ETHOS cohort (n=387)

Characteristic	Overall (n=387)
Age, mean (±SD)	41 (±9)
Male gender, n (%) [μ]	275 (71%)
Aboriginal ethnicity, n (%)	59 (15%)
Finished high school or higher education, n (%)[*]	74 (19%)
Living with spouse or other relatives/friends, n (%)[*]	193 (50%)
Owned or rented housing, n (%)[*]	313 (81%)
Full- or part-time employment, n (%)[*]	36 (9%)
Current opioid substitution treatment, n (%)	307 (79%)
Imprisonment, n (%) [¥]	36 (9%)
Drug use (injecting and non-injecting), n (%) [¥]	248 (64%)
Benzodiazepine [¶]	137 (55%)
Methamphetamine [¶]	106 (43%)
Injecting drug use, n (%) [¥]	196 (51%)
Benzodiazepine [¶]	14 (7%)
Cocaine [¶]	27 (14%)
Heroin [¶]	132 (67%)
Methadone [¶]	22 (11%)
Methamphetamine [¶]	96 (49%)
Morphine [¶]	55 (28%)
High risk alcohol consumption, n (%) [α]	
Female	49 (45%)
Male	86 (31%)
Social functioning score, median (range)	4 (0-18)
Mental health parameters, DASS-21, n (%)[*]	
Depression (normal to mild)	142 (48%)
Depression (moderate to extremely severe)	154 (52%)
Anxiety (normal to mild)	120 (41%)
Anxiety (moderate to extremely severe)	176 (59%)
Stress (normal to mild)	176 (59%)
Stress (moderate to extremely severe)	120 (41%)
HCV genotype, n (%)	
1	148 (38%)
2, 3, 6	161 (41%)
Unknown	78 (20%)

[μ]other/unknown gender is not included, [*]among those with available survey results, [¥]in the six months prior to study enrolment, [¶]denominator is the total number reported using and injecting drug use, respectively, [α] denominator is females and males reported alcohol consumption

Table 2. Unadjusted and adjusted analysis of factors associated with HCV specialist assessment in the ETHOS cohort (n=387)

Characteristic, n	Assessed by a specialist (n=191)	OR (95% CI)	Adjusted OR (95% CI)	*P*
Age				
<35 years	43	1.00	-	-
35-45 years	75	1.38 (0.84, 2.27)	-	-
≥45 years	73	2.17 (1.28, 3.68)	-	-
Ethnicity				
Aboriginal	13	1.00	1.00	
Non-Aboriginal	178	4.20 (2.18, 8.07)	4.02 (2.05, 7.90)	<0.001
OST				
Current	142	1.00	-	-
Previous, not current	14	1.82 (0.76, 4.33)	-	-
Never	35	1.86 (1.04, 3.32)	-	-
Drug use (injecting and non-injecting)[¥]				
Yes	104			
No	87	2.33 (1.52, 3.57)	-	-
Benzodiazepine use (injecting and non-injecting)[¥]				
Yes	55	1.00	1.00	-
No	136	1.80 (1.18, 2.74)	2.06 (1.31, 3.24)	0.002
Methamphetamine use (injecting and non-injecting)[¥]				
Yes	43	1.00	-	-
No	148	1.62 (1.02, 2.54)	-	-
Injecting drug use[¥]				
Yes	82	1.00	-	-
No	109	1.86 (1.25, 2.79)	-	-
HCV genotype				
Genotype 1	65	1.00	1.00	-
Genotypes 2, 3, 6	101	2.15 (1.36, 3.39)	2.13 (1.32, 3.43)	0.002
Unknown[Σ]	25	0.59 (0.33, 1.05)	0.63 (0.34, 1.14)	0.125

[¥]in the six months prior to study enrolment, [Σ] Wald test *P*-overall is <0.001

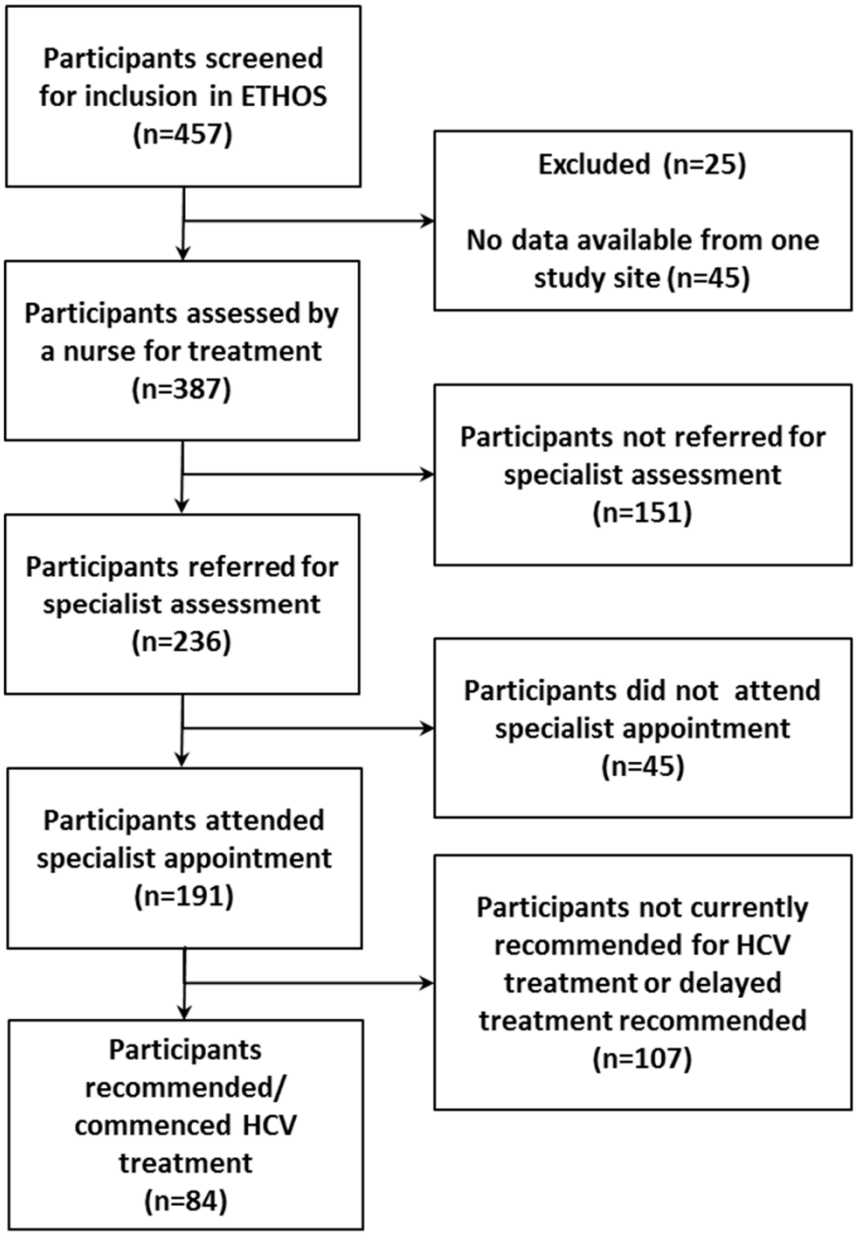
Table 3. Unadjusted and adjusted analysis of factors associated with HCV treatment in the ETHOS cohort (n=387)

Characteristic, n	Treated (n=84)	OR (95% CI)	Adjusted OR (95% CI)	*P*
Age				
<35 years	15	1.00	-	-
35-45 years	38	1.98 (1.02, 3.81)		
≥45 years	31	2.07 (1.05, 4.08)	-	-
Ethnicity				
Aboriginal	4	1.00	1.00	-
Non-Aboriginal	80	4.43 (1.56, 12.62)	4.59 (1.49, 14.12)	0.008
Living status				
Alone	30	1.00	1.00	-
With spouse or other relatives/friends	54	2.12 (1.29, 3.50)	2.15 (1.25, 3.71)	0.006
Source of income				
Casual, pension, temporary benefit, other sources	70	1.00	-	-
Full-/part-time	14	2.55 (1.24, 5.25)	-	-
OST				
Current	51	1.00	1.00	-
Previous, not current	6	1.78 (0.67, 4.73)	1.83 (0.64, 5.27)	0.262
Never [Σ]	27	4.54 (2.49, 8.27)	4.40 (2.27, 8.54)	<0.001
Drug use (injecting and non-injecting)[¥]				
Yes	36	1.00	-	-
No	48	3.12 (1.90, 5.13)	-	-
Benzodiazepine use (injecting and non-injecting)[¥]				
Yes	19	1.00	-	-
No	65	2.20 (1.26, 3.85)	-	-
Methamphetamine use (injecting and non-injecting)[¥]				
Yes	12	1.00	1.00	-
No	72	2.69 (1.39, 5.18)	2.26 (1.12, 4.57)	0.023
Injecting drug use[¥]				
Yes	28	1.00	-	-
No	56	2.50 (1.51, 4.16)	-	-
Heroin injecting[¥]				
Yes	19	1.00	-	-
No	65	2.02 (1.15, 3.55)	-	-
Methamphetamine injecting[¥]				
Yes	12	1.00	-	-
No	72	2.29 (1.18, 4.44)	-	-
HCV genotype, n				
Genotype 1	21	1.00	1.00	-
Genotypes 2, 3, 6	54	3.05 (1.73, 5.37)	3.07 (1.67, 5.64)	0.001
Unknown[Σ]	9	0.78 (0.34, 1.79)	0.97 (0.40, 2.34)	0.951

[¥]in the six months prior to study enrolment, [Σ] Wald test *P*-overall is <0.001

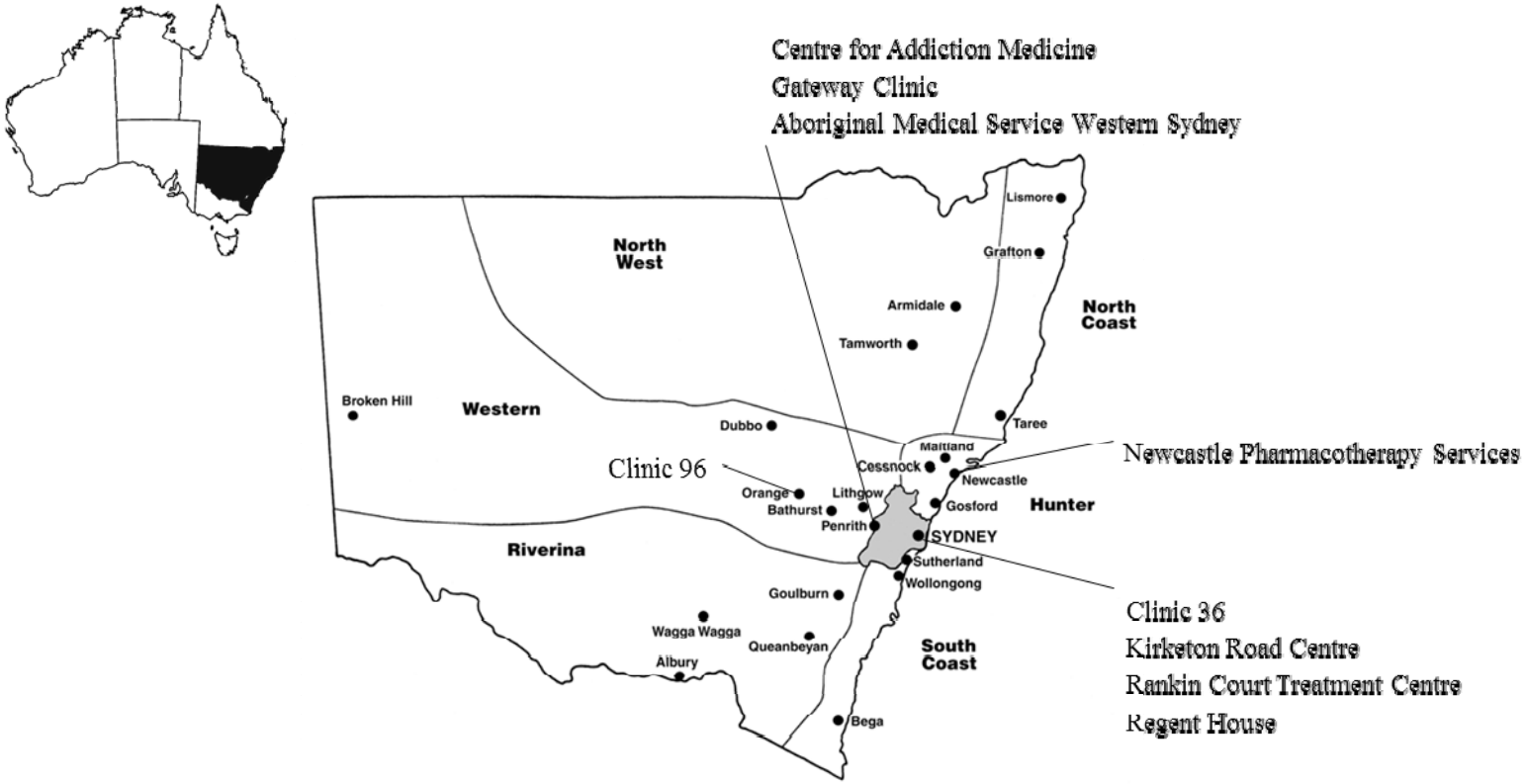
4.13. Figures

Figure 1. HCV specialist assessment and treatment among participants in the ETHOS study



4.14. Supplementary material

Figure 1. Geographic Location of ETHOS Study Sites, NSW, Australia



Supplementary material

Table 1. Clinical Profile of the ETHOS Study Sites, NSW, Australia

					Clinical Services					
Clinic Name	**Location**	**Type**	**Public or Private**	**HCV Service in Same Location as OST**	**HCV Specialist Frequency (hours)**	**HCV Nurse Frequency (hours)**	**Peer Support Frequency (hours)**	**Number enrolled (n)**	**HCV Specialist assessment (n, %)**	**HCV treatment (n, %)**
Aboriginal Medical Service Western Sydney	Mt Druitt[μ]	General Practice	NGO	No	Nil	x2 month (1-2)	Nil	26	3 (12%)	0 (0%)
Centre for Addiction Medicine	Parramatta[μ]	OST	Public	Yes (all clients)	x1 week (4-6)	x1 week (4-6)	Nil	54	37 (69%)	10 (19%)
Clinic 36	Chippendale[μ]	OST	Private	Yes (all clients)	x1 month (2-4)	x1 week (>6)	x1 week (2-4)	49	8 (16%)	1 (2%)
Clinic 96	Orange[*]	Community Health Centre	Public	Yes (some clients)	x3-4 week (2-4)	x3-4 week (2-4)	Nil	73	48 (66%)	35 (48%)
Gateway Clinic	Penrith[μ]	OST	Public	Yes (all clients)	x2 week (2-4)	x2 month (4-6)	Nil	Not available	Not available	Not available
Kirketon Road Centre	Kings Cross[μ]	Integrated Primary Health Care	Public	Yes (all clients)	x1 month (1-2)	x1 week (2-4)	Nil	11	9 (82%)	1 (9%)
Newcastle Pharmacotherapy Services	Newcastle[¶]	OST	Public	Yes (all clients)	x1 week(1-2)	x2 week(8-12)	x2 week (4-6)	77	38 (49%)	16 (21%)
Rankin Court Treatment Centre	Darlinghurst[μ]	OST	Public	Yes (all clients)	x2 month (1-2)	x1 week (2-4)	Nil	59	37 (63%)	13 (22%)
Regent House	Waterloo[μ]	OST	Private	Yes (all clients)	x1 month (2-4)	x1 week (4-6)	x1 week (2-4)	38	11 (29%)	8 (21%)

[μ] Urban, [*]Rural, [¶] Regional

Supplementary material

Table 2. Characteristics of participants with chronic HCV infection and a history of injecting drug use by OST status, ETHOS study, n=387

Characteristics	Never OST n=57	Previous OST n=23	Current OST n=307
Age, mean (±SD)	45±9.8	41±8.9	40±8.5
Male gender, n (%) [μ]	42 (75%)	15 (65%)	218 (71%)
Aboriginal ethnicity, n (%)	8 (14%)	2 (9%)	49 (16%)
Finished high school or higher education, n (%)[*]	13 (23%)	3 (13%)	58 (19%)
Living with spouse or other relatives/friends, n (%)[*]	30 (54%)	10 (43%)	153 (50%)
Owned or rented housing, n (%)[*]	45 (80%)	16 (70%)	252 (82%)
Full- or part-time employment, n (%)[*]	12 (21%)	5 (22%)	19 (6%)
Imprisonment, n (%)[¶]	24 (42%)	18 (78%)	203 (66%)
Drug use (injecting and non-injecting), n (%)[¥]	16 (28%)	16 (70%)	216 (70%)
Injecting drug use, n (%)[¥]	11 (19%)	13 (57%)	172 (56%)
High risk alcohol consumption (male and female), n (%) [α]	25 (44%)	8 (35%)	102 (33%)
Social functioning score, median (range)	2 (0-12)	2 (0-14)	5 (0-18)
Mental health parameters, DASS-21, n (%)[*]			
Depression (moderate to extremely severe)	18 (39%)	10 (48%)	126 (55%)
Anxiety (moderate to extremely severe)	24 (52%)	9 (43%)	143 (62%)
Stress (moderate to extremely severe)	13 (28%)	7 (33%)	100 (44%)
HCV genotype, n (%)			
1	19 (33%)	8 (35%)	121 (39%)
2, 3, 6	30 (53%)	8 (35%)	123 (40%)
Unknown	8 (14%)	7 (30%)	63 (21%)

[μ]other/unknown gender is not included, [*]among those with available survey results, [¶]ever or in the six months prior to study enrolment, [¥]in the six months prior to study enrolment, [α] denominator is females and males reported alcohol consumption

Supplementary material

Table 3. Unadjusted analysis of factors associated with HCV specialist assessment and treatment in the ETHOS cohort (n=387)

Characteristic, n (%)	HCV specialist assessment* n (%)	HCV specialist assessment* OR (95% CI)	HCV treatment* n (%)	HCV treatment* OR (95% CI)
Age				
<35 years	43 (40%)	1.00	15 (14%)	1.00
35-45 years	75 (48%)	1.38 (0.84, 2.27)	38 (25%)	1.98 (1.02, 3.81)
≥45 years	73 (59%)	2.17 (1.28, 3.68)	31 (25%)	2.07 (1.05, 4.08)
Sex[µ]				
Male	145 (53%)	1.00	64 (23%)	1.00
Female sex	46 (42%)	0.65 (0.42, 1.01)	20 (18%)	0.74 (0.42, 1.29)
Ethnicity				
Aboriginal	13 (22%)	1.00	4 (7%)	1.00
Non-Aboriginal	178 (54%)	4.20 (2.18, 8.07)	80 (24%)	4.43 (1.56, 12.62)
Education				
Sub-high school	149 (48%)	1.00	64 (21%)	1.00
Finished high school or up	42 (57%)	1.44 (0.87, 2.41)	20 (27%)	1.44 (0.81, 2.58)
Living status				
Alone	93 (48%)	1.00	30 (16%)	1.00
With spouse or other relatives/friends	98 (51%)	1.12 (0.75, 1.67)	54 (28%)	2.12 (1.29, 3.50)
Accommodation				
Boarding, hostel, shelter, homeless, other housing types	32 (44%)	1.00	16 (22%)	1.00
Owned or rented	159 (51%)	1.36 (0.81, 2.26)	68 (22%)	1.01 (0.54, 1.86)
Employment				
Casual, pension, temporary benefit, other income sources	169 (48%)	1.00	70 (20%)	1.00
Full-/part-time employment	22 (61%)	1.69 (0.84, 3.41)	14 (39%)	2.55 (1.24, 5.25)
OST				
Current	142 (46%)	1.00	51 (17%)	1.00
Previously, not current	14 (61%)	1.82 (0.76, 4.33)	6 (26%)	1.78 (0.67, 4.73)
Never	35 (61%)	1.86 (1.04, 3.32)	27 (47%)	4.54 (2.49, 8.27)
Imprisonment				
Ever or recent[¥]	116 (47%)	1.00	47 (19%)	1.00
Never	75 (53%)	1.25 (0.83, 1.90)	37 (26%)	1.49 (0.91, 2.44)
Drug use (injecting/ non-injecting) [¥]				
Yes	104 (42%)	1.00	36 (14%)	1.00
No	87 (63%)	2.33 (1.52, 3.57)	48 (35%)	3.12 (1.90, 5.13)
Benzodiazepine use (injecting/ non-injecting) [¥]				
Yes	55 (40%)	1.00	19 (14%)	1.00
None/other than benzodiazepine use	136 (54%)	1.80 (1.18, 2.74)	65 (26%)	2.20 (1.26, 3.85)
Methamphetamine use (injecting/ non-injecting) [¥]				
Yes	43 (41%)	1.00	12 (11%)	1.00
None/other than methamphetamine use	148 (52%)	1.62 (1.02, 2.54)	72 (26%)	2.69 (1.39, 5.18)
Injecting drug use[¥]				
Yes	82 (42%)	1.00	28 (14%)	1.00
No	109 (57%)	1.86 (1.25, 2.79)	56 (29%)	2.50 (1.51, 4.16)
Benzodiazepine injecting[¥]				
Yes	5 (36%)	1.00	3 (21%)	1.00
None/other than benzodiazepine injecting	186 (50%)	1.78 (0.59, 5.41)	81 (22%)	1.01 (0.28, 3.72)
Cocaine injecting[¥]				
Yes	9 (33%)	1.00	3 (11%)	1.00
None/other than cocaine injecting	182 (50%)	2.03 (0.89, 4.65)	81 (22%)	2.31 (0.68, 7.88)
Heroin injecting[¥]				
Yes	56 (42%)	1.00	19 (14%)	1.00
None/other than heroin injecting	135 (53%)	1.51 (0.99, 2.31)	65 (25%)	2.02 (1.15, 3.55)
Methadone injecting[¥]				
Yes	12 (39%)	1.00	7 (23%)	1.00
None/other than methadone injecting	179 (50%)	1.59 (0.75, 3.38)	77 (22%)	0.94 (0.39, 2.27)
Methamphetamine injecting[¥]				
Yes	39 (41%)	1.00	12 (13%)	1.00
None/other than methamphetamine injecting	152 (52%)	1.59 (0.99, 2.53)	72 (25%)	2.29 (1.18, 4.44)
Morphine injecting[¥]				
Yes	24 (43%)	1.00	11 (20%)	1.00
None/other than morphine injecting	167 (50%)	1.35 (0.76, 2.39)	73 (22%)	1.15 (0.57, 2.34)
Alcohol consumption				
High risk	63 (46%)	1.00	28 (21%)	1.00
No/low risk	128 (51%)	1.20 (0.79, 1.82)	56 (22%)	1.10 (0.66, 1.84)
Social functioning score				
≥ 4	76 (40%)	1.00	35 (18%)	1.00

<4	115 (58%)	2.08 (1.39, 3.12)	49 (25%)	1.46 (0.89, 2.37)
Symptoms of depression				
Moderate to extremely severe	66 (43%)	1.00	25 (16%)	1.00
Normal to mild	79 (55%)	1.65 (1.04, 2.60)	34 (24%)	1.61 (0.90, 2.86)
Symptoms of anxiety				
Moderate to extremely severe	80 (45%)	1.00	29 (16%)	1.00
Normal to mild	65 (54%)	1.43 (0.90, 2.28)	30 (25%)	1.70 (0.96, 3.02)
Symptoms of stress				
Moderate to extremely severe	57 (48%)	1.00	14 (12%)	1.00
Normal to mild	88 (50%)	1.09 (0.69, 1.74)	45 (25%)	2.58 (1.34, 4.95)
HCV genotype				
Genotype 1	65 (44%)	1.00	21 (14%)	1.00
Genotype 2, 3, 6 (vs. 1)	101 (63%)	2.15 (1.36, 3.39)	54 (34%)	3.05 (1.73, 5.37)
Unknown (vs. 1)	25 (32%)	0.59 (0.33, 1.05)	9 (11%)	0.78 (0.34, 1.79)

*total number assessed by an HCV specialist, n=191, total number treated, n=84, [u]other/unknown gender is not included, [*]in the six months prior to study enrolment

Chapter 5

HCV treatment willingness and subsequent HCV assessment and treatment uptake

5.1. Chapter Introduction

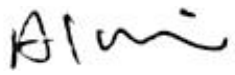
Effective engagement of PWID in HCV care programs is essential in order to enhance HCV assessment and treatment uptake in this population and to lower the future disease burden of HCV infection at the population level. The Enhancing Treatment for Hepatitis C in Opioid Substitution Settings (ETHOS) study has utilised an innovative model for the provision of HCV care among people with chronic HCV infection and a history of injecting drug us. Integration of HCV nursing and specialist support within existing infrastructures for addiction care was a successful model and allowed for evaluation of the impact of high HCV treatment willingness and early treatment intent on subsequent HCV assessment and treatment uptake. Improved engagement of marginalised populations with HCV care services in this study has broadened our understanding of the role of high treatment willingness on subsequent HCV specialist assessment and treatment uptake. While new interferon-free regimes are anticipated to remove many barriers to HCV care services, evidence-based strategies are required to further engage those willing to receive antiviral therapy and develop programs to support those less willing to receive therapy. The manuscript is under review in Journal of Viral Hepatitis:

Publication IV

Alavi M, Micallef M, Dunlop AJ, Balcomb AC, Day CA, Treloar C, Bath N, Haber PS, Dore GJ, Grebely J. Effect of treatment willingness on specialist assessment and treatment uptake for hepatitis C virus infection among people who use drugs: The ETHOS study. Journal of Viral Hepatitis 2014 (Accepted, JVH-00022-2014)

5.2. 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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5.3. Co-authorship Acknowledgemnet

In the case of Chapter Five, the nature and extent of my contribution to the work was the following:

Name	Contribution (%)	Nature of contribution
Maryam Alavi	50	Conducted data analysis and led the development, writing and critical revisions of the manuscript.
Michelle Micallef	8	Coordinated implementation of the study and data collection. Contributed to writing and revision of the manuscript.
Adrian Dunlop	2	Contributed to study design, implementation of the study and data collection.
Annie Balcomb	2	Contributed to study design, implementation of the study and data collection.
Carolyn Day	2	Contributed to study design, implementation of the study and data collection.
Carla Treloar	2	Contributed to study design, implementation of the study and data collection.
Nicky Bath	2	Contributed to study design, implementation of the study and data collection.
Paul Haber	2	Contributed to study design, implementation of the study and data collection.
Gregory Dore	15	Contributed to study design, implementation and interpretation of findings and writing and critical revision of the manuscript.
Jason Grebely	15	Supervised data analysis and contributed to data interpretation. Contributed to writing and critical revision of the manuscript.

5.4. Effect of treatment willingness on specialist assessment and treatment uptake for hepatitis C virus infection among people who use drugs: The ETHOS study

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Running title: effects of HCV treatment willingness on assessment and treatment uptake

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5.5. Abbreviations

HCV, hepatitis C virus; PWID, people who inject drugs, ETHOS, Enhancing Treatment for Hepatitis C in Opioid Substitution Settings; AUDIT-C, Alcohol Use Disorders Identification Test-Consumption; AOR, adjusted odds ratio

5.6. Abstract

Background: HCV treatment uptake is low among people who inject drugs (PWID). We evaluated whether HCV treatment willingness and intent were predictive of subsequent HCV specialist assessment and treatment among PWID with chronic HCV infection. **Methods:** The Enhancing Treatment for Hepatitis C in Opioid Substitution Settings (ETHOS) is a prospective observational cohort. Recruitment occurred between 2009-2012 through six opioid substitution treatment clinics, two community health centres and one Aboriginal community controlled health organisation in Australia. Analyses were performed using logistic regression. **Results:** Among 387 participants (mean age 41 years, 71% male), 70% (n=269) were 'definitely willing' to receive HCV treatment and 73% (n=282) reported plans to initiate therapy 12 months post-enrolment. Overall, 49% (n=191) were assessed by an HCV specialist and 22% (n=84) commenced treatment. Those definitely willing to receive HCV treatment were more likely to be assessed by a specialist (56% vs. 34%, *P*<0.001) and initiate therapy (28% vs. 8%, *P*<0.001), compared to those with lower levels of willingness. Those with early HCV treatment plans were more likely to be assessed by a specialist (57% vs. 28%, *P*<0.001) and initiate therapy (28% vs. 4%, *P*<0.001), compared to those without early plans. In adjusted analyses, HCV treatment willingness independently predicted specialist assessment (AOR 2.17, 95% CI 1.35, 3.51) and treatment uptake (AOR 3.50, 95% CI 1.61, 7.59). In adjusted analysis, having early HCV treatment plans independently predicted specialist assessment (AOR 2.95, 95% CI 1.76, 4.94) and treatment uptake (AOR 6.75, 95% CI 2.34, 19.48). **Conclusion:** HCV treatment willingness was high among this PWID population and predicted HCV specialist assessment and treatment. The development and implementation of strategies for enhanced specialist assessment and treatment should be expanded with an initial focus on people more willing to receive treatment and to increase treatment willingness and intent among those less willing.

Keywords hepatitis C virus; people who inject drugs; treatment willingness; treatment uptake

5.7. Introduction

In most high-income countries, the majority of new and existing cases of hepatitis C virus (HCV) occur among people who inject drugs (PWID) (4). Although HCV treatment is safe and effective among PWID (8, 9, 195), HCV assessment and treatment uptake remain suboptimal (10, 48, 110, 357). As such, the effective engagement of PWID in programs to enhance HCV assessment and treatment is essential in order to lower the future disease burden of HCV infection (5).

Among studies of PWID, 53-86% of people report that they would be willing to receive treatment for HCV infection (112, 115, 162-164, 166). However, despite this high willingness, barriers to HCV treatment at the system, provider and patient levels (142, 143) often contribute to low levels of HCV assessment (14-21%) (82, 110) and treatment (1-6%) (10, 48, 110, 357) among PWID. Further, given that the majority of studies to assess HCV treatment willingness have been cross-sectional, there is a limited understanding about whether HCV treatment willingness actually predicts subsequent assessment and treatment uptake.

The Enhancing Treatment for Hepatitis C in Opioid Substitution Settings (ETHOS) Study is an observational cohort study to evaluate the provision of HCV assessment and treatment among people with a history of injecting drug use attending opioid substitution therapy (OST) and community health clinics in New South Wales, Australia. The aim of this study was to evaluate whether high HCV treatment willingness and early treatment intent were predictive of subsequent HCV assessment and treatment uptake in the ETHOS study.

5.8. Methods

Study population and design

The ETHOS study is a prospective observational cohort. The core components of the ETHOS model include the provision of on-site HCV nursing and physician assessment and treatment in clinics with existing infrastructure for addiction care (the majority of services had limited previous experience in providing HCV care). Study recruitment was performed through a collaborative network of nine clinics (described below) undertaking HCV assessment, treatment and monitoring among people with a history of injecting drug use.

Inclusion criteria included age being ≥18 years, a history of injecting drug use and chronic HCV infection (HCV antibody and RNA positive). Exclusion criteria included acute HCV infection, negative or unknown HCV antibody status and current HCV treatment.

People attending one of the study sites who satisfied these inclusion and exclusion study criteria were invited to participate in ETHOS and receive HCV assessment. Study recruitment occurred between February 2009 and December 2012. Ongoing follow-up is planned through mid-2014. All study participants provided written informed consent and were reimbursed for their time with a $20 voucher (or gift card) at each study visit. The study was approved by local research ethics committees.

Study sites

ETHOS study sites have been fully described (346). Recruitment was performed through a network of nine clinics in NSW, Australia (four public sector OST clinics, two private sector for-profit OST clinics, two community health centres and one Aboriginal community controlled health organisation); including one rural, one regional and seven urban clinics. One of the public sector OST clinics did not have available enrolment data and was excluded from analyses. At study enrolment, participants were assessed for HCV infection by a clinical nurse or general practitioner. HCV nursing services were available at seven of

eight clinics, with one clinic only providing general practitioner services. Following assessment by a nurse or general practitioner, all participants were considered for referral to a specialist (including infectious disease specialist, hepatologist, gastroenterologist, or a general practitioner with HCV training and prescribing rights) for HCV assessment. HCV specialist medical services were provided on-site at five clinics, on-site and off-site at two clinics, and off-site at one clinic. Two clinics offered HCV peer-support services.

Data collection

All patients enrolled in the study were recommended to return for six-monthly follow-up visits. At enrolment and each six-monthly visit, forms were completed comprising of a practitioner-administered questionnaire, standard clinical assessment and structured case note review. The practitioner-administered questionnaire included demographics, drug use behaviours, receipt of OST, social functioning, mental health and history of HCV treatment. The clinical assessment and case note review collected information on HCV testing, assessment for an initiation of HCV treatment and medical and psychiatric history. Participants were withdrawn from the study if they had not attended the HCV clinic for ≥18 months.

Study assessments and end points

All participants were asked the following question about their HCV treatment willingness; "Given that you are hepatitis C positive, how willing would you be in receiving treatment?" HCV treatment willingness was described using a five point Likert scale as follows; definitely unwilling, somewhat unwilling, neither willing or unwilling, somewhat willing and definitely willing. All participants were asked the following question about their HCV treatment intent; "Do you plan to go onto treatment for hepatitis C in the future?" HCV treatment intent was described in five levels as follows; yes, in the next 12 months, yes, in the next 1-2 years, yes, in the next 2-5 years, yes, but not at least for another five years and no, never.

Participants who were referred to a specialist and attended their appointment were considered assessed for HCV treatment. Participants who commenced treatment (i.e. those with a defined date of HCV treatment initiation) were considered as having received treatment.

Statistical analysis

Factors associated with HCV treatment willingness and early treatment intent were evaluated. In unadjusted and adjusted analyses, those definitely willing to receive HCV treatment (high treatment willingness) were compared with other participants (lower levels of treatment willingness). In unadjusted and adjusted analyses, those with intention to initiate HCV treatment over the next 12 months (early treatment intent) were compared with other participants (no early treatment intent).

Factors hypothesised to be associated with high HCV treatment willingness and early treatment intent were assessed. Unadjusted analyses were performed using Chi-square or Fisher's exact test, as appropriate. Potential factors hypothesised to be associated with high HCV treatment willingness and early treatment intent were determined *a priori* based on factors previously shown to be associated with HCV specialist assessment or treatment uptake. These factors included age (107, 112, 116), sex (10, 112, 116), ethnicity (10, 107, 116), education level (115), current employment status (124), living alone (124), housing status (107, 112, 277), ever and/or recent imprisonment (348), alcohol consumption (112, 126, 153), ever and/or current enrolment in OST programs (107, 112, 115, 153, 162, 164), drug use (methamphetamine, benzodiazepine) and injecting drug use (heroin, methadone, morphine, methamphetamine cocaine, benzodiazepines) (10, 107, 116, 153, 166) and HCV genotype (116, 124).

With respect to education level, participants who had completed high school and/or a higher degree were compared with those who had not completed high school education. Current

employment and living status were defined at the time of study enrolment. Participants with full- or part-time employment were compared with the rest of the study population. Participants who were living with a spouse/partner, spouse/partner and child(ren), parents, other relative(s) or friend(s) were compared with those living alone or alone with child(ren). Housing status, recent imprisonment and drug use behaviour were defined over the six months prior to study enrolment date. Those who privately owned or were renting a house or flat were compared with the rest of the study population. Recent drug use was defined by non-injecting and/or injecting use of heroin, methadone (or buprenorphine or suboxone), morphine (or other opiates), methamphetamine (including all forms), cocaine, crack cocaine and benzodiazepines. Additionally, recent non-injecting and/or injecting use of methamphetamine and benzodiazepines were analysed separately in unadjusted analyses. Recent injecting drug use was defined by injecting use of any of the drugs listed above. Additionally, recent injecting use of heroin, methadone, morphine, methamphetamine cocaine and benzodiazepines were analysed separately in unadjusted analyses. Alcohol consumption was evaluated by Alcohol Use Disorders Identification Test-Consumption (AUDIT-C), derived from the first three questions of the full AUDIT (scores higher than three and four indicate high-risk consumption among women and men, respectively) (351).

Following unadjusted analyses, multivariable logistic regression was performed to evaluate factors associated with high treatment willingness and early treatment intent, considering factors significant at the 0.20 level in unadjusted analyses. Model selection was performed according to a stepwise backwards elimination, subject to a likelihood ratio test. Multivariable logistic regression models were also performed to assess whether high HCV treatment willingness and early treatment intent were predictive of subsequent HCV specialist assessment and treatment uptake. These models were adjusted for factors previously shown to be associated with HCV specialist assessment (non-Aboriginal ethnicity, no recent benzodiazepine use and non-1 HCV genotype) and treatment uptake (non-

Aboriginal ethnicity, living with spouse or other relatives/friends, never receiving OST, no recent methamphetamine use and non-1 HCV genotype) in the ETHOS study (346).
At study enrolment, participants in seven clinics were assessed for HCV infection by a clinical nurse. However, in one site, participants were assessed by a general practitioner at enrolment. Further, the majority of participants with Aboriginal ethnicity were recruited from this study site. The sensitivity of multivariable models was investigated by excluding participants recruited from the study site which differed in provision of HCV assessment services, compared with other study sites.

For all analyses, statistically significant differences was assessed at $p<0.05$; *P*-values were two-sided. All analyses were performed using the statistical package Stata v12.0 (College Station, TX, United States).

5.9. Results

Study participants

Between 2009 and 2012, 387 participants were recruited into the ETHOS study (Figure 1). Mean age was 41 years, 71% (n=275) were male, 15% (n=59) were of Aboriginal ethnicity and 51% (n=196) had recently injected drugs. The majority were enrolled through OST clinics (72%, n=277) and 79% (n=307) were currently receiving OST (Table 1). Compared to those who were currently receiving OST, participants with no history of OST were older (mean age 45 vs. 40, *P*<0.001), more often had full- or part-time employment (21% vs. 6%, *P*<0.001), had lower proportions of current/ever imprisonment (42% vs. 66%, P=0.001), recent drug use (28% vs. 70%, *P*<0.001) and recent injecting drug use (19% vs. 56%, *P*<0.001) (supplementary Table 1).

HCV treatment willingness

The majority (70%, n=269) of participants were definitely willing to receive HCV treatment. Sixteen percent (n=62) were somewhat willing, 6% were definitely unwilling (n=24), 4% were neither willing nor unwilling (n=16) and 4% who were somewhat unwilling to receive antiviral therapy (n=14).

In unadjusted analysis, high willingness (definitely willing) to receive HCV treatment was associated with living with a spouse or other relatives/friends, never receiving OST and no recent heroin use (Table 2). There were no differences between high and lower levels of willingness to receive HCV treatment, with respect to other demographic characteristics and drug use. In adjusted analysis, high HCV treatment willingness was associated with non-Aboriginal ethnicity [adjusted odds ratio (AOR) 1.94, 95% CI 1.08, 3.53], living with a spouse or other relatives/friends (AOR 1.62, 95% CI 1.03, 2.53) and never receiving OST (AOR 3.57, 95% CI 1.45, 8.81). No recent heroin use trended towards high HCV treatment willingness, but was not statistically significant at the 0.05 significance level (AOR 1.58, 95% CI 0.98, 2.54) (Table 2).

HCV treatment intent

The majority of participants (74%, n=282) had early plans to initiate HCV treatment over the next 12 months. Thirteen percent (n=51) had plans to initiate treatment over the next 1-2 years, 8% were planning to initiate treatment over the next 2-5 years (n=31), 3% were not planning to initiate treatment for at least five years (n=13) and 2% did not have any plans to initiate antiviral therapy (n=6).

In unadjusted analysis, early HCV treatment intent (next 12 months) was associated with being aged 35-45 years (vs. <35 years), living with a spouse or other relatives/friends, never receiving OST, no recent heroin use, no recent heroin injecting and non-1 HCV genotype (supplementary Table 2). There were no differences between those with and without early HCV treatment intent with respect to other demographics and drug and alcohol use. In adjusted logistic regression analysis, early HCV treatment intent was associated with being aged 35-45 years (vs. <35 years) (AOR 2.08, 95% CI 1.15, 3.75), non-Aboriginal ethnicity (AOR 2.03, 95% CI 1.08, 3.84), living with spouse or other relatives/friends (AOR 1.66, 95% CI 1.02, 2.68), no recent heroin use (AOR 2.02, 95% CI 1.23, 3.32) and non-1 HCV genotype (AOR 2.63, 95% CI 1.51, 4.65) (supplementary Table 1).

HCV specialist assessment and treatment uptake

As previously demonstrated in the ETHOS study (346), among the 387 participants enrolled and assessed by a clinic nurse or a general practitioner, 49% (n=191) were referred to a specialist and attended their specialist appointment (Figure 1). Following HCV specialist assessment, HCV treatment was recommended and commenced by 22% (n=84) of the overall study population (Figure 1). Compared to those with lower levels of willingness to receive treatment, participants with high treatment willingness were more often assessed by a specialist (65% vs. 34%, P<0.001) and treated (28% vs. 8%, P<0.001) (Figure 2). Compared to those without early treatment intent, participants with early treatment intent

were more often assessed by a specialist (57% vs. 28%, *P*<0.001) and treated (28% vs. 4%, *P*<0.001) (Figure 3).

After adjusting for factors associated with HCV specialist assessment including non-Aboriginal ethnicity, no recent benzodiazepine use and non-1 HCV genotype (346), high treatment willingness independently predicted subsequent HCV specialist assessment (AOR 2.17, 95% CI 1.35, 3.51, *P*=0.001) (Table 3). After adjusting for factors associated with HCV treatment uptake including non-Aboriginal ethnicity, living with a spouse or other relatives/friends, never receiving OST, no recent methamphetamine use and non-1 HCV genotype (346), high treatment willingness independently predicted subsequent HCV treatment uptake (AOR 3.50, 95% CI 1.61, 7.59, *P*=0.002) (Table 4).

Very similar associations were found with early treatment intent and HCV specialist assessment and treatment uptake. After adjusting for factors associated with HCV specialist assessment including non-Aboriginal ethnicity, no recent benzodiazepine use and non-1 HCV genotype (346), early treatment intent independently predicted subsequent HCV specialist assessment (AOR 2.95, 95% CI 1.76, 4.94, *P*<0.001) (Table 3). After adjusting for factors associated with HCV treatment uptake including non-Aboriginal ethnicity, living with a spouse or other relatives/friends, never receiving OST, no recent methamphetamine use and non-1 HCV genotype (346), early treatment intent independently predicted subsequent HCV treatment uptake (AOR 6.75, 95% CI 2.34, 19.48, *P*<0.001) (Table 4).

5.10. Discussion

HCV treatment willingness and intent were high in this large prospective study of people with chronic HCV infection and a history of injecting drug use assessed for HCV infection. Factors independently associated with HCV treatment willingness included non-Aboriginal ethnicity, living with a spouse or other relatives/friends and never receiving OST. Factors independently associated with HCV treatment intent included age (35-54 years), non-Aboriginal ethnicity, living with a spouse or other relative/friends, no recent heroin use and non-1 HCV genotype. High HCV treatment willingness and early treatment intent were both predictive of subsequent HCV specialist assessment and treatment uptake. These findings highlight the need for development and implementation of strategies for enhanced specialist assessment and treatment with an initial focus on people more willing to receive treatment. Strategies are needed to increase treatment willingness and intent among those less willing.

The majority of participants were definitely willing to receive HCV treatment (70%) and had plans to initiate antiviral therapy in the short-term (74%). Previous findings have similarly shown high levels of HCV treatment willingness (53-86%) among cohorts of PWID (112, 115, 162-164, 166). In one of the earlier studies, 53% of PWID were willing to receive an HCV treatment regimen which had very low efficacy (20%) and required a liver biopsy (163). Higher levels of HCV treatment willingness and intent in the current study are therefore unsurprising, given that liver biopsy is no longer required for treatment in Australia and current antiviral regimes have higher efficacy (50-90%).

Almost half of participants in the ETHOS study (49%) were assessed by an HCV specialist and 22% initiated antiviral therapy. In adjusted analyses, high HCV treatment willingness increased the odds of specialist assessment and treatment uptake by two and four fold, respectively. Notably, early HCV treatment intent increased the odds of specialist assessment and treatment uptake by three and seven fold, respectively. Continuing attention

to factors associated with HCV treatment willingness and intent, is required to enhance HCV care among those less willing to receive antiviral therapy.

In adjusted analysis, several demographic, behavioural and clinical factors were independently associated with high HCV treatment willingness and early treatment intent. Older age (35-45 vs. 18-35 years) was found to be associated with early HCV treatment intent. It has been suggested that the risk of developing HCV-related complications increases with age (5, 70). Given than the mean age at first injecting drug use among ETHOS participants was 19 years, older PWID may be more likely to have more progressive liver disease or have witnessed others with HCV-related ill-health (358), and therefore more driven to consider HCV treatment uptake in the short-term.

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Aboriginal participants were less likely to have high treatment willingness and early treatment intent. Minority ethnicity has been shown to be associated with lower HCV treatment uptake (124, 126). Access to HCV testing is similar between Aboriginal and non-Aboriginal Australians (353). However, compared to non-Aboriginal Australians, Aboriginal people have lower levels of health education and limited access to culturally appropriate health programs (353, 359). Similarly, these factors may contribute to lower levels of HCV treatment willingness and lack of early treatment intent among Aboriginal Australians.

Living with a spouse or other relatives/friends was associated with high HCV treatment willingness and early treatment intent. Social support has been shown to be associated with HCV assessment (107). As an indicator of greater social support, living with family and/or friends may contribute to a patients' readiness to consider HCV treatment and engage with HCV care services.

A high HCV treatment willingness was associated with not having a history of OST. No recent heroin use trended towards higher HCV treatment willingness and was associated

with early treatment intent. Compared to ETHOS participants who were currently receiving OST, those with no history of OST appeared to be older, less drug dependent and less marginalized. Previous findings suggest that people with HCV infection are more willing to receive antiviral therapy if they are in stable drug dependence treatment programs (162), not currently enrolled in drug treatment or considering quitting drug use (112), receiving detoxification treatment (164) and not currently injecting drugs (166). Participants' reports of lower willingness may reflect their concerns about the tolerability of current HCV treatment regimens (346, 358), given their social and drug use situations. Treatment programs are required that provide support for complex needs of those who are less willing to receive HCV treatment and appear less suitable for antiviral therapy.

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HCV genotype 1 was found to be associated with lack of early HCV treatment intent, compared with other genotypes (predominantly genotypes 2/3). HCV genotype 1 is associated with lower sustained virological response among patients receiving interferon-based therapy (8). Given the limited access to HCV genotype 1 triple therapy (including telaprevir or boceprevir) during the study period, ongoing evaluation of the impact of HCV genotype on treatment intent will be of great interest as direct-acting antiviral (DAA) therapy becomes more broadly available (telaprevir and boceprevir were approved for Australian government subsidization from April 2013).

There are a number of limitations of this study. Given the recruitment methodology and that all participants were assessed by a nurse or general practitioner at enrolment, the study population may represent a group that is more engaged in health services, leading to an overestimation of proportions with HCV treatment willingness and intent. Similarly, the proportions receiving HCV specialist assessment and treatment might not reflect those in populations that are not connected with health services. Further, these findings may not be generalizable to other populations of people with HCV infection, particularly those less engaged in health services.

A multidisciplinary approach has been the core of many successful models delivering HCV care services to drug-using populations (273). Given that many clinics in the current study had limited prior expertise with specialised HCV care, provision of HCV nursing and specialist support within the existing infrastructure for addiction treatment has produced encouraging results. Improved engagement of marginalised populations with HCV care services has broadened our understanding of the role of treatment willingness on subsequent HCV specialist assessment and treatment uptake. While new interferon-free regimes are anticipated to remove many barriers to HCV care services, evidence-based and sustainable strategies are required to further engage those willing to receive antiviral therapy and develop programs to support those less willing to receive therapy.

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Disclaimer

The findings and views expressed in this publication are those of the authors and do not represent the position of the Australian Government.

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Role of the funding source

The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Potential Conflicts of Interest

None of the authors has commercial relationships that might pose a conflict of interest in connection with this manuscript.

5.12. Tables

Table 1. Characteristics of participants with chronic HCV infection, a history of injecting drug use and assessed by a nurse in the ETHOS study (n=387)

Characteristics, n (%)	Overall (n=387)
Age, mean (±SD)	41 (±9)
Male gender [μ]	275 (71%)
Aboriginal ethnicity	59 (15%)
Finished high school or higher education[*]	74 (19%)
Living with a spouse or other relatives/friends[*]	193 (50%)
Owned or rented housing[*]	313 (81%)
Full- or part-time employment[*]	36 (9%)
Opioid substitution treatment	
Current	307 (79%)
Previous, not current	23 (6%)
Never	57 (15%)
Imprisonment[¥]	36 (9%)
Age at first injecting drug use, mean (±SD)	19 (±6)
Recent drug use (injecting and non-injecting)[¥]	248 (64%)
Benzodiazepine [¶]	137 (55%)
Heroin[¶]	133 (54%)
Methamphetamine [¶]	106 (43%)
Recent injecting drug use[¥]	196 (51%)
Benzodiazepine [¶]	14 (7%)
Cocaine [¶]	27 (14%)
Heroin [¶]	132 (67%)
Methadone [¶]	22 (11%)
Methamphetamine [¶]	96 (49%)
Morphine [¶]	55 (28%)
High risk alcohol consumption [α]	
Female	49 (45%)
Male	86 (31%)
HCV genotype	
1	151 (39%)
2, 3, 6	166 (43%)
Unknown	70 (18%)

[μ]other/unknown gender is not included, [*]among those with available survey results, [¥]in the six months prior to study enrolment, [¶]denominator is the total number reported using and injecting drug use, respectively, [α] denominator is females and males reported alcohol consumption

Table 2. Unadjusted and adjusted analysis of factors associated with high HCV treatment willingness in the ETHOS study (n=387)

Characteristic, n (%)	High HCV treatment willingness (n=269)	OR (95% CI)	Adjusted OR (95% CI)	*P*
Age (years)				
<35	72 (67%)	1.00	-	-
35-45	114 (73%)	1.32 (0.77, 2.26)	-	-
≥45[μ]	82 (67%)	0.97 (0.56, 1.69)	-	-
Gender				
Female	74 (67%)	1.00	-	-
Male	195 (71%)	1.17 (0.73, 1.88)	-	-
Ethnicity				
Aboriginal	35 (59%)	1.00	1.00	-
Non-Aboriginal	234 (71%)	1.72 (0.97, 3.06)	1.94 (1.08, 3.53)	0.030
Finished high school or higher education				
No	218 (70%)	1.00	-	-
Yes	51 (69%)	0.97 (0.56, 1.67)	-	-
Living with a spouse or other relatives/friends				
No	125 (64%)	1.00	1.00	-
Yes	144 (75%)	1.60 (1.03, 2.48)	1.62 (1.03, 2.53)	0.036
OST				
Current	205 (67%)	1.00	1.00	-
Previous, not current	14 (61%)	0.77 (0.32, 1.85)	0.70 (0.29, 1.70)	0.425
Never[¶]	50 (88%)	3.55 (1.56, 8.12)	3.57 (1.45, 8.81)	0.006
Recent drug use (injecting and non-injecting)[¥,*]				
Yes	167 (67%)	1.00	-	-
No	102 (73%)	0.74 (0.47, 1.17)	-	-
Benzodiazepine use				
Yes	91 (66%)	1.00	-	-
No	178 (71%)	1.28 (0.82, 1.99)	-	-
Heroin use				
Yes	82 (62%)	1.00	1.00	-
No	187 (73%)	1.71 (1.09, 2.67)	1.58 (0.98, 2.54)	0.058
Methamphetamine use				
Yes	76 (72%)	1.00	-	-
No	193 (68%)	1.17 (0.71, 1.91)	-	-
Recent injecting drug use[¥,*]				
Yes	128 (65%)	1.00	-	-
No	141 (74%)	1.52 (0.98, 2.35)	-	-
Heroin injecting[*]				
Yes	83 (63%)	1.00	-	-
No	186 (73%)	1.57 (1.00, 2.45)	-	-
Methamphetamine injecting				
Yes	70 (73%)	1.00	-	-
No	199 (68%)	0.79 (0.48, 1.33)	-	-
Morphine injecting				
Yes	33 (59%)	1.00	-	-
No	236 (71%)	1.71 (0.96, 3.07)	-	-
HCV genotype				
1	99 (67%)	1.00	-	-
2, 3, 6	122 (76%)	1.56 (0.95, 2.57)	-	-
Unknown[Σ]	48 (61%)	0.64 (0.36, 1.15)	-	-

[μ]unadjusted Wald test *P*-overall 0.440, [*]unadjusted *P*<0.20, but not included in the adjusted model due to co-linearity, [¥]in the six months prior to study enrolment, [¶]unadjusted and adjusted Wald test *P*-overalls 0.008 and 0.013, respectively, [Σ] unadjusted Wald test *P*-overall 0.057

Table 3. Adjusted analyses of the association between HCV specialist assessment and high treatment willingness (model 1) and early treatment intent (model 2) in the ETHOS study (n=387)

			Model 1 (High treatment willingness)		Model 2 (Early treatment intent)	
Characteristic, n (%)	**HCV specialist assessment (n=191)**	**OR (95% CI)**	**Adjusted OR (95% CI)**	***P***	**Adjusted OR (95% CI)**	***P***
Ethnicity						
Aboriginal	13 (22%)	1.00	1.00	-	1.00	-
Non-Aboriginal	178 (54%)	4.20 (2.18, 8.07)	3.82 (1.93, 7.54)	<0.001	3.76 (1.89, 7.46)	<0.001
Recent benzodiazepine use[¥]						
Yes	55 (40%)	1.00	1.00	-	1.00	-
No	136 (54%)	1.80 (1.18, 2.74)	2.04 (1.29, 3.23)	0.002	1.96 (1.23, 3.10)	0.004
HCV genotype						
Genotype 1	65 (44%)	1.00	1.00	-	1.00	-
Genotypes 2, 3, 6	101 (63%)	2.15 (1.36, 3.39)	2.04 (1.26, 3.30)	0.004	1.86 (1.14, 3.03)	0.013
Unknown[Σ]	25 (32%)	0.59 (0.33, 1.05)	0.63 (0.34, 1.17)	0.144	0.61 (0.33, 1.12)	0.110
High treatment willingness						
No	40 (34%)	1.00	1.00	-	-	-
Yes	151 (56%)	2.50 (1.59, 3.92)	2.17 (1.35, 3.51)	0.001	-	-
Early treatment intent						
No	29 (27%)	1.00	-	-	1.00	
Yes	162 (57%)	3.54 (2.17, 5.77)	-	-	2.95 (1.76, 4.94)	<0.001

[¥]injecting and non-injecting use, in the six months prior to study enrolment, [Σ] Wald test *P*-overall <0.001

Table 4. Adjusted analyses of the association between HCV treatment uptake and high treatment willingness (model 1) and early treatment intent (model 2) in the ETHOS study (n=387)

			Model 1 (High treatment willingness)		Model 2 (Early treatment intent)	
Characteristic, n (%)	**HCV Treatment (n=84)**	**OR (95% CI)**	**Adjusted OR (95% CI)**	***P***	**Adjusted OR (95% CI)**	***P***
Ethnicity						
Aboriginal	4 (7%)	1.00	1.00	-	1.00	-
Non-Aboriginal	80 (24%)	4.43 (1.56, 12.62)	3.95 (1.28, 12.24)	0.017	4.05 (1.28, 12.81)	0.017
Living status						
Alone	30 (16%)	1.00	1.00	-	1.00	-
With a spouse or other relatives/friends	54 (28%)	2.12 (1.29, 3.50)	1.93 (1.11, 3.36)	0.021	1.90 (1.09, 3.33)	0.024
OST						
Current	51 (17%)	1.00	1.00	-	1.00	-
Previous, not current	6 (26%)	1.78 (0.67, 4.73)	2.05 (0.68, 6.16)	0.202	1.86 (0.62, 5.57)	0.265
Never [ƛ]	27 (47%)	4.54 (2.49, 8.27)	3.68 (1.88, 7.22)	<0.001	3.74 (1.89, 7.39)	<0.001
Recent methamphetamine use[¥]						
Yes	12 (11%)	1.00	1.00	-	1.00	-
No	72 (26%)	2.69 (1.39, 5.18)	2.47 (1.21, 5.03)	0.013	2.34 (1.15, 4.78)	0.019
HCV genotype, n						
Genotype 1	21 (14%)	1.00	1.00	-	1.00	-
Genotypes 2, 3, 6	54 (34%)	3.05 (1.73, 5.37)	3.03 (1.63, 5.63)	<0.001	2.65 (1.42, 4.95)	0.002
Unknown[ƛ]	9 (12%)	0.78 (0.34, 1.79)	1.06 (0.43, 2.57)	0.902	1.01 (0.41, 2.47)	0.986
High treatment willingness						
No	9 (8%)	1.00	1.00	-	-	-
Yes	75 (28%)	4.68 (2.26, 9.72)	3.50 (1.61, 7.59)	0.002	-	-
Early treatment intent						
No	4 (4%)	1.00	-	-	1.00	-
Yes	80 (28%)	10.00 (3.56, 28.07)	-	-	6.75 (2.34, 19.48)	<0.001

[¥]injecting and non-injecting use, in the six months prior to study enrolment, [ƛ] Wald test *P*-overall <0.001

5.13. Figures

Figure 1. HCV specialist assessment and treatment among participants in the ETHOS study

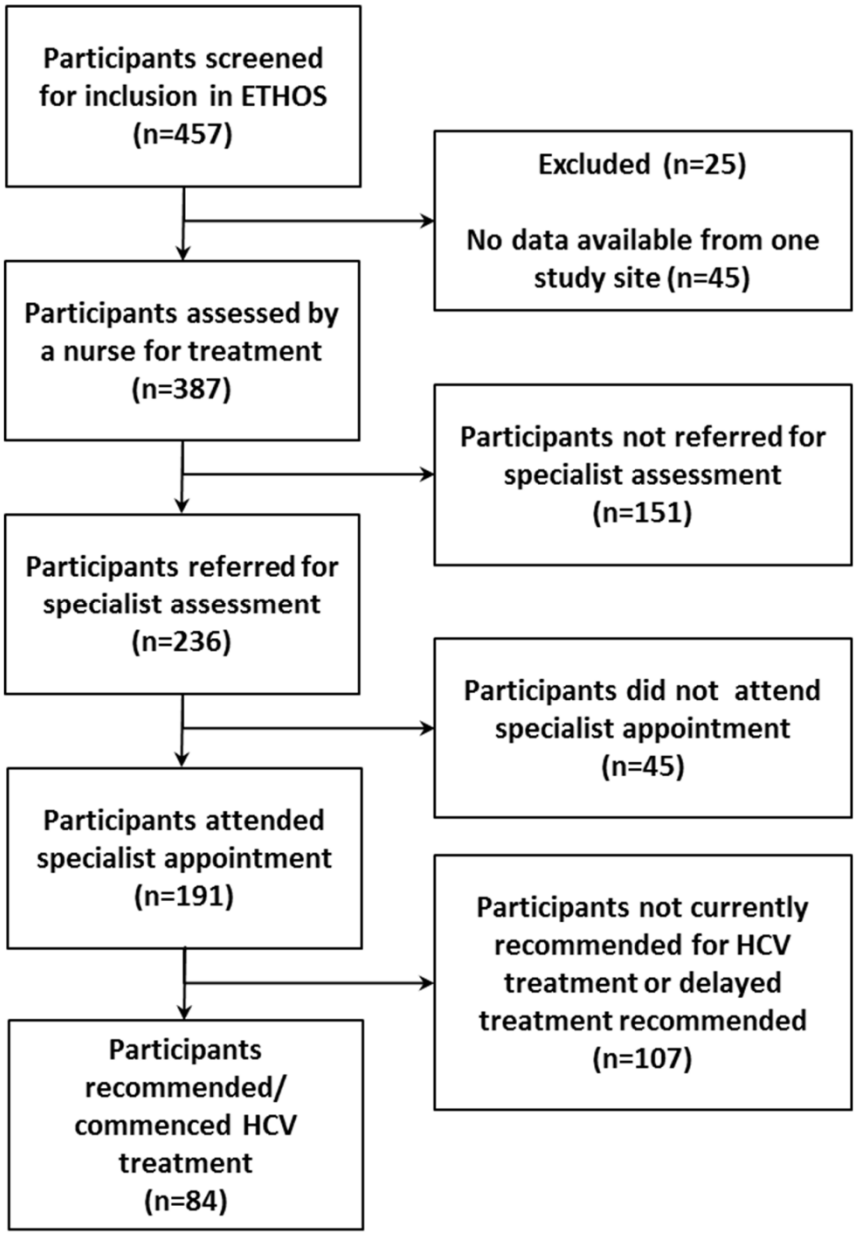


Figure 2. A and B) HCV specialist assessment and C and D) HCV treatment among participants in the ETHOS study stratified by treatment willingness

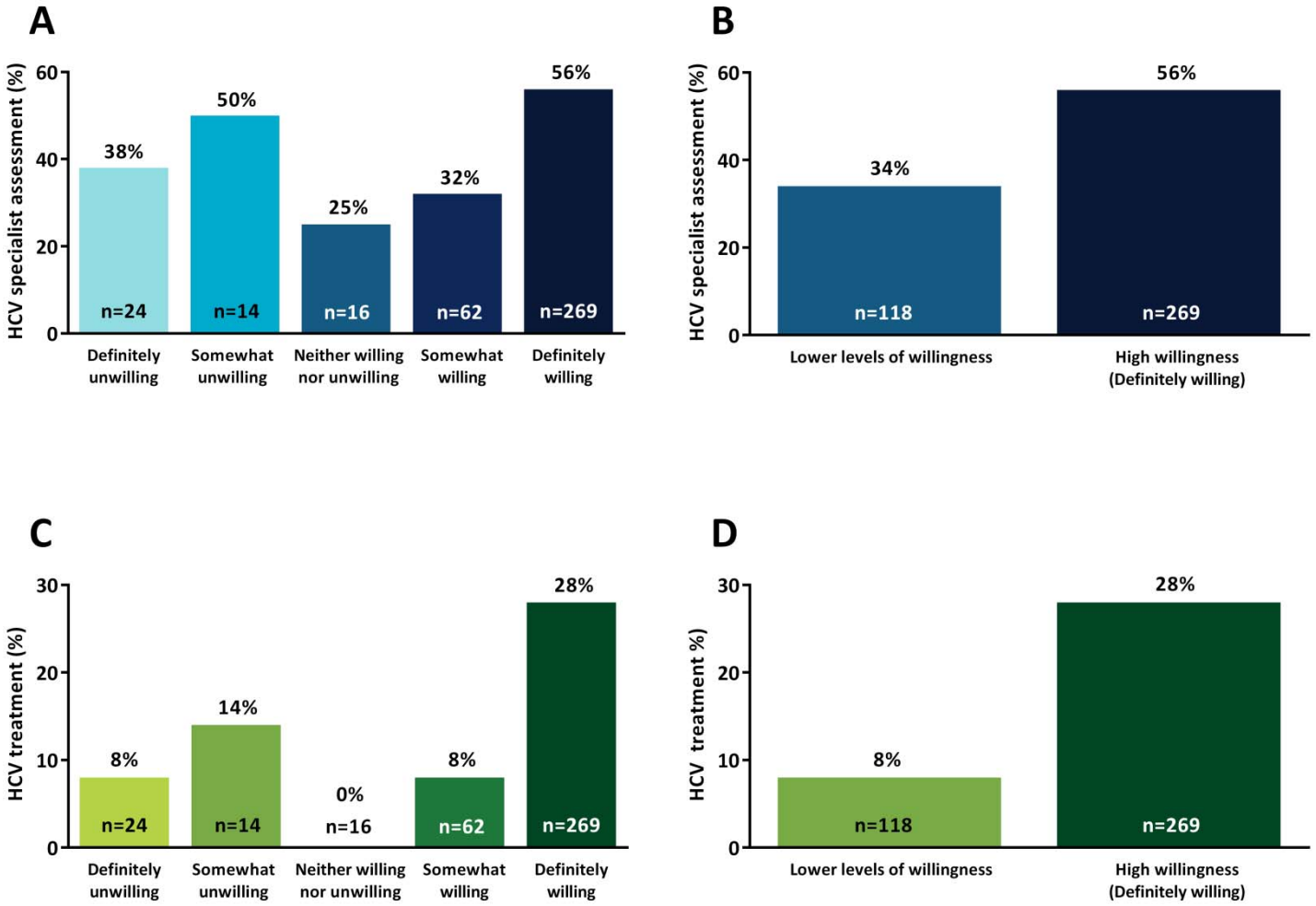
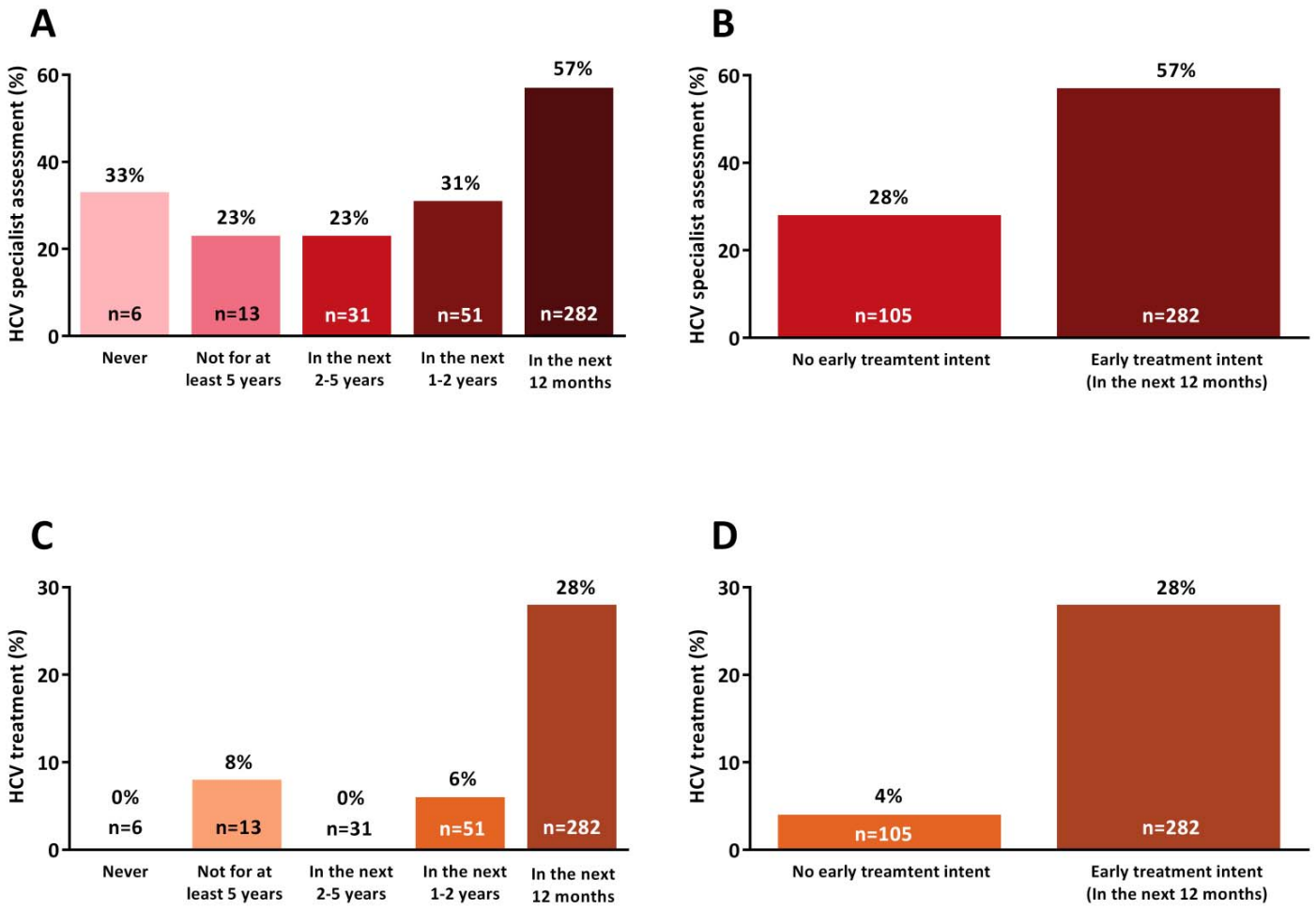


Figure 3. A and B) HCV specialist assessment and C and D) HCV treatment among participants in the ETHOS study stratified by treatment intent



5.14. Supplementary Material

Table 1. Characteristics of participants with chronic HCV infection and a history of injecting drug use by OST status in the ETHOS study (n=387)

Characteristics	Never OST	Previous OST	Current OST
	n=57	n=23	n=307
Age, mean (±SD)	45±9.8	41±8.9	40±8.5
Male gender, n (%)[μ]	42 (75%)	15 (65%)	218 (71%)
Aboriginal ethnicity, n (%)	8 (14%)	2 (9%)	49 (16%)
Finished high school or higher education, n (%)[*]	13 (23%)	3 (13%)	58 (19%)
Living with a spouse or other relatives/friends, n (%)[*]	30 (54%)	10 (43%)	153 (50%)
Owned or rented housing, n (%)[*]	45 (80%)	16 (70%)	252 (82%)
Full- or part-time employment, n (%)[*]	12 (21%)	5 (22%)	19 (6%)
Imprisonment, n (%)[¶]	24 (42%)	18 (78%)	203 (66%)
Recent drug use (injecting and non-injecting), n (%)[¥]	16 (28%)	16 (70%)	216 (70%)
Recent injecting drug use, n (%)[¥]	11 (19%)	13 (57%)	172 (56%)
High risk alcohol consumption (male and female), n (%)[α]	25 (44%)	8 (35%)	102 (33%)
HCV genotype, n (%)			
1	19 (33%)	8 (35%)	121 (39%)
2, 3, 6	30 (53%)	8 (35%)	123 (40%)
Unknown	8 (14%)	7 (30%)	63 (21%)

[μ]other/unknown gender is not included, [*]among those with available survey results, [¶]ever or in the six months prior to study enrolment, [¥]in the six months prior to study enrolment, [α] denominator is females and males reported alcohol consumption.

Supplementary Material

Table 2. Unadjusted and adjusted analysis of factors associated with early HCV treatment intent in the ETHOS study (n=387)

Characteristic, n (%)	Early HCV treatment intent (n=282)	OR (95% CI)	Adjusted OR (95% CI)	*P*
Age				
<35 years	71 (66%)	1.00	1.00	-
35-45 years	125 (80%)	2.04 (1.17, 3.59)	2.08 (1.15, 3.75)	0.015
≥45 years[μ]	85 (69%)	1.13 (0.65, 1.97)	1.03 (0.57, 1.88)	0.913
Gender				
Female	209 (76%)	1.00	-	-
Male	73 (66%)	1.58 (0.98, 2.56)	-	-
Ethnicity				
Aboriginal	37 (63%)	1.00	1.00	-
Non-Aboriginal	245 (75%)	1.76 (0.98, 3.15)	2.03 (1.08, 3.84)	0.029
Finished high school or higher education				
No	229 (73%)	1.00		
Yes	53 (72%)	0.93 (0.53, 1.63)		
Living with a spouse or other relatives/friends				
No	131 (68%)	1.00	1.00	-
Yes	151 (78%)	1.73 (1.10, 2.73)	1.66 (1.02, 2.68)	0.040
OST				
Current	217 (70%)	1.00	-	-
Previous, not current	16 (70%)	0.96 (0.38, 2.41)	-	-
Never[¶]	49 (86%)	2.57 (1.17, 5.64)	-	-
Recent drug use (injecting and non-injecting)[¥]				
Yes	177 (71%)	1.00	-	-
No	105 (76%)	0.80 (0.50, 1.28)	-	-
Benzodiazepine use				
Yes	94 (68%)	1.00	-	-
No	188 (75%)	1.42 (0.90, 2.25)	-	-
Heroin use				
Yes	86 (65%)	1.00	1.00	-
No	196 (77%)	1.82 (1.15, 2.87)	2.02 (1.23, 3.32)	0.006
Methamphetamine use				
Yes	78 (74%)	1.00	-	-
No	204 (72%)	0.94 (0.57, 1.55)	-	-
Recent injecting drug use[¥]				
Yes	138 (70%)	1.00	-	-
No	144 (75%)	1.31 (0.84, 2.05)	-	-
Heroin injecting[*]				
Yes	86 (65%)	1.00	-	-
No	196 (77%)	1.75 (1.10, 2.77)	-	-
Methamphetamine injecting				
Yes	71 (74%)	1.00	-	-
No	211 (72%)	0.92 (0.54, 1.55)	-	-
Morphine injecting				
Yes	39 (70%)	1.00	-	-
No	243 (73%)	1.19 (0.64, 2.21)	-	-
HCV genotype				
1	101 (67%)	1.00	1.00	-
2, 3, 6	137 (83%)	2.34 (1.38, 3.95)	2.58 (1.49, 4.45)	0.001
Unknown[Σ]	44 (63%)	0.84 (0.46, 1.51)	1.18 (0.62, 2.22)	0.617

[μ]unadjusted and adjusted Wald test *P*-overalls 0.027 and 0.021, respectively, [¥]in the six months prior to study enrolment, [¶]unadjusted Wald test *P*-overall 0.061, [Σ] unadjusted and adjusted Wald test *P*-overall 0.003 and 0.003, respectively

Chapter 6

The impact of treatment for HCV infection on depression and mental health parameters

6.1. Chapter Introduction

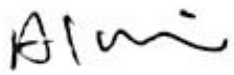
HCV treatment is often withheld from PWID and individuals with co-morbid psychiatric disease due to concerns of poor adherence, ongoing drug use, psychosocial instability and exacerbation of pre-existing psychiatric disease mediated by interferon-based therapy. This paper provides evidence of safety and efficacy of interferon-based antiviral therapy among a population of PWID with high prevalence of depression and poor social functioning. Given appropriate monitoring for patients with psychiatric co-morbidities, PWID can safely receive currently available HCV treatment regimens. The manuscript has been published in Journal of Gastroenterology and Hepatology:

Publication V

Alavi M, Grebely J, Matthews GV, Petoumenos K, Yeung B, Day C, Lloyd AR,Van Beek I, Kaldor JM, Hellard M, Dore GJ and Haber PS on behalf of the ATAHC Study Group. Impact of pegylated interferon alfa-2a treatment on mental health during recent hepatitis C virus infection. Journal of Gastroenterology and Hepatology 2012;27(5):957-6

6.2. 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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6.3. Co-authorship Acknowledgemnet

In the case of Chapter Six, the nature and extent of my contribution to the work was the following:

Name	Contribution (%)	Nature of contribution
Maryam Alavi	50	Conducted data analysis and led the development, writing and critical revisions of the manuscript.
Jason Grebely	5	Supervised data analysis and contributed to data interpretation. Contributed to writing and critical revision of the manuscript.
Gail Matthews	7	Contributed to the design of the study and overall concept and structure of the manuscript.
Kathy Petoumenos	3	Contributed to data management
Barbara Yeung	3	Contributed to the design of the study and data collection.
Carolyn Day	3	Contributed to the design of the study and data collection.
Andrew Lloyd	3	Contributed to the design of the study and data collection.
Ingrid Van Beek	3	Contributed to the design of the study and data collection.
John Kaldor	3	Contributed to the design of the study and data collection.
Margaret Hellard	5	Contributed to the design of the study and data collection.
Gregory Dore	10	Contributed to the design of the study, data interpretation, writing and critical revision of the manuscript.
Paul Haber	5	Contributed to the design of the study, data interpretation, writing and critical revision of the manuscript.

6.4. Impact of pegylated interferon alfa-2a treatment on mental health during recent hepatitis C virus infection

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Running title: PEG-IFN-induced depression in recent HCV

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6.5. Abbreviations

PEG-IFN, pegylated interferon; HCV, hepatitis C virus; IDU, injecting drug users; SVR, sustained virological response; ATAHC, Australian Trial in Acute Hepatitis C; ALT, alanine aminotransferase; OTI, opiate treatment index; M.I.N.I, mini-international neuropsychiatric interview; DASS, depression, anxiety and stress scale; SCID-I, structured clinical interview for DSM-IV-TR axis I; CIDI, composite international diagnostic interview; MDE, major depressive episode.

6.6. Abstract

Background: Pegylated interferon (PEG-IFN) treatment for hepatitis C virus (HCV) infection has neuropsychiatric side effects. Data on the impact of HCV treatment on mental health among injecting drug users (IDUs) are limited. We assessed mental health during treatment of recently acquired HCV, within a predominantly IDU population. **Methods:** Participants with HCV received PEG-IFN α-2a (180μg/week) for 24 weeks; HCV/HIV received PEG-IFN with ribavirin. Depression was assessed using the Mini-International Neuropsychiatric Interview (MINI). Logistic regression was used to identify factors associated with depression at enrolment and during treatment. Also, the impact of depression prior to and during treatment on SVR was assessed. **Results:** Of 163 participants, 111 received treatment (HCV, n=74; HCV/HIV, n=37), with 76% ever reporting IDU. At enrolment, 16% had depression (n=25). In adjusted analysis, depression at enrolment occurred less often in participants full-/part-time employed (AOR 0.23; 95% CI: 0.06, 0.82, *P*=0.023) and more often in recent IDUs (AOR 3.04; 95% CI: 1.19, 7.72, *P*=0.019). During treatment, 35% (n=31) developed new-onset depression. In adjusted analysis, poorer social functioning (higher score) was associated with new-onset depression (score $\leq$9 vs. score $\geq$17; OR 5.69; 95% CI: 1.61, 20.14, *P*=0.007). SVR was similar among participants with and without depression at enrolment (60% vs. 61%, *P*=0.951) and in those with and without new-onset depression (74% vs. 63%, *P*=0.293). **Conclusions:** Although depression at enrolment and during treatment was common among participants with recent HCV, neither impacted SVR. Participants with poor social functioning may be most at risk of developing depression during HCV therapy.

Keywords: injecting drug users, HCV, depression, anxiety, psychiatric

6.7. Introduction

Pegylated interferon (PEG-IFN) and ribavirin is the standard of care for treatment of hepatitis C virus (HCV) infection (185, 186). PEG-IFN treatment is complicated by neuropsychiatric side effects including suicidal thoughts and development or worsening of depressive symptoms (187, 188). During PEG-IFN treatment, up to 48% of participants develop depressive symptoms (188, 210, 238, 239, 242). However, the incidence and severity of IFN-induced depression varies between studies, presumably related to several factors including different socio-demographic characteristics between studies, varying doses and durations of therapy, differences in study designs, variations in the methodological approaches for depression assessment and different classifications of depression (251).

Since people with HCV infection have a high prevalence of psychiatric illness, studying neuropsychiatric side effects during HCV treatment is important. The lifetime prevalence of major depressive disorder is higher in individuals with HCV as compared to the general population (22-49% vs. 17%) (232-234). Moreover, in the developed world, 50-80% of individuals with HCV infection are injecting drug users (IDUs) (360), who also have a high prevalence of co-morbid psychiatric disease (236, 237, 361).

HCV treatment is often withheld from IDUs and individuals with co-morbid psychiatric disease due to concerns of poor adherence, ongoing drug use, psychosocial instability and exacerbation of pre-existing psychiatric disease mediated by interferon (137). However, studies have consistently demonstrated that among IDUs and individuals with psychiatric disease treated with interferon-based therapy, treatment completion and sustained virological response (SVR) are comparable to non-IDUs (195) and those without a history of psychiatric disease (210). Although a number of studies have assessed depression during HCV treatment (188, 210, 238, 239, 242), there is still a limited understanding of depression prior to and during HCV treatment among IDUs, particularly in the setting of recently acquired infection.

The Australian Trial in Acute Hepatitis C (ATAHC) was designed specifically to investigate treatment for recent HCV, predominantly in those with IDU-acquired infection. The aims of this study were to evaluate depression prior to and during treatment for HCV infection, identify risk factors associated with depression and assess the impact of depression on response to HCV treatment in the ATAHC study.

6.8. Methods

Study design

ATAHC was a multicenter, prospective cohort study of the natural history and treatment of recent HCV infection, as previously described (218). Recruitment of HIV infected and uninfected participants was from June 2004 through November 2007. Recent infection with either acute or early chronic HCV infection with the following eligibility criteria:

First positive anti-HCV antibody within 6 months of enrolment; *and either*

a. *Acute clinical hepatitis C infection*, defined as symptomatic seroconversion illness or alanine aminotransferase (ALT) level greater than 10 times the upper limit of normal (>400 IU/L) with exclusion of other causes of acute hepatitis, at most 12 months before the initial positive anti-HCV antibody; *or*
b. *Asymptomatic hepatitis C infection with seroconversion*, defined by a negative anti-HCV antibody in the two years prior to the initial positive anti-HCV antibody.

All participants with HCV RNA during the screening period (maximum 12 weeks) were assessed for HCV treatment eligibility. Heavy alcohol intake and active drug use were not exclusion criteria. From enrolment, participants were followed for up to 12 weeks to allow for spontaneous HCV clearance and if HCV RNA remained detectable were offered treatment.

All study participants provided written informed consent. The study protocol was approved by St Vincent's Hospital, Sydney Human Research Ethics Committee (primary study committee) as well as through local ethics committees at all study sites. The study was registered with clinicaltrials.gov registry (NCT00192569).

HCV treatment

Participants who began HCV treatment received PEG-IFN -α2a 180 micrograms weekly for 24 weeks. Due to non-response at week 12 in the initial two participants with HCV/HIV co-

infection, the study protocol was amended to provide PEG-IFN and ribavirin combination therapy for 24 weeks in HIV positive individuals. Ribavirin was prescribed at a dose of 1000-1200 mg for those with genotype 1 infection and 800 mg in those with genotype 2/3.

Study assessments

Participants who did not receive HCV treatment were seen at study enrolment and 12 weekly intervals for up to 144 weeks. Among treated participants, additional study visits occurred at enrolment, every two weeks from baseline (beginning of treatment) to week 8 and every four weeks from week 8 until the end of treatment. At each study visit, data on concomitant medications (including psychiatric medications) were collected.

Questionnaires were administered at enrolment and every 12 weeks during the first year (every 24 weeks during second and third years), to obtain information on injecting drug use, social functioning [Opiate Treatment Index (OTI) - Social Functioning scale] (362), psychological parameters [Mini-International Neuropsychiatric Interview (M.I.N.I.) (363) and the short version of the Depression Anxiety Stress Scale (DASS-21)] (349).

Social Functioning Scale of the Opiate Treatment Index (OTI): addresses employment, residential stability, and inter-personal conflict as well as social support (362). This scale has been validated among opiate users in Australia and higher scores are indicative of poorer social functioning (range score: 0-48) (362).

Mini-International Neuropsychiatric Interview (MINI): is a validated structured diagnostic interview covering 17 Axis I categories in a short format (363). It has good correlation with Structured Clinical Interview for DSM-IV-TR Axis I (SCID-I) (364) and the Composite International Diagnostic Interview (CIDI) (365). The first section of the MINI consists of nine questions assessing the presence of current major depressive episode (MDE). The second section of the MINI consists of six questions assessing current suicide risk. Suicide risk

score is then categorized in three levels: low, moderate and high. MINI was used as the primary instrument to assess depression in the current study, given its correlation with Structured Clinical Interview for DSM-IV-TR Axis I diagnosis of depression.

Depression, Anxiety and Stress Scale (DASS-21): is a 21 item self-administered survey consisting of three scales (seven questions each) assessing the severity of the core symptoms of depression, anxiety and stress in the past week (349). The score ranges from 0 to 42, with increasing score indicating increasing severity. Depression, anxiety and stress can also be categorized according to normal, mild, moderate, severe and extremely severe. DASS scores also have high internal consistency. DASS corresponds to mood disorders and was used as a secondary instrument to assess depressive symptoms (363, 365).

Study definitions

Depression: current major depressive disorder, as assessed by the MINI.

Depressive symptoms: having moderate (score range 14-20), severe (score range 21-27) or extremely severe (score range 28+) levels measured according to the DASS depression scale.

New-onset depression: development of current major depressive episode during treatment among participants who were not depressed prior to the initiation of therapy.

New-onset suicide risk: development of suicide risk (low, moderate or high) during treatment, among those with no suicide risk prior to the initiation of therapy.

Statistical analyses

Characteristics associated with depression at enrolment and new-onset depression during treatment were assessed. The impact of depression prior to treatment and new-onset depression and suicide risk during treatment on SVR were also evaluated. Characteristics were compared using two-sample t-tests for quantitative variables and Chi-squared test, Fisher's exact test or McNemar's test as appropriate, for testing differences in proportions. Logistic regression analyses were performed to identify factors associated with depression at enrolment and new-onset depression in those receiving treatment. Potential factors associated with depression were determined *a priori* and included sex, age, education, accommodation, employment, methadone/ buprenorphine treatment, social functioning, IDU at enrolment (ever, past 6 months and past month), alcohol, and HIV/HCV co-infection. For logistic regression analyses, continuous factors were categorized either using the median (age) or tertiles (social functioning and alcohol), given the absence of a linear effect with the outcome variable. Multivariable logistic regression was performed using a backwards stepwise approach subject to a likelihood ratio test, considering factors that were significant at the 0.20 level in unadjusted analyses. We also assessed the impact of pre-treatment depression, pre-treatment suicide risk, new-onset depression and suicide risk on SVR. Statistically significant differences were assessed at $p<0.05$; p-values are two-sided. All analyses were performed using the statistical package Stata v10.1 (College Station, TX).

6.9. Results

Participant characteristics

Overall, 163 participants were enrolled in the ATAHC study between June 2004 and February 2008. The majority of participants were male (71%), Caucasian (91%), the mean age was 34.3 years (standard deviation (SD) ±9.9) and 31% were HCV/HIV co-infected (Table 1). Overall, 76% (n=124) reported a history of injecting drug use, with 44% (55 of 124) injecting in the past month. A total of 111 participants received treatment and 52 participants were untreated.

Among those enrolled (n=163), 145 were HCV RNA positive at enrolment and thus eligible to receive treatment for HCV infection. The remaining 18 participants had spontaneous clearance of HCV infection and were thus not eligible to receive HCV treatment. In Table 1, the characteristics of participants who were treated (n=111), untreated but HCV RNA positive (n=34), and untreated but HCV RNA negative (ineligible to receive treatment) (n=18) is shown. Among HCV RNA positive participants (n=145), depression at study enrolment was more common among untreated as compared to treated participants (26% vs. 9%, *P*=0.008). As previously shown 17, after adjusting for other behavioural and clinical factors, participants with depression demonstrated a trend to be less likely to receive treatment [adjusted odds ratio (AOR) 0.40; 95% Confidence Interval (95% CI) 0.14, 1.17, P=0.093]. Suicide risk (moderate to high) was more common among untreated compared to treated participants (35% vs. 10%, P< 0.001).

Among the final treated population (n=111), 74 HCV mono-infected participants received PEG-IFN, 35 HCV/HIV co-infected participants received PEG-IFN/ribavirin and 2 HCV/HIV participants received PEG-IFN therapy (these participants were excluded from intention-to-treat analyses, given the protocol modification). As reported previously, among participants who received PEG-IFN treatment for HCV infection (n=109), 82% (89 of 109) received ≥80%

of scheduled PEG-IFN doses for ≥80% of the scheduled treatment period (201). PEG-IFN dose modification occurred in 5% of patients (n = 5) (201).

Depression at study enrolment

Among the 163 participants enrolled in ATAHC, 160 participants had available mental health assessments (MINI and DASS) at study enrolment (Table 2). At study enrolment, 16% (n=25) had depression (current major depressive disorder as assessed by the MINI, Table 2). Moderate to high suicide risk was reported in 18% (n=28). Moderate to extremely severe depressive, anxiety and stress symptoms (assessed by the DASS-21) were reported by 36% (n=57), 40% (n= 64) and 24% (n=38), respectively (Table 2). The mean DASS-21 score was 11.1 (SD ± 10.7) for depressive, 8.7 (SD ± 8.0) for anxiety and 13.1 (SD ± 9.8) for stress symptoms. Compared to those with HCV mono-infection, HCV/HIV co-infected participants had a lower proportion with depression (6% vs. 20%, *P*=0.033) and depressive symptoms (19% vs. 44%, *P*=0.036). Compared to those without recent drug injecting, recent IDUs (over the past month) had a higher proportion with depression (27% vs. 9%, *P*=0.002) and depressive symptoms (54% vs. 26% *P*=0.012).

Factors associated with depression at study enrolment in unadjusted analyses included unstable employment (no full-time/part-time employment), recent injecting drug use (past month), higher social functioning score (poorer social function) and not being infected with HIV (Table 3). In adjusted analysis (Table 3), depression occurred less often among those with full-time/part-time employment (AOR 0.23, 95% CI, 0.06, 0.82, *P*=0.023) and more often among those with recent injecting drug use (AOR 3.04, 95% CI, 1.19, 7.72, *P*=0.019).

New-onset depression during treatment for recent HCV infection

Among those who received HCV treatment (n=111), 88 did not have depression at study enrolment and had available follow-up information following treatment. Among these 88 participants, 35% developed new-onset depression (n=31) during treatment (HCV, 33%;

HCV/HIV, 38%, *P*=0.639) and 35% (11 of 31) of these received antidepressants. Longitudinal changes in depression and depressive symptoms prior to, during and following treatment are shown in Table 4 and Figures 2A and 2B. Participants who developed new-onset depression demonstrated a trend toward higher depressive symptoms prior to treatment compared to those who did not develop new-onset depression (mean score 7.0 vs. 10.2, *P*=0.093).

In unadjusted analysis, factors associated with developing new-onset depression included recent injecting prior to treatment initiation (past six months), alcohol use (>5 standard alcoholic drinks/day over the past month), and higher (poorer) social functioning score (Table 5). In adjusted analysis, poorer social functioning (higher score) was the only factor associated with new-onset depression (score $\leq$9 vs. score $\geq$17 OR 5.69, 95% CI, 1.61, 20.14, *P*=0.007).

Impact of depression and suicide risk on HCV treatment response

Depression and suicide risk prior to and during HCV treatment did not impact SVR (Figure 1). Of the 110 participants who received treatment, SVR was similar in those with (60%, 6 of 10) and without (61%, 61 of 100) depression at study enrolment (*P*=0.951). SVR was also similar in those with (82%, 9 of 11) and without (59%, 58 of 99) suicide risk (moderate to high) at study enrolment (*P*=0.196). SVR was similar in those who did (74%, 23 of 31) and did not (63%, 36 of 57) develop new-onset depression (*P*=0.293). Lastly, there was no significant difference in SVR among participants with (56%, 9 of 16) and without (68%, 48 of 71) new-onset suicide risk (moderate to high) during treatment (*P*=0.388).

Overall, 6% of treated participants (n=7) discontinued therapy early due to psychiatric side effects. At enrolment, none of these seven participants demonstrated depression as measured by MINI and all participants were in the normal/mild range of depressive symptoms as assessed by the DASS. Two of these participants were receiving

antidepressants prior to HCV treatment. However, four of the seven developed new-onset depression during therapy.

Use of antidepressant medication prior to and during HCV treatment

Among treated participants, 41% (46 of 111) received antidepressants at any time from study enrolment to the end of HCV treatment: half (n=23) were receiving antidepressants at enrolment (six of whom discontinued antidepressants before HCV treatment initiation) and half (n=23) initiated antidepressants during treatment. Thirty five percent (11 of 31) of participants with new-onset depression initiated antidepressants during HCV treatment, while 16% (9 of 57) of those without enrolment or new-onset depression initiated antidepressants during HCV therapy (3 participants did not have available MINI assessments). Participants receiving antidepressants during HCV treatment were more likely to achieve SVR compared to those not receiving antidepressants (77% vs. 51%, *P*=0.006).

Post-treatment depression

Among treated participants with available assessments at both enrolment and six months following HCV treatment, there was no significant difference in the proportion with depression (9%, n=6 vs. 14%, n=9; *P*=0.065) and moderate/high suicide risk (14%, n=9, 12%, n=8; *P*=1.00) at enrolment compared to six months following treatment.

6.10. Discussion

In this study of treatment of recently acquired HCV infection among a predominantly IDU population, depression prior to and during treatment was common, but did not impact response to therapy. Further, depression was an important indicator of treatment deferral, with relatively low rates of depression at study enrolment among those commencing treatment. Social marginalization characteristics were the major predictors of enrolment and new-onset depression. New-onset depression was also reversible, with similar rates of depression and suicide risk six months post-treatment compared to enrolment levels. Favourable HCV treatment outcomes among participants with enrolment and new-onset depression suggest that appropriate clinical and psychiatric management enabled successful delivery of therapy.

At study enrolment, the proportion with depression was three-fold higher among the untreated group with detectable HCV RNA who were eligible for therapy. This is consistent other studies which have demonstrated that depression is associated with HCV treatment (125, 126, 153, 155, 243). The association of depression with treatment deferral indicates appropriate initial clinical and psychiatric assessment.

In the ATAHC study, depression at study enrolment was associated with sociodemographic characteristics, including recent IDU and lack of employment. There has been limited evaluation of factors associated with depression among HCV-infected IDUs (prior to IFN based treatment). However, poor health related quality of life and personal wellbeing in IDUs with (366) and without HCV infection (367, 368) is well documented in previous cross-sectional studies. Further, among IDUs, depression has been associated with sociodemographic factors such as unemployment and recent public injection (236). In ATAHC, social functioning was associated with new-onset depression. Measurement of social functioning prior to treatment may provide a useful tool for predicting who may be at

risk of developing psychiatric side effects during HCV treatment and require enhanced psychiatric assistance and monitoring.

Favourable HCV treatment outcomes were observed among participants with depression at enrolment and those with new-onset depression. The observation that psychiatric disease does not impair HCV treatment response is consistent with other studies of IDUs (231) and non-IDUs (208, 210). A recent study in patients with chronic HCV infection which excluded IDUs and those with severe psychiatric disorders, also did not find any significant association between new-onset depression and SVR rates (240). In fact, some studies have demonstrated a higher SVR in those with depression. The suggested mechanism for an observed increase in SVR among those with depression is that depression may act as a pharmacodynamic surrogate for adequate drug levels of PEG-IFN (240, 244, 369). In the ATAHC study, similar SVR rates among those with and without new-onset depression would appear to indicate appropriate psychiatric monitoring and management. Interestingly, only a third of participants with new-onset depression were commenced on anti-depressants, with high SVR in this group compared to the overall treated population.

This study has a number of limitations. Our definition of depression was based on participant self-report, rather than a medical diagnosis following consultation with a psychiatrist. However, MINI has good correlation with Structured Clinical Interview for DSM-IV-TR Axis I (SCID-I) (364) and the Composite International Diagnostic Interview (CIDI) (365). The MINI categorizes participants based on the presence or absence of major depressive episode as a dichotomous variable. The result of this is two-fold. First, the proportion with depression at enrolment may be underestimated, given that some patients with mild symptoms of depression may not have been detected using the MINI. Second, those with mild depression at baseline may have had a lower threshold for the development of new-onset depression, thus overestimating the proportion that developed new-onset depression during treatment.

Lastly, the results may not be generalizable to other populations with HCV infection and particularly non-IDUs.

In conclusion, this study identified depression as an indicator of HCV treatment deferral at enrolment. Given the association between lower social functioning and depression at enrolment and during treatment, social functioning assessment may be a useful method to identify those at increased risk of depression before and/or during treatment. In addition, it was shown that mental health parameters (depression and/or suicide ideation) at enrolment or during treatment do not impact SVR. Therefore, given appropriate monitoring, patients with depression should be considered for HCV treatment.

6.11. Acknowledgments

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6.12. Tables

Table 1. Characteristics among all participants enrolled in ATAHC (n= 163)

	Total study population (n=163)	Treated (n=111)	Untreated HCV RNA positive at enrolment (n=34)	Untreated HCV RNA negative at enrolment (n=18)
Male, n (%)	116 (71%)	83 (75%)	22 (65%)	11 (61%)
Age (yrs), mean ±SD	34.3 ± 9.9	34.5 ± 10.4	34.7 ± 9.0	32.2 ± 8.4
Tertiary education or greater, n (%)	66 (40%)	51 (46%)	9 (26%)	6 (33%)
Full-time or part-time employment, n (%)	63 (39%)	52 (47%)	9 (26%)	2 (11%)
Methadone or buprenorphine treatment				
Ever (not current)	17 (10%)	12 (11%)	4 (12%)	1 (6%)
Current	22 (14%)	12 (11%)	6 (18%)	4 (22%)
Social functioning score, median (IQR)*	13 (8-18)	11 (6-17)	15 (9-19)	18 (13-20)
Injecting drug use ever, n (%)	124 (76%)	84 (76%)	28 (82%)	12 (67%)
Injected over the past month, n (%)†	53 (43%)	31 (37%)	15 (54%)	7 (58%)
HIV infection, n (%)	50 (31%)	37 (33%)	11 (32%)	2 (11%)
Hepatitis B virus (HBV) surface antigen, n (%)	2 (1%)	1 (1%)	0 (0%)	1 (6%)
Log_{10} HCV RNA - screening, median (log IU/L)	5.6	5.8	4.0	0
HCV genotype				
Genotype 1	75 (46%)	62 (56%)	13 (38%)	0
Genotype 2	6 (4%)	4 (4%)	2 (6%)	0
Genotype 3	56 (34%)	40 (36%)	16 (47%)	0
Genotype 4	1 (1%)	0 (0%)	1 (3%)	0
Missing genotype	25 (15%)	5 (4%)	2 (6%)	18 (100%)

* IQR (interquartile range), †among participants who reported injecting

Table 2. Mental health characteristics among participants enrolled in ATAHC with available mental health assessments at enrolment*

	Total study population	Treated	Untreated HCV RNA positive at enrolment	Untreated HCV RNA positive at enrolment
Mental health parameters/DASS-21	n= 158	n= 108	n= 34	n= 16
Depression, median (range)	8 (0-42)	6 (0-42)	13 (0-40)	14 (0-36)
Normal, n (%)	81 (51%)	64 (59%)	11 (32%)	6 (37%)
Mild, n (%)	20 (13%)	12 (11%)	6 (18%)	2 (12%)
Moderate, n (%)	28 (18%)	18 (17%)	9 (26%)	1 (6%)
Severe, n (%)	12 (8%)	4 (4%)	4 (12%)	4 (25%)
Extremely severe, n (%)	17 (11%)	10 (9%)	4 (12%)	3 (19%)
Anxiety, median (range)	6 (0-40)	6 (0-40)	10 (0-26)	11 (0-40)
Normal, n (%)	81 (51%)	62 (57%)	12 (35%)	7 (44%)
Mild, n (%)	13 (8%)	9 (8%)	3 (9%)	1 (6%)
Moderate, n (%)	34 (22%)	22 (20%)	8 (24%)	4 (25%)
Severe, n (%)	15 (9%)	9 (8%)	6 (18%)	0 (0%)
Extremely severe, n (%)	15 (9%)	6 (6%)	5 (15%)	4 (25%)
Stress, median (range)	12 (0-42)	10 (0-42)	14 (0-36)	15 (0-38)
Normal, n (%)	99 (63%)	73 (68%)	18 (53%)	8 (50%)
Mild, n (%)	21(13%)	13 (12%)	6 (17%)	2 (12%)
Moderate, n (%)	17 (11%)	13 (12%)	3 (9%)	1 (6%)
Severe, n (%)	12 (8%)	5 (5%)	4 (12%)	3 (19%)
Extremely severe, n (%)	9 (6%)	4 (4%)	3 (9%)	2 (12%)
Mental health parameters/ MINI	n= 160	n= 110	n= 34	n= 16
Current major depressive episode, n (%)	25 (16%)	10 (9%)	9 (26%)	6 (37%)
Suicide risk (moderate and high), n (%)	28 (18%)	11 (10%)	12 (35%)	5 (31%)
Psychiatric medication- total, n (%)[¶]	49 (30%)	31 (28%)	12 (35%)	6 (33%)
Antidepressants- total , n (%)[¶]	37 (23%)	23 (21%)	8 (24%)	6 (33%)

*total n=158 for DASS-21 & total n=160 for MINI, † denominator is participants with current major depressive episode, ¶ some participants take more than one type of medication

Table 3. Characteristics associated with major depressive episode prior to treatment for recent HCV infection (n=160) [*]

Characteristic	Depressed, n= 25	OR	95% CI	*P*	*P*-Overall	AOR	95% CI	*p*
Age, >34 (vs. ≤34)	11 (14%)	0.73	0.31-1.72	0.472	–	–	–	–
Female sex (vs. male)	9 (20%)	1.50	0.6-3.7	0.385	–	–	–	–
Caucasian ethnicity (vs. other)	21 (14%)	0.42	0.12-1.46	0.173	–	–	–	–
Tertiary education or greater (vs. less than tertiary)	8 (12%)	0.66	0.27-1.64	0.376	–	–	–	–
Full time/part time employment (vs. no employment/other)	3 (5%)	0.11	0.05-0.61	0.007	–	0.23	0.06-0.82	0.023
Rental accommodation (vs. owned)	5 (13%)	0.72	0.24-2.10	0.545	0.818	–	–	–
Other types of accommodation (vs. owned)	3 (14%)	0.81	0.21-3.07	0.761	–	–	–	–
Methadone/Buprenorphine therapy- ever (vs. never)	2 (12%)	0.70	0.15-3.33	0.655	0.882	–	–	–
Current therapy (vs. never)	3 (14%)	0.83	0.22-3.09	0.782	–	–	–	–
Injecting drug use ever (vs. never)	22 (18%)	2.47	0.69-8.77	0.162	–	–	–	–
Injecting drug use past 6 months (vs. not in past 6 months)	21 (21%)	3.95	1.29-12.15	0.016	–	–	–	–
Injecting drug use past 30 days, yes (vs. not in past month)	15 (27%)	3.87	1.57-9.58	0.003	–	3.04	1.19-7.72	0.019
Social functioning score, 10-16 (vs. 0-9)[†]	8 (17%)	3.37	0.84-13.57	0.088	0.064	–	–	–
≥17 (vs. 0-9)	11 (24%)	5.03	1.30-19.37	0.019	–	–	–	–
Alcohol- standard drinks/day past month, 3-4 (vs. ≤2)[†]	2 (7%)	0.24	0.05-1.15	0.074	–	–	–	–
≥5 (vs. ≤2)	3 (10%)	0.36	0.09-1.38	0.136	0.103	–	–	–
Antipsychotic medication (vs. no antipsychotic)	3 (27%)	2.16	0.53-8.80	0.280	–	–	–	–
Antidepressant (SSRI, SNRI,TCA,TeCA) (vs. no antidepressant)	9 (25%)	2.25	0.90-5.64	0.084	–	–	–	–
HCV/HIV co-infection (vs. HCV mono-infection)	3 (6%)	0.27	0.08-0.96	0.040	–	–	–	–

[*] three participants had missing MINI survey prior to HCV treatment, [†] variables divided to tertiles by distribution

Table 4. Longitudinal changes in MINI and DASS scores in ATAHC among all participants treated for recent HCV infection[*]

Scale	Pre-treatment	Week 12	Week 24	Week 36	Week 48
MINI	(n= 110)	(n= 96)	(n= 82)	(n= 72)	(n= 67)
Major depressive episode, n (%)	10 (9%)	30 (31%)	21 (26%)	11 (15%)	13 (19%)
Suicide risk, n (%)	37 (34%)	33 (34%)	28 (34%)	18 (25%)	21 (32%)
Suicide risk level, n (%)[¶]					
Low	26 (70%)	20 (61%)	15 (54%)	10 (57%)	12 (60%)
Moderate	7 (19%)	4 (12%)	4 (14%)	2 (11%)	3 (15%)
High	4 (11%)	9 (27%)	9 (32%)	6 (33%)	5 (25%)
DASS-21	(n= 108)	(n= 97)	(n= 83)	(n= 71)	(n= 71)
Depression					
Median (IQR)[¥]	6 (1-14)	12 (4-22)	10 (2-20)	8 (2-14)	8 (2-20)
Normal, n (%)	64 (59%)	44 (45%)	37 (45%)	45 (63%)	38 (54%)
Mild, n (%)	12 (11%)	13 (13%)	10 (12%)	5 (7%)	8 (11%)
Moderate, n (%)	18 (17%)	13 (13%)	17 (20%)	10 (14%)	9 (13%)
Severe, n (%)	4 (4%)	13 (13%)	10 (12%)	3 (4%)	6 (8%)
Extremely severe, n (%)	10 (9%)	14 (14%)	9 (11%)	8 (11%)	10 (14%)
Anxiety					
Median (IQR)[¥]	6 (2-11)	10 (4-18)	10 (4-16)	4 (2- 12)	6 (2-12)
Normal, n (%)	62 (57%)	41 (42%)	28 (34%)	42 (59%)	37(52%)
Mild, n (%)	9 (8%)	6 (6%)	9 (11%)	4 (6%)	7 (10%)
Moderate, n (%)	22 (20%)	18 (19%)	24 (29%)	11 (15%)	14 (20%)
Severe, n (%)	9 (8%)	12 (12%)	8 (10%)	5 (7%)	3 (4%)
Extremely severe, n (%)	6 (6%)	19 (21%)	14 (17%)	9 (13%)	10 (14%)
Stress					
Median (IQR)[¥]	10 (4-17)	16 (6-24)	14 (6-24)	12 (4-18)	10 (4-18)
Normal, n (%)	73 (68%)	46 (47%)	45 (54%)	47 (66%)	43 (61%)
Mild, n (%)	13 (12%)	12 (12%)	8 (10%)	8 (11%)	11 (15%)
Moderate, n (%)	13 (12%)	19 (20%)	17 (20%)	9 (13%)	5 (7%)
Severe, n (%)	5 (5%)	13 (13%)	10 (12%)	5 (7%)	7 (10%)
Extremely severe, n (%)	4(4%)	7 (7%)	3 (4%)	2 (3%)	5 (7%)

[*]number of participants with available MINI and DASS surveys varies at each time point, [†]among participants with current major depressive episode, [¶] among participants with suicide risk, [¥] IQR (interquartile range)

Table 5. Characteristics associated with new onset major depressive episode among participants without depression prior to the initiation of treatment for recent HCV infection (n=88)

	Depressed, n= 31	OR	95% CI	*P*	*P*-Overall
Caucasian ethnicity (vs. other)	26 (33%)	0.39	0.09-1.58	0.189	–
Full time/part time employment (vs. no employment, other)	13 (29%)	0.56	0.23-1.37	0.205	–
HCV/HIV co- infection (vs. HCV mono-infection)	13 (38%)	1.24	0.51-3.03	0.639	–
Injecting drug use ever (vs. never)	24 (37%)	1.46	0.53-4.02	0.467	–
Injecting drug use past 6 months (vs. not in past 6 months)	21 (45%)	2.50	1.00-6.26	0.050	–
Injecting drug use past 30 days (vs. not in past month)	9 (41%)	1.45	0.53-3.93	0.464	–
Social functioning score, 10-16 (vs. ≤9)*	11 (42%)	1.59	0.49-5.15	0.439	–
≥17 (vs. ≤9)	10 (53%)	5.69	1.61-20.14	0.007	0.018
Alcohol-number of drinks/day past month, 3-4 (vs. ≤2)*	2 (12%)	0.14	0.03-0.76	0.022	–
≥5 (vs. ≤2)	5 (24%)	0.31	0.09-1.11	0.071	0.035
Depression by DASS, moderate to extremely severe symptoms (vs. normal, mild symptoms)	12 (52%)	2.73	1.02-7.29	0.046	–
Depression by DASS, mild to extremely severe symptoms (vs. normal symptoms)	15 (47%)	2.29	0.92-5.73	0.075	–
Antidepressant (SSRI, SNRI, TCA, TeCA) (vs. no antidepressant)	9 (45%)	1.71	0.62-4.73	0.301	–

* variables divided to tertiles by distribution

6.13. Figures

Figure 1. Sustained virological response (SVR) among participants with and without depression and suicide risk (moderate to high levels)

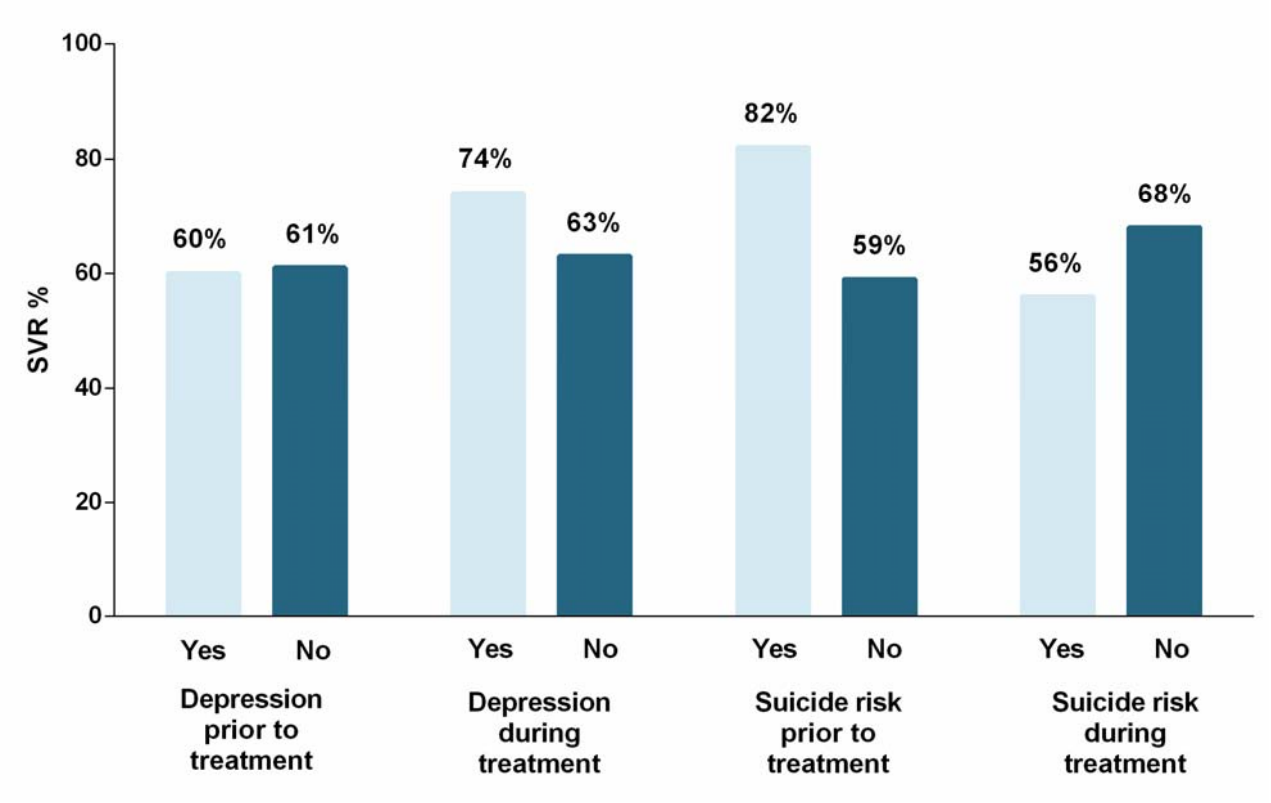


Figure 2A. Longitudinal changes of depression among treated participants, assessed by MINI. Depression defined as: current major depressive episode (MDE)

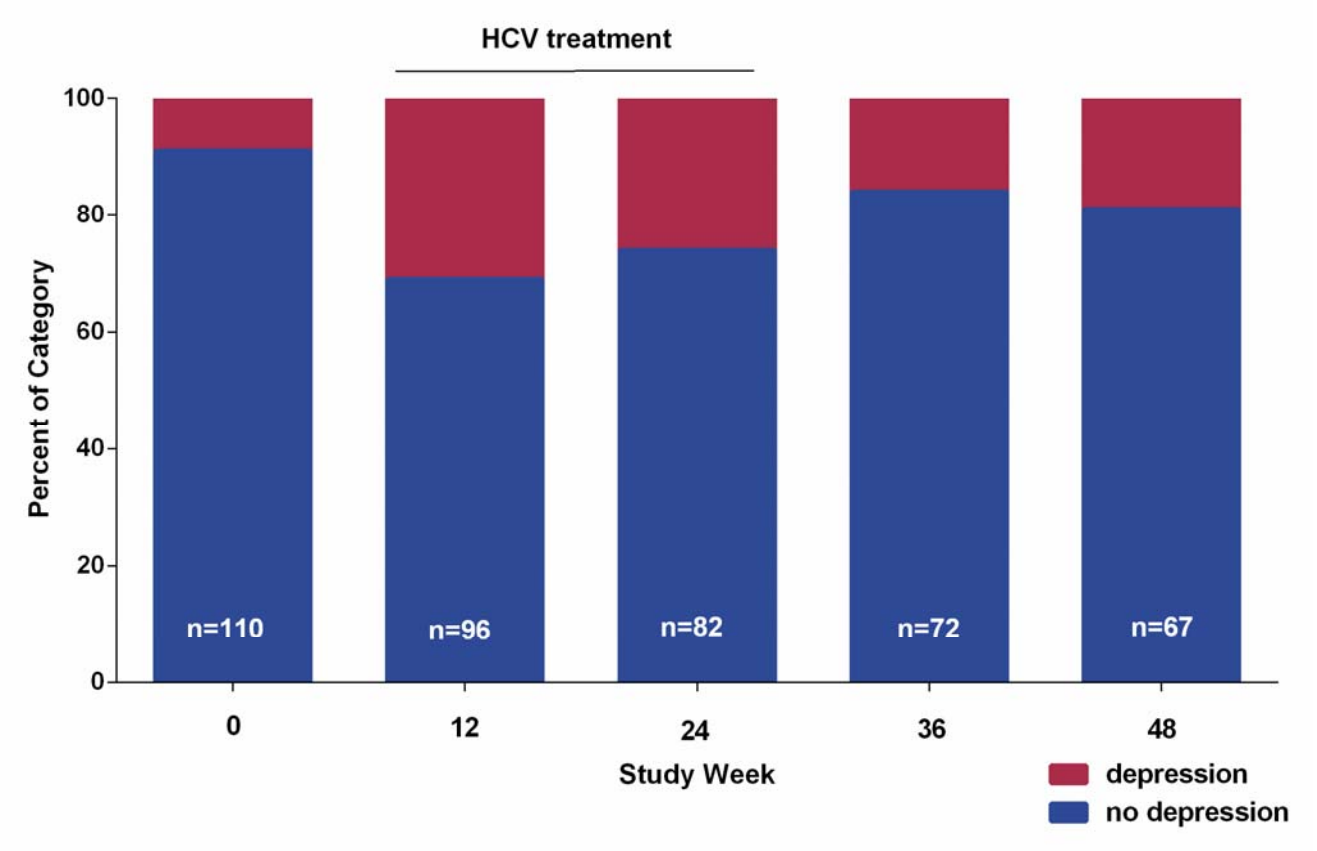
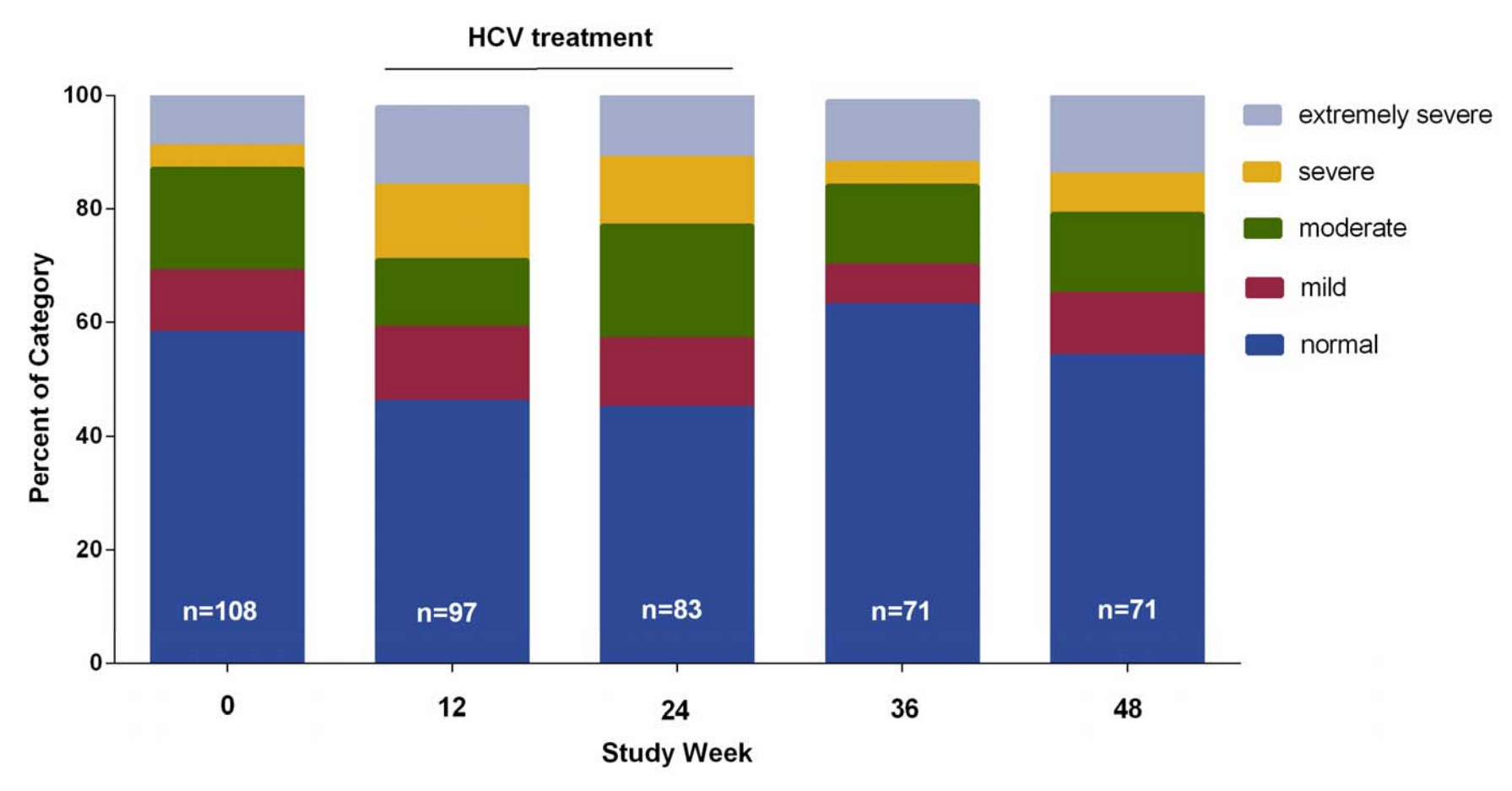


Figure 2B. Longitudinal changes of depressive symptoms among treated participants, categorized according to DASS severity rating chart: normal (0-9), mild (10-13), moderate (14-20), severe (21-27), and extremely sever (28+)



Chapter Seven

Integrated Discussion

7.1. Chapter Introduction

The broad aim of the research described in this thesis was to inform barriers to the assessment and treatment of HCV infection among PWID. There were also five specific aims and hypotheses. In this chapter, the key findings of the research are summarised with respect to the five specific aims and hypotheses. The implications for enhanced access to HCV care, directions for future research, and thesis strengths and limitations are discussed.

Key Findings

7.2. Aim 1: To evaluate mortality and life expectancy among people with chronic HCV infection

Hypothesis: Without therapeutic intervention, people with chronic HCV infection are at higher risk of liver-related mortality and reduction in life expectancy.

This aim is addressed in Chapter Two. Despite two decades of research on the natural history of HCV infection, uncertainty remains on the individual mortality risk and estimates of life expectancy among people with HCV infection. Chapter Two was a population-based linkage study. HCV notifications (mandatory notification of anti-HCV positive serology since 1991) reported to the NSW Health Department from 1992-2006 were linked to cause of death data. Abridged life tables were constructed from age-specific mortality rates, using a competing risk methodology. Following removal of drug-related causes of death, NSW people with an HCV notification had a significant reduction in life expectancy, compared to the general population of Australia. Concurrent with the ageing cohort effect among people with HCV infection, major causes of death shift from drug- to liver-related causes. Liver-related deaths are expected to further increase as the cohort is ageing and duration of infection increases.

7.3. Aim 2: To evaluate HCV treatment uptake and associated factors among inner city residents

Hypothesis: Despite advances in antiviral therapy, HCV treatment uptake has remained suboptimal. Several clinical (including HCV/HIV co-infection) and socio-demographic factors (including age, ethnicity, employment status, housing status and recent drug use) are associated with low HCV treatment uptake.

This aim is addressed in Chapter Three. Despite high HCV treatment willingness among PWID and safety and efficacy of HCV treatment for this population, treatment uptake remains suboptimal among PWID. There are few recent data on the surveillance of HCV treatment uptake, particularly among people who use drugs, including recent trends and factors associated with HCV treatment. Chapter Three was a large community-based study of inner city residents recruited from 2003 to mid-2004. HCV status and treatment were retrospectively and prospectively determined through data linkages with provincial virology and pharmacy databases. Follow-up continued until 2009. Between 2003 and 2009, there was a modest increase in the number of individuals who received treatment for HCV infection. However, HCV treatment uptake remained suboptimal. Several demographic and behavioural factors were shown to be associated with impaired access to HCV care in this population. Aboriginal ethnicity, crack cocaine use and methamphetamine injecting were associated with lower treatment uptake.

7.4. Aim 3: To evaluate HCV assessment and treatment uptake among PWID in opioid substitution setting

Hypothesis: Integration of HCV care within the existing infrastructure of opioid substitution clinics is a successful strategy to increase HCV assessment and treatment uptake among PWID.

This aim is addressed in Chapter Four. The traditional management of HCV infection via referral to secondary or tertiary healthcare centres has not been successful in expanding HCV care services among PWID, resulting in low HCV assessment and treatment uptake in this population. Chapter Four was an observational cohort study to evaluate the provision of HCV assessment and treatment among people with chronic HCV infection and a history of injecting drug use. Recruitment occurred between 2009 and 2012 through six OST clinics, two community health centres and one Aboriginal community controlled health organisation in NSW. HCV specialist assessment and treatment were relatively high in this study. Factors independently associated with HCV specialist assessment included non-Aboriginal ethnicity, no recent benzodiazepine use and non-1 HCV genotype. Factors independently associated with HCV treatment uptake included non-Aboriginal ethnicity, living with the support of family and/or friends, never receiving OST, no recent methamphetamine use and non-1 HCV genotype. Participants who had never sought HCV treatment described lack of HCV-related knowledge as the major reason for not having ever sought treatment.

7.5. Aim 4: To evaluate willingness to receive HCV treatment among PWID

Hypothesis: Despite self-reported barriers to HCV treatment, PWID have a high willingness to receive antiviral therapy. High willingness to receive HCV treatment is associated with subsequent HCV assessment and treatment uptake.

This aim is addressed in Chapter Five. Effective engagement of PWID in programs to enhance HCV assessment and treatment is essential in order to lower the future disease burden of HCV infection. However, the impact of patient treatment willingness and intent on subsequent HCV assessment and treatment uptake has not been studied before. Similar to the previous chapter, Chapter Five was an observational cohort study to evaluate the provision of HCV assessment and treatment among people with chronic HCV infection and a history of injecting drug use. Recruitment occurred between 2009 and 2012 through six OST clinics, two community health centres and one Aboriginal community controlled health

organisation in NSW. HCV treatment willingness and intent were high in this study. Factors independently associated with HCV treatment willingness included non-Aboriginal ethnicity, living with a spouse or other relatives/friends and never receiving OST. Factors independently associated with HCV treatment intent included age (35-54 years), non-Aboriginal ethnicity, living with a spouse or other relative/friends, no recent heroin use and non-1 HCV genotype. High HCV treatment willingness and early treatment intent were both predictive of subsequent HCV specialist assessment and treatment uptake.

7.6. Aim 5: To evaluate the impact of treatment for HCV infection on depression and mental health parameters

Hypothesis: PWID have a higher risk of mental health disorders (including depression). However, HCV treatment does not increase the risk of mental health issues in this group of patients.

This aim is addressed in Chapter Six. HCV treatment is often withheld from PWID and individuals with co-morbid psychiatric disease due to concerns of poor adherence, ongoing drug use, psychosocial instability and exacerbation of pre-existing psychiatric disease mediated by interferon-based therapy. Chapter Six was a multicenter, prospective cohort study of the natural history and treatment of recent HCV infection among a predominantly PWID population. Recruitment of people with HCV mono- and HCV/HIV co-infection occurred between 2004 and 2007. All participants had recent infection with either acute or early chronic HCV infection. Participants with HCV mono-infection received PEG-IFN α-2a (180μg/week) for 24 weeks; those with HCV/HIV co-infection received PEG-IFN with ribavirin. In this study, depression prior to and during treatment was common, but did not impact response to therapy. Further, depression was an important indicator of treatment deferral, with relatively low rates of depression at study enrolment among those commencing treatment. Social marginalization characteristics were the major predictors of enrolment and

new-onset depression. New-onset depression was also reversible, with similar rates of depression and suicide risk six months post-treatment compared to enrolment levels.

7.7. Implications for Enhanced Access to HCV Care

In the majority of high income countries, people with HCV infection are ageing and at risk of progressive liver disease (5). Successful HCV treatment with viral eradication is associated with improved quality of life, liver disease regression, and reduction in liver- and all cause-related mortality (180). The treatment landscape for hepatitis C is rapidly changing (6, 7). From 2002 to 2011, the standard of care treatment for chronic HCV infection was combination therapy with PEG-IFN/RBV (9). For people with HCV genotype 1, the likelihood of achieving a SVR was approximately 40% after 48 weeks of therapy (9). The recent addition of the HCV protease inhibitors telaprevir and boceprevir to interferon-based therapy has significantly increased the likelihood of SVR for people with HCV genotype 1 (6, 7). More effective, interferon-free antiviral regimens are likely to dominate the HCV therapeutic landscape within the next five years (6, 7). Anticipated HCV treatment regimens will have reduced toxicity, shorten treatment durations, improved dosing schedules, and enhanced cure rates (6, 7). However, these therapeutic developments will be associated with considerable additional expense, at least during the initial decade of their implementation. Cost-effectiveness analyses will therefore need to incorporate parameters associated with disease progression and lowered life expectancy based on representative population-based cohorts. Findings in Chapter Two highlight the significant reduction in life expectancy among people with an HCV notification. These findings will facilitate public health strategic planning in response to increasing disease burden among people with HCV infection.

Given the considerable burden of HCV-related morbidity and mortality and suboptimal rates of HCV assessment and treatment in most settings (5), continuous efforts are needed to enhance access to HCV care, particularly among PWID. Findings in Chapter Three highlight the importance of ongoing surveillance of HCV treatment uptake. Further, these findings

contribute to a better understanding of the complex barriers to access HCV care. Impaired access to HCV treatment among Aboriginal people indicates the need for delivery of culturally appropriate treatment programs developed by and for marginalised populations. Furthermore, variations in the characteristics of PWID highlight the importance of developing HCV treatment programs that are designed to address specific needs of this population. Findings in Chapter Three underscore the need for a major shift in the public health approach to HCV care and treatment to expand access and reduce the future burden of HCV-related disease among PWID.

The traditional management of HCV infection via referral to secondary or tertiary healthcare centres has not been successful in expanding HCV services among PWID (142-144). However, the implementation of different integrated models across various settings has been effective at addressing barriers to care to enhance HCV assessment and treatment in this population (273). Findings in Chapter Four demonstrate that PWIDs engagement in the healthcare system can significantly improve, given that HCV services are delivered in settings that are adapted for the needs of this population. Further, findings in Chapter Four underscore the importance of continuous attention to barriers at the provider and system levels (such as the availability of support for patients with complex needs) to enhance management of hepatitis C and move towards uptake of treatment in the longer term.

Among PWID, willingness to receive PEG-IFN/RBV treatment for HCV infection lies between 53% and 86% (112, 113, 162-167). Findings in Chapter Five have demonstrated that high treatment willingness and intent are associated with subsequent HCV specialist assessment and treatment uptake. While new interferon-free regimes are anticipated to remove many barriers to HCV services, evidence-based and sustainable strategies are required to further engage those willing to receive antiviral therapy and develop programs to support those less willing to receive therapy. Given that several demographic and clinical factors are associated with lower treatment willingness and intent, tailored treatment programs are required that

provide support for complex needs of those who are less willing to receive HCV treatment and appear less suitable for antiviral therapy.

Interferon-based therapy is complicated by several neuropsychiatric side effects (190); however, it has been shown to be safe and effective among PWID (8). Findings in Chapter Six have demonstrated favourable HCV treatment outcomes among participants with enrolment and new-onset depression. These findings suggest that appropriate clinical and psychiatric management enabled successful delivery of therapy. Given that interferon-based regimens are still administrated in the majority of settings, identifying patients who are at increased risk of developing psychiatric symptoms during antiviral therapy will contribute to improved treatment management.

7.8. Directions for Future Research

At this time of novel HCV treatment opportunities, new strategies are needed to expand access to HCV services (370). In settings such as Australia, the majority of all HCV infections are estimated to have been notified (43). Enhanced engagement of diagnosed people in treatment programs should become a priority in public health response to the HCV epidemic.

As antiviral therapy shifts to interferon-free regimens (6, 7), increased treatment willingness among PWID is likely to occur due to reduced treatment toxicity, elimination of neuropsychiatric side effects, and higher cure rates. Educating patients and healthcare providers about the natural history of HCV infection and new treatment options will be a key step toward increasing the number of individuals who receive treatment in the future. Providers will need to be educated about best practices for screening, assessment and treatment of HCV infection. Given the rapid development of HCV therapeutic regimens and the associated expenses, updated treatment guidelines will be needed to serve as a valuable resource for healthcare providers and to influence governments funding policies.

Further, training community-based healthcare providers to treat people with HCV infection should become a key element for broadening access to HCV care. Community-based health centres are more accessible to people in both urban and rural areas and are more likely to offer culturally appropriate care. Ongoing relationships with healthcare providers in these settings further establish trust and create opportunities for patients to engage with the healthcare system. Future research in HCV should include evaluations of screening, assessment and treatment in community healthcare clinics, drug and alcohol treatment programmes and other settings which have the infrastructure to offer accessible care to people with HCV infection. Finally, improved and expanded national disease surveillance is needed to improve our understanding of trends in HCV disease progression and treatment uptake. As novel approaches towards HCV assessment and treatment are developed, it will be necessary to monitor outcomes so that successful strategies to increase access to HCV care can be developed.

7.9. Thesis Strengths and Limitations

In this thesis, a variety of study designs were used to investigate HCV assessment and treatment uptake among PWID, including population-based linkage, community-based linkage and prospective cohort studies. These methods have allowed for a contribution to the current knowledge in the field of hepatitis C research. Nonetheless, several limitations have been outlined and discussed in each chapter.

Linkage studies are based on date of HCV notification and therefore may present some uncertainty with respect to the duration of infection. The nature of linkage studies does not allow for ongoing evaluation of lifestyle or behavioural data. In Chapter Two, this limitation has not allowed to evaluate the potential impact of specific behavioural and lifestyle exposures on increased mortality. In Chapter Three, this limitation has not allowed to evaluate potential changes in behavioural and lifestyle factors during the follow-up. Further, PWID are a difficult population to recruit and follow, therefore, some findings may not be

generalizable to other PWID populations, particularly to those who might be less engaged in health services. Finally, behavioural analyses have largely relied on self-reported data which might be biased.

7.10. Conclusions

The new therapeutic opportunities have created great hope to remarkably reduce the rising disease burden of HCV infection. However, barriers to HCV assessment and treatment among PWID are complex and require a multidimensional approach. Partnerships between members of academia, community health centres, people with HCV infection, the pharmaceutical industry, and government entities are needed to expand access to HCV services. Delivery of affordable, effective, safe, and broad healthcare to all people with HCV infection should be the goal for the future of HCV research.

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