

Assessment and Treatment of Hepatitis C Virus Infection Among People Who Inject Drugs in the Opioid Substitution Setting: ETHOS Study

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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 5 opioid substitution treatment (OST) clinics, 2 community health centers, and 1 Aboriginal community controlled health organization in New South Wales, Australia.

Results. Among 387 enrolled participants, mean age was 41 years, 71% were male, and 15% were of Aboriginal ethnicity. Specialist assessment was undertaken in 191 (49%) participants, and 84 (22%) commenced interferon-based treatment. In adjusted analysis, HCV specialist assessment was associated with non-Aboriginal ethnicity (adjusted odds ratio [AOR], 4.02; 95% confidence interval [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).

Conclusions. HCV treatment uptake was relatively high among this highly marginalized population of PWID. Potentially modifiable factors associated with treatment include drug use and social support.

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

Injection drug use (IDU) is the major risk factor driving the hepatitis C virus (HCV) epidemic in most developed countries [1]. Chronic HCV infection is associated with excess risk of morbidity and mortality [2]. Antiviral therapy is associated with reduction in HCV disease burden [2] and is effective among people who inject drugs (PWID) [3]. The broadened inclusion of

PWID in HCV treatment is supported by international guidelines [4]. However, the traditional management of HCV infection via referral to secondary or tertiary healthcare centers has not been successful in expanding HCV care among PWID, resulting in low HCV assessment and treatment uptake [5].

HCV treatment among PWID presents multiple challenges due to barriers of care at the patient, provider, and systems levels [2]. 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 [6–8]. A multidisciplinary approach has been the foundation of successful integrated models [8], including

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close collaboration between clinicians, nursing staff, and other support services for delivery of HCV care [8]. Opioid substitution treatment (OST) clinics and community health centers offer an opportunity for integration of HCV care within existing infrastructures for addiction care, and such models can increase HCV assessment and treatment [7, 9, 10]. However, the majority of studies have consisted of small participant numbers, are often limited to 1 center, and rely on retrospective data collection. There is a need for larger, multicenter, 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 in Opioid Substitution Settings (ETHOS) study recruited participants between 2009 and 2012 within a network of 9 clinics in New South Wales (NSW), Australia. This study aimed to evaluate HCV specialist assessment, treatment uptake, and associated factors among people with chronic HCV and a history of IDU.

METHODS

Study Population and Design

The ETHOS study is a prospective observational cohort evaluating an innovative model for the provision of HCV assessment and treatment among people with a history of IDU 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 network of 9 clinics (6 OST clinics, 2 community health centers, and 1 Aboriginal community controlled health organization) undertaking HCV assessment, treatment, and monitoring among people with a history of IDU.

Inclusion criteria included age ≥ 18 years, a history of IDU, 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 (close of study enrollment). 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 visit. The study was approved by local research ethics committees.

Study Sites

Recruitment was performed through a network of 9 clinics in NSW, Australia (6 OST clinics, 2 community health centers, and 1 Aboriginal community controlled health

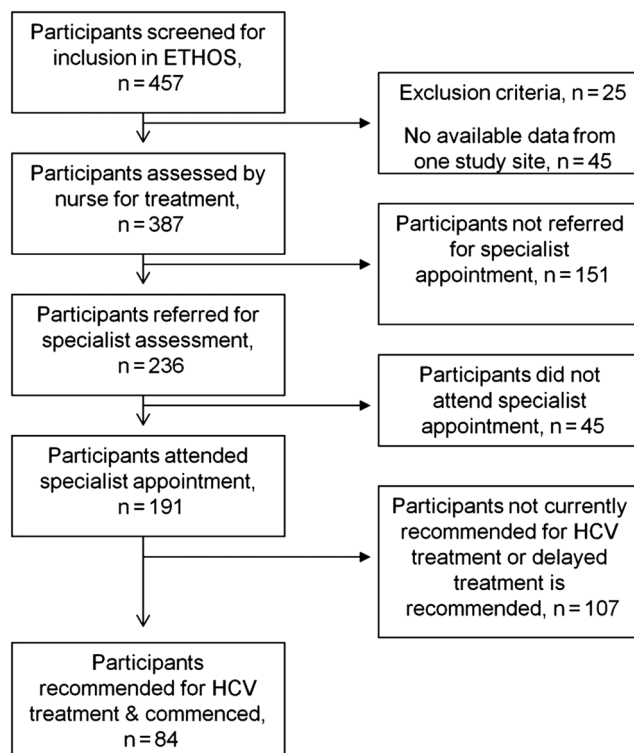


Figure 1. Hepatitis C virus (HCV) specialist assessment and treatment among participants in the Enhancing Treatment for Hepatitis C in Opioid Substitution Settings (ETHOS) study.

organization), including 1 rural, 1 regional, and 7 urban clinics. One of the clinics (Gateway clinic) did not have available enrollment data and was excluded from analyses (Supplementary Figure 1 and Supplementary Table 1).

At study enrollment, participants were assessed for HCV infection by a clinical nurse or general practitioner. HCV nursing services were available at 7 of 8 clinics, with 1 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 disease specialist, hepatologist, gastroenterologist, or a general practitioner with HCV training and prescribing rights) for HCV assessment. HCV specialist services occurred on-site at 5 clinics, on-site/off-site at 2 clinics, and off-site at 1 clinic. Two clinics offered HCV peer-support services (Supplementary Table 1).

Data Collection

All patients enrolled in the study were recommended to return for follow-up every 6 months. At enrollment and each 6-monthly visit, forms were completed comprising a practitioner-administered questionnaire, standard clinical assessment, and structured case note review. The practitioner-administered questionnaires included demographics, injecting behaviors, OST social functioning,

Table 1. Characteristics of Participants With Chronic Hepatitis C Virus Infection and History of Injection Drug Use in the ETHOS Cohort

Characteristic	Overall (N = 387)
Age, mean (SD)	41 (9)
Male sex ^a	275 (71%)
Aboriginal ethnicity	59 (15%)
Finished high school or higher education ^b	74 (19%)
Living with spouse or other relatives/friends ^b	193 (50%)
Owned or rented housing ^b	313 (81%)
Full- or part-time employment ^b	36 (9%)
Current opioid substitution treatment	307 (79%)
Imprisonment ^c	36 (9%)
Drug use (injection and noninjection) ^c	248 (64%)
Benzodiazepine ^d	137 (55%)
Methamphetamine ^d	106 (43%)
Injection drug use ^c	196 (51%)
Benzodiazepine ^d	14 (7%)
Cocaine ^d	27 (14%)
Heroin ^d	132 (67%)
Methadone ^d	22 (11%)
Methamphetamine ^d	96 (49%)
Morphine ^d	55 (28%)
High-risk alcohol consumption ^e	
Female	49 (45%)
Male	86 (31%)
Social functioning score, median (range)	4 (0–18)
Mental health parameters, DASS-21 ^b	
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	
1	148 (38%)
2, 3, 6	161 (41%)
Unknown	78 (20%)

Data are No. (%) unless otherwise specified.

Abbreviations: DASS-21, 21-item Depression, Anxiety and Stress Scale; ETHOS, Enhancing Treatment for Hepatitis C in Opioid Substitution Settings; HCV, hepatitis C virus.

^a Other/unknown sex is not included.

^b Among those with available survey results.

^c In the 6 months prior to study enrollment.

^d Denominator is the total number who reported using and injection drug use, respectively.

^e Denominator is females and males who reported alcohol consumption.

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 [11, 12], sex [5, 11], ethnicity [5, 11, 12], education level [13], housing status [12], current employment status [14], living alone [14], ever and/or recent imprisonment [15], alcohol consumption [16, 17], ever and/or current enrollment in OST programs [12, 16], mental health parameters [11, 17], social functioning [12], drug use (benzodiazepines, methamphetamine) and IDU (benzodiazepines, cocaine, heroin, methadone, methamphetamine, morphine) [5, 11, 12, 16], and HCV genotype [11, 14]. Unadjusted analyses were performed using χ^2 test or Fisher exact test, as appropriate.

Mental health was evaluated by the 21-item Depression, Anxiety and Stress Scale (DASS-21), a self-administered survey assessing the severity of depression, anxiety, and stress [18]. Social functioning was evaluated by the shortened scale from the Opiate Treatment Index, addressing employment, residential stability, and interpersonal conflict as well as social support (higher scores indicate lower social functioning, measured over the previous 3 months) [19]. Housing status, recent imprisonment, and recent drug-using behavior were defined over the 6 months prior to study enrollment. Alcohol consumption was evaluated by the Alcohol Use Disorders Identification Test (AUDIT)–C (scores >3 and >4 indicate high-risk consumption among women and men, respectively) [20].

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 $P < .05$; P values were 2-sided. All analyses were performed using the statistical package Stata version 12.0 (College Station, Texas).

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

Table 2. Unadjusted and Adjusted Analysis of Factors Associated With Hepatitis C Virus Specialist Assessment in the ETHOS Cohort (N = 387)

Characteristic	Assessed by a Specialist, No. (n = 191)	OR (95% CI)	Adjusted OR (95% CI)	P Value
Age				
<35 y	43	1.00
35–45 y	75	1.38 (.84–2.27)
≥45 y	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)	<.001
OST				
Current	142	1.00
Previous, not current	14	1.82 (.76–4.33)
Never	35	1.86 (1.04–3.32)
Drug use (injection and noninjection)^a				
Yes	104			
No	87	2.33 (1.52–3.57)
Benzodiazepine use (injection and noninjection)^a				
Yes	55	1.00	1.00	...
No	136	1.80 (1.18–2.74)	2.06 (1.31–3.24)	.002
Methamphetamine use (injection and noninjection)^a				
Yes	43	1.00
No	148	1.62 (1.02–2.54)
Injection drug use^a				
Yes	82	1.00
No	109	1.86 (1.25–2.79)
HCV genotype				
1	65	1.00	1.00	...
2, 3, 6	101	2.15 (1.36–3.39)	2.13 (1.32–3.43)	.002
Unknown ^b	25	0.59 (.33–1.05)	0.63 (.34–1.14)	.125

Abbreviations: CI, confidence interval; ETHOS, Enhancing Treatment for Hepatitis C in Opioid Substitution Settings; HCV, hepatitis C virus; OR, odds ratio; OST, opioid substitution therapy.

^a In the 6 months prior to study enrollment.

^b Wald test *P* value overall is <.001.

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-time/part-time employment, had poorer social functioning, and had higher proportions of imprisonment, drug use, and IDU (Supplementary Table 2).

HCV Treatment Willingness

Although the majority of enrolled participants (331/387 [86%]) were definitely or somewhat willing to receive treatment, 59% (213/387) 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

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 enrollment and HCV treatment initiation was 0.2 years (range, 0.0–2.0 years).

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 IDU, no recent benzodiazepine use, no recent methamphetamine use, and non-1 HCV genotype (Table 2). There were no differences with respect to other factors assessed (Supplementary Table 3). In adjusted 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 to extremely severe stress, non-Aboriginal ethnicity, never receiving OST, no recent drug use, no recent IDU, no recent benzodiazepine and methamphetamine use, no recent heroin and methamphetamine injection use, and non-1 HCV genotype (Table 3). There were no differences with respect to other factors assessed (Supplementary Table 3). In adjusted 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 HCV treatment (Table 3).

DISCUSSION

In this prospective study of people with chronic HCV infection and a history of IDU assessed for HCV infection within existing OST clinics and community health centers in NSW, Australia, HCV specialist assessment and treatment were 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 [12]. However, the majority of participants were willing to receive antiviral therapy in the 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 the near future [13]. 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 [21, 22]. Treatment uptake was 22%, which is higher than treatment uptake observed among drug-user cohorts in the community (1%–6%) [5, 21–23] and consistent with that observed in tertiary-based clinics (15%–42%) [12, 16, 24] and community-based integrated models (22%–52%) [7, 9, 10, 25]. The proportions of HCV specialist assessment and treatment in ETHOS are encouraging, particularly as many untreated participants plan to initiate HCV treatment over the next 12 months. Ongoing follow-up will assess HCV treatment outcomes and further uptake of HCV treatment, including the relationship between treatment willingness and treatment uptake.

In adjusted analysis, several demographic, behavioral, 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 [14, 17]. 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 IDU [26]. Despite similar access to HCV testing between the 2 populations [26], the sociodemographic 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.

Table 3. Unadjusted and Adjusted Analysis of Factors Associated With Hepatitis C Virus Treatment in the ETHOS Cohort (N = 387)

Characteristic	Treated, No. (n = 84)	OR (95% CI)	Adjusted OR (95% CI)	P Value
Age				
<35 y	15	1.00
35–45 y	38	1.98 (1.02–3.81)		
≥45 y	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)	.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)	.006
Source of income				
Casual, pension, temporary benefit, other sources	70	1.00
Full/part-time work	14	2.55 (1.24–5.25)
OST				
Current	51	1.00	1.00	...
Previous, not current	6	1.78 (.67–4.73)	1.83 (.64–5.27)	.262
Never ^a	27	4.54 (2.49–8.27)	4.40 (2.27–8.54)	<.001
Drug use (injection and noninjection)^b				
Yes	36	1.00
No	48	3.12 (1.90–5.13)
Benzodiazepine use (injection and noninjection)^b				
Yes	19	1.00
No	65	2.20 (1.26–3.85)
Methamphetamine use (injection and noninjection)^b				
Yes	12	1.00	1.00	...
No	72	2.69 (1.39–5.18)	2.26 (1.12–4.57)	.023
Injection drug use^b				
Yes	28	1.00
No	56	2.50 (1.51–4.16)
Heroin injection^b				
Yes	19	1.00
No	65	2.02 (1.15–3.55)
Methamphetamine injection^b				
Yes	12	1.00
No	72	2.29 (1.18–4.44)
HCV genotype				
1	21	1.00	1.00	...
2, 3, 6	54	3.05 (1.73–5.37)	3.07 (1.67–5.64)	.001
Unknown ^a	9	0.78 (.34–1.79)	0.97 (.40–2.34)	.951

Abbreviations: CI, confidence interval; ETHOS, Enhancing Treatment for Hepatitis C in Opioid Substitution Settings; HCV, hepatitis C virus; OR, odds ratio; OST, opioid substitution therapy.

^a Wald test *P* value overall is <.001.

^b In the 6 months prior to study enrollment.

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 and therefore more likely to be assessed for treatment [12] and to initiate therapy.

Benzodiazepine use 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 [27]. Compared to opioid users, opioid and benzodiazepine users are more likely to use additional drugs, to inject more frequently, and to have higher rates of psychiatric comorbidities including self-harm ideation [27]. Frequent crystal methamphetamine use among regular drug users has been shown to be associated with earlier initiation to injecting, greater risk-taking injecting behavior, psychotic symptoms, and dependence [28]. 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 [29].

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 IDU and compared to participants currently receiving OST, those with no history of OST would appear to be less drug dependent (recent IDU, 19% vs 56%, respectively) and less marginalized. Current drug use has been identified as a predictor of treatment deferral [16] and no treatment uptake [5, 12, 17, 21, 24]. Likewise, previous findings have demonstrated that receiving OST is associated with lower treatment deferral and treatment uptake [5, 16]. Although OST is associated with a reduction in injecting risk behavior and improved social functioning among individuals with drug dependence, there clearly remain sociodemographic 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 toward 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 virologic response among patients receiving interferon-based therapy [3]. 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 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 enrollment, 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 Aboriginal Medical Service Western Sydney clinic, which recruited the majority of Aboriginal participants, had a different HCV management pathway prior to specialist referral, which may have impacted the low numbers of HCV specialist assessment

observed. Finally, these findings may not be generalizable 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 [8]. Given that many clinics in the current study had limited prior expertise with specialized HCV care, provision of HCV nursing and specialist support within the existing infrastructure for addiction treatment has produced encouraging results. Expanding specialized care and expertise from secondary or tertiary clinics to primary care centers has been highly successful in accessing marginalized populations and increasing the numbers effectively treated for HCV infection [6]. While new interferon-free direct-acting antiviral 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 marginalized populations.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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