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Elimination of hepatitis C virus infection among PWID: The beginning of a new era of interferon-free DAA therapy

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The ability to cure hepatitis C virus (HCV) infection, a chronic infectious disease, with all-oral interferon-free direct-acting antiviral (DAA) therapies has brought considerable energy to the HCV sector. WHO has set an ambitious goal to eliminate HCV as a major public health threat by 2030 (WHO, 2017a). This is a goal certainly worth striving for, but it will take a massive investment to enhance HCV prevention, awareness, linkage of people with HCV to testing, care and treatment. Also, given the burden of HCV in people who inject drugs (PWID), they will need to be key partners and a priority population for this endeavour to be successful globally.

This special issue published in the *International Journal of Drug Policy* includes original research articles, systematic and expert reviews, and commentaries focused on the "Elimination of hepatitis C virus infection among PWID: The beginning of a new era of interferon-free DAA therapy". Following a call for abstracts, these articles were received and guest-edited in collaboration with members from the International Network on Hepatitis in Substance Users (INHSU), an international organization dedicated to scientific knowledge exchange, knowledge dissemination, education, and advocacy focused on improving HCV prevention and care among PWID. This guest-edited special issue focuses on HCV among PWID and addresses: epidemiology and prevention; the cascade of HCV care; strategies to enhance testing, linkage to care, and treatment uptake; and HCV treatment, with a focus on real-world data on the efficacy of interferon-free DAA therapy. This issue also includes a set of research priorities to achieve universal access to HCV prevention, management and direct-acting antiviral treatment among PWID (Grebely et al. THIS ISSUE).

Epidemiology and prevention of HCV infection among PWID

PWID include those who have injected an illicit drug at least once in their life. This population consists of both former injectors having ceased injecting and "recent" injectors (with definitions for "recent" varying in the literature from one month to one year). Among people with a history of injecting, a population of people receiving opioid substitution therapy (OST) for opioid dependence also exists, some of whom may continue to inject drugs (Larney, et al., 2015).

Globally, among the 71 million people infected with HCV, there is a large burden of HCV infection among recent PWID, with a 50% prevalence of chronic infection (Nelson, et al., 2011; WHO, 2017b), representing an estimated 5.6 million PWID with chronic HCV infection (8% of all infections globally) (Nelson, et al., 2011; WHO, 2017b). There is also a large, but unquantified, number of chronic HCV infections among PWID who have ceased injecting (B. Hajarizadeh, Grebely, & Dore, 2013; Nelson, et al., 2011). Morbidity and mortality due to HCV infection continues to rise among recent and former PWID (B. Hajarizadeh, et al., 2013; Stanaway, et al., 2016).

In 2015, there were 1.7 million new HCV infections globally, with 23% attributable to current injecting drug use (WHO, 2017b), related to the high HCV incidence among PWID in many settings (Hagan, Pouget, Des Jarlais, & Lelutiu-Weinberger, 2008; Morris, et al., 2017; Page, Morris, Hahn, Maher, & Prins, 2013; Wiessing, et al., 2014), particularly in the initial years of injecting (Hagan, et al., 2008; Roy, Boudreau, & Boivin, 2009), and in key vulnerable populations.

Aboriginal PWID are disproportionally affected by HCV in many countries (Graham, Harrod, Iversen, & Simone Hocking, 2016; Lelutiu-Weinberger, et al., 2009; Miller, et al., 2002). In this issue, Graham et al. evaluate trends in HCV antibody prevalence among Aboriginal and Torres Strait Islander people attending Australian needle and syringe programmes (NSP) between 1996 and 2015 (Graham et al THIS ISSUE). Among 16,948 PWID, 11% identified as Aboriginal, with the proportion of Aboriginal respondents increasing from 7% in 1996-2000 to 16% in 2011-2015. While the reason for this increase in proportion of Aboriginal respondents is unclear, this is a concern if it represents an increase in the Aboriginal PWID population as compared to the number of Aboriginal PWID accessing NSP services. The HCV antibody prevalence was higher among Aboriginal PWID (60%), compared to non-Aboriginal PWID (52%, $P<0.001$). Also, injecting risk behaviours remained consistently high among Aboriginal PWID with no change over the last two decades, compared to a decrease observed among non-Aboriginal PWID. This study clearly demonstrates that further work is needed to develop improve culturally appropriate education and health promotion about safer injecting practices among Aboriginal PWID to prevent HCV infection.

Prescription opioid injecting has been associated with increased incidence (Bruneau, Roy, Arruda, Zang, & Jutras-Aswad, 2012) and prevalence of HCV infection (Hadland, et al., 2014; Havens, et al., 2013; Havens, Walker, & Leukefeld, 2007; Zibbell, Hart-Malloy, Barry, Fan, & Flanigan, 2014). The injecting of prescription opioids has increased considerably over the past two decades in North America (Fischer & Argento, 2012; Jordan, Blackburn, Des Jarlais, & Hagan, 2017; B. D. Marshall, Green, Yedinak, & Hadland, 2016) and internationally (B. D. Marshall, et al., 2016). This is a major concern with respect to HCV prevention efforts. Many prescription opioid users are also poly-drug users; an evidenced barrier to opioid substitution therapy (OST) access (Strike, Millson, Hopkins, & Smith, 2013).

In this issue, Puzhko et al. examined the association between specific drugs and number of drugs used in addition to injected prescription opioids, and HCV seroconversion in a cohort study of HCV seronegative PWID in Montreal (Puzhko et al. THIS ISSUE). Among 356 participants, 35% reported injecting prescription opioids in the past month at enrolment. The relative excess risk was highest for co-use of injecting prescription opioids with injecting cocaine, smoked/crack cocaine, and non-injected tranquilizers. Higher risk was also observed with increasing the number of these three drugs used in combination with prescription opioids. These findings suggest that poly-drug use among people who inject prescription opioids must be addressed to reduce HCV transmission.

The cascade of HCV care among PWID

The cascade of HCV care has been modified from initial applications in the field of HIV (Gardner, McLees, Steiner, Del Rio, & Burman, 2011). In the setting of HCV, it often includes those tested and diagnosed, linked to care, initiating treatment and achieving a successful treatment outcome (Behzad Hajarizadeh, Grebely, Matthews, Martinello, & Dore, 2016; Yehia, Schranz, Umscheid, & Lo Re, 2014). Cascades of care provide a framework for monitoring population-level clinical and public health outcomes, identify gaps in the continuum of care, and provide insight into potential opportunities for intervention.

There have been few studies evaluating the HCV cascade of care among PWID. In this issue, Iversen et al. estimated the cascade of HCV testing, care and treatment among PWID prior to the introduction of broadly accessible DAA therapies in Australia (Iversen THIS ISSUE). Among the estimated 93,000 PWID in Australia, 89% had a history of HCV antibody testing, with 57% testing positive for HCV antibodies and less than half (46%) of HCV antibody positive people having received confirmatory HCV RNA testing. Among the estimated

43,201 PWID with active HCV infection or chronic infection that had been successfully treated, 31% had received specialist HCV assessment, 8% had received antiviral treatment and 3% were cured.

This is consistent with another article in this issue by Butler et al. from a different national sample (n=888) of PWID in Australia demonstrating that 93% reported a history of HCV antibody testing, with only 60% having confirmatory testing (Butler THIS ISSUE). Among participants who reported a positive result (n=435), 54% identified their regular general practitioner as the setting where their most recent antibody test was conducted. These findings highlight the importance of further work to enhance education and training about HCV testing among general providers to ensure that people receive testing for active infection (HCV RNA) following testing for previous exposure (HCV antibody) or the development of new technologies to obviate the need for a second test such as reflex testing or point of care RNA tests (J. Grebely, F. M. J. Lamoury, et al., 2017; Hirsch, et al., 2014).

In a cohort of rural PWID in Kentucky, Stephens et al. demonstrated that despite 59% of participants reporting having contact with a healthcare provider within 18 months of a detectable test for HCV infection and counselling, only 14% reported seeking HCV treatment and only 8% reported receiving treatment (Stephens et al. THIS ISSUE). Having health insurance, internet access, and prior treatment for substance use increased the odds of making contact for follow-up, while major depressive disorder and prior methadone use (either legal or illegal) were associated with decreased likelihood. Clearly, novel strategies to support integrated services among those already accessing services are needed to improve the proportion of people engaging in HCV care are needed, particularly in rural settings. Considerable barriers to accessing DAA therapies due to reimbursement restrictions based on

fibrosis stage, recent drug/alcohol use, and provider type also remain in the United States, which further restrict access (Barua, et al., 2015; Ooka, Connolly, & Lim, 2017).

In some countries, such as the Netherlands, access and reimbursement for DAA therapy occurred earlier (since 2014) than many other settings. Van Santen et al. evaluated HCV treatment uptake among people who use drugs participating in the Amsterdam Cohort Studies between 1985 and 2015 (Van Santen et al. THIS ISSUE). Among 1,305 people who use drugs, 20% were HIV antibody positive and 62% were HCV antibody positive at study entry. In contrast to the studies by Iversen and Butler, 95% of HCV antibody positive individual received HCV RNA testing, partly related to the well-characterized nature of this cohort. The proportion of people receiving HIV antiretroviral therapy increased from 5.7 in 1990, and 42.2% in 1996, to 91.7% in 2015. HCV-treatment coverage increased from 7% in 2005 to 44% in 2015. The highest proportion of people who use drugs initiating HCV treatment (9.7%) was observed in 2006, but this decreased to 1.9% in 2013. During 2015, the first full year of DAA availability, HCV treatment initiation remained low (3%, 1 of 33 people who were HCV RNA positive). Of those with available Fibroscan results in 2015, 58% had no or mild fibrosis (F0-F1). As such, the lower treatment uptake was likely related to the fact that until November 2015, access to HCV treatment was restricted, based on fibrosis stage (Metavir >=F3), so physicians may have awaited the dismissal of such restriction.

This is consistent with a recent study of DAA restrictions in Europe demonstrating that DAA reimbursement was restricted to ≥F2 in 57% of countries, required a specialist prescriber in 97% of countries, and required abstinence of substance use prior to treatment in 14% of countries (A. D. Marshall, et al., 2017). As raised by a study by Lazarus et al. in this issue

(Lazarus THIS ISSUE), the barriers based on drug and alcohol use in practice are probably much greater, given perceptions by some providers about poor adherence, lower response to therapy, and the risk of reinfection may preclude successful treatment (Asher, et al., 2016; Grebely & Tyndall, 2011). Many physicians are also unwilling to treat people actively using drugs with DAA therapies. In a 2016 study of HCV practitioners in the DAA era (72% were gastroenterology and hepatology specialists), only 15% were willing to treat people who are actively injecting drugs with all-oral regimens (Asher, et al., 2016). Reinfection, adherence and medication cost were cited as the most important concerns when determining candidacy (Asher, et al., 2016). Further work is needed to improve education and training for providers, particularly with respect to information about successful HCV treatment outcomes and low rates of reinfection among recent PWID and strategies for reducing stigma and discrimination. Indeed, as other barriers (such as concerns about efficacy and side-effects) diminish, the importance of stigma and discrimination as barriers to HCV treatment may increase (Brener, Horwitz, von Hippel, Bryant, & Treloar, 2015). Also, as highlighted by Lazarus et al. further work is needed to drive policy change to remove the restrictions place for DAA therapy reimbursement and community-based patient organizations will be a key stakeholder in moving this agenda forward (Lazarus THIS ISSUE).

Enhancing testing, linkage to care, and treatment for PWID

Reducing the burden of HCV infection among PWID will require targeted strategies focused on different stages of the HCV cascade of care. In this issue, Bajis et al. performed a systematic review to evaluate the effectiveness of interventions to enhance HCV testing, linkage to care, and treatment uptake among PWID (Bajis THIS ISSUE). Among 10,116 records identified, a total of 14 studies were included, of which 57% were randomised controlled trials. Interventions to enhance HCV testing included on-site testing with pre-test

counselling and education (Cullen, et al., 2006; Hagedorn, et al., 2007; Lacey, Ellen, Devlin, Wright, & Mijch, 2007; Merchant, et al., 2014; Merchant, DeLong, Liu, & Baird, 2015; Rosenberg, et al., 2010; Roux, et al., 2016); and dried blood spot testing (Hickman, et al., 2008; Radley, et al., 2017). Interventions to enhance linkage to care included facilitated referral for HCV assessment and scheduling of specialist appointments for clients (Cullen, et al., 2006; Masson, et al., 2013; Tait, McIntyre, McLeod, Nathwani, & Dillon, 2010). Interventions to enhance HCV treatment uptake included integrated HCV care, drug use and psychiatric services delivered by a multidisciplinary team with case management services, with or without non-invasive liver disease assessment (Ho, et al., 2015; Moussalli, et al., 2010). All studies were conducted in the interferon treatment era and there were no studies conducted in low- and middle-income countries. Although a number of other strategies were assessed, they lacked a comparator group, so measuring the effect of these interventions was difficult. This study highlights that further data is needed to identify strategies to enhance HCV testing, linkage to care, and treatment in the DAA era to strive towards HCV elimination among PWID.

Mathematical modelling suggests that HCV treatment as prevention (modest scale-up of DAA HCV treatment to 8 per 100 PWID) could lead to substantial reductions in HCV prevalence among PWID, thereby lowering HCV incidence and preventing transmission (de Vos, Prins, & Kretzschmar, 2015; European Union, 2017; Hellard, et al., 2014; Lima, et al., 2015; Martin, Hickman, Hutchinson, Goldberg, & Vickerman, 2013; Martin, et al., 2011; Martin, Vickerman, et al., 2013; Scott, McBryde, Thompson, Doyle, & Hellard, 2016). In a study by Scott et al. in this issue, mathematical modelling was used to assess potential strategies that could be used to enhance HCV testing, linkage to care, and treatment to achieve HCV elimination targets in Australia, a setting where all people living with HCV have access to

DAA therapy (Scott et al. THIS ISSUE). Interventions included point of care HCV RNA testing, increased testing of PWID, use of non-invasive biomarkers (e.g. AST to platelet ratio index, APRI) in place of liver stiffness measurements, and scaling up treatment delivery in primary care. Without additional health systems interventions, the projected increase in DAA treatment had a substantial impact on reducing the number of people living with HCV by 2030. However, most remaining infections were undiagnosed and occurred among PWID. The scale-up of primary care delivery and use of biomarkers in place of liver stiffness measurement produced modest impacts on HCV transmission, but saved AU$32 million by 2030. Additional screening of PWID was required to achieve HCV elimination targets, and the addition of point of care RNA testing increased the healthcare cost savings to AU$62 million. This study provides important data to highlight that even with unlimited and unrestricted access to HCV DAA treatment, interventions to improve the HCV cascade of care and address HCV among PWID will be required to achieve elimination targets.

Enhancing HCV case finding is one strategy that could be used to enhance HCV testing. In the Netherlands, Helsper et al. evaluated effectiveness and cost-effectiveness of a nationwide HCV case finding campaign aimed at drug users (individual counseling and testing at drug treatment centres) and high-risk people in the general population (health education through mass-media and education of health care professionals) as part of a national non-randomized controlled trial (Helsper THIS ISSUE). The intervention targeted towards PWID identified 257 additional people with HCV and was cost-effective (ICER was €9,056 compared to no intervention), while the intervention targeted towards the general population identified 38 additional people with HCV and was less cost-effective (ICER was €18,421 compared to no intervention). Further studies are needed to evaluate the cost-effectiveness of strategies to improve HCV testing among PWID.

Pharmacies may also present an interesting setting to enhance HCV testing and treatment. In a study from Scotland, Radley et al performed an exploratory cluster randomised controlled trial with mixed methods evaluation to compare the uptake of dried blood spot testing and treatment of people with HCV genotype 1 infection in a conventional service pathway versus a pharmacist-led pathway in a population receiving OST (Radley THIS ISSUE). Participants in the pharmacist-led pathway were more likely to take a dried blood spot test (36% vs. 24%, P=0.003) and attend for subsequent assessment (77% vs. 27%, P=0.002). This study provides interesting preliminary data to suggest that pharmacy-based testing, assessment, and treatment could be a feasible model of HCV care to explore in future studies.

Non-invasive liver disease assessment via transient elastography (e.g. Fibroscan) has also been shown to be effective for enhancing liver disease screening and linkage to HCV care among PWID attending drug treatment clinics (Foucher, et al., 2009; A. D. Marshall, et al., 2015; Moessner, et al., 2011). In this issue, Marshall et al evaluated the decisions and experiences of people having received a liver disease assessment as part of a liver health education and promotion campaign, including interpretation of their transient elastography score and subsequent health behaviours, using a health literacy framework (Marshall THIS ISSUE). Among the participants interviewed, most participants interpreted their level of liver disease correctly based on their transient elastography score. Participants with higher transient elastography scores frequently described feeling surprised by their result and, often incorrectly identified drug use as a cause of advanced liver disease. In contrast, persons with lower transient elastography scores felt encouraged by their result and spoke more to maintenance of healthy behaviours. Findings highlight some positive health changes made by

PWID following liver disease assessment as well as ongoing misunderstandings of chronic liver disease in relation to illicit drug use.

Among PWID, despite a high willingness to receive HCV therapy, poor knowledge about HCV testing, factors which influence liver disease progression, and the chance of cure with new HCV treatments has been observed (A. D. Marshall, et al., 2015; Treloar, et al., 2011; Treloar, Hull, Dore, & Grebely, 2012). In this issue, Mah et al evaluated factors associated with HCV knowledge and treatment willingness among PWID in Vancouver, Canada in the era of DAA therapy (Mah et al. THIS ISSUE). Among 630 participants, the mean scores for HCV knowledge and treatment willingness were high, with mean composite scores of 25 out of 30, and 6.8 out of 10, respectively. Overall, 61% strongly agreed or agreed to consider starting HCV treatment in the next year. Interestingly, when asked if they prioritized treatment duration versus risk of side effects, 58% reported risk of side effects as a more important treatment consideration while only 16% were more concerned about treatment duration. Also, 57% of participants reported that what they have heard about the side effects of HCV treatment scares them. Further, only 66% answered "agree" or "strongly agree" to the question "Treatment for hepatitis C can cure the infection in most people", with 51% still believing that HCV treatment included a weekly interferon injection. This clearly indicates the need to improve knowledge and address patient perceptions that are influenced by the 'horror stories' of negative experiences of liver biopsies and HCV treatment propagated within peer networks in the interferon-era (Swan, et al., 2010). Overall, among 630 participants, 53% reported having ever been offered HCV treatment and of those offered therapy, only 9% ever initiated treatment. A greater degree of HCV knowledge was associated with an increased willingness to pursue HCV treatment. These data suggest that strategies to

increase HCV knowledge among PWID may be an integral component for enhancing the HCV cascade of care.

Novel strategies to improve knowledge about HCV among PWID are needed. In a study of people attending OST and NSP services in Malaysia, Mukherjee et al. evaluated a standardized, 45-minute HCV education program to measure change in knowledge and treatment willingness (Mukherjee THIS ISSUE). Baseline knowledge was consistently low across OST and NSP clients. More specifically, most OST clients were unaware that HCV often has no symptoms, sterilizing used needles often does not kill HCV, re-infection is possible, that HCV treatment is not always effective, and that treatment is not life-long. Most NSP clients seemed to be unaware that HCV is a virus that affects the liver (18%). Following the short educational intervention, knowledge scores and treatment interest among people receiving OST increased by 68% and 16%, respectively ($p<0.001$), although similar improvements were not observed in people in NSP. Integrating a brief, but comprehensive HCV education session may be a low-cost and effective strategy to improve HCV knowledge. However, further work is needed to evaluate whether the improvements in knowledge are sustained long-term. Further work is needed to develop education and health promotion initiatives to improve knowledge among PWID with HCV. This will be a crucial component to enhance engagement in HCV care among PWID moving forward.

HCV treatment for PWID

Although interferon-based HCV therapy is safe and effective among PWID (Aspinall, et al., 2013; Dimova, et al., 2013; Hellard, Sacks-Davis, & Gold, 2009), patient, provider, health system, structural, and societal barriers (Grebely, Oser, Taylor, & Dore, 2013; Harris & Rhodes, 2013; Wolfe, et al., 2015) have led to low diagnosis and treatment for HCV infection

in the interferon-era (Alavi, et al., 2014; Iversen, et al., 2014). The availability of tolerable and simple direct-acting antiviral (DAA) therapies for HCV infection with cure rates >95% represents one of the greatest medical advances in decades (Dore & Feld, 2015; Falade-Nwulia, et al., 2017). New DAA therapies have overcome many barriers associated with interferon-based therapy for PWID as they have fewer psychiatric side effects, are simpler (oral, once-daily vs. weekly injections), and shorter in duration (8-12 weeks vs. 24-48 weeks).

Treatment of HCV infection among PWID provides benefits at the population level and the individual level. At a population level, treatment of HCV in PWID with ongoing injecting drug use represents a potential tool to prevent onward HCV transmission among PWID (Martin, Vickerman, et al., 2013). Mathematical modelling also indicates that DAA treatment of PWID is cost-effective, given the prevention benefit (Martin, et al., 2016). At an individual level, successful treatment of HCV infection improves health-related quality of life (Younossi & Henry, 2015), reduces the progression of liver disease (Grebely & Dore, 2011) and reduces all-cause mortality in people with advanced liver disease (van der Meer, et al., 2014). International guidelines also support the prioritization of HCV treatment among PWID (AASLD/IDSA, 2015; European Association for Study of, 2015; Grebely, et al., 2015; WHO, 2014).

Globally, DAA availability is uneven; with many countries restricting access to contain costs (Barua, et al., 2015; A. D. Marshall, et al., 2017; A. D. Marshall, et al., 2016). DAA prioritisation can negatively impact access for PWID, particularly if it is based on disease staging criteria. Harris et al examined and critiqued HCV prioritisation discourses based on clinical and population-based markers, with reference to the social and individual-level treatment benefits experienced by her UK participants (Harris, et al. IJDP THIS ISSUE). In

this issue, she reports findings from a longitudinal qualitative study following participants through HCV treatment in the UK. Data were collected during a time of transition to DAAs; many participants were offered triple therapy comprising interferon, ribavirin and a first-generation protease inhibitor. Despite the forthcoming availability of less toxic DAA treatments, all but one participant chose to commence treatment immediately. Reasons for commencing treatment related to expectations and hopes for reconnection with loved ones and the broader community; through removal of HCV stigma, symptoms and transmission fears. Longitudinal methods enabled investigation of how expectations mapped to outcomes; for many these HCV treatment benefits were realised. This work is important in that it evidences patient-reported HCV treatment benefits beyond the clinical; crucial to account for in contexts of restricted access but also to harness in the design of HCV treatment engagement interventions for PWID.

Interferon-based therapy is safe and effective among PWID (Aspinall, et al., 2013; Dimova, et al., 2013; Hellard, et al., 2009). In this issue, Grebely et al. present the results from the first international clinical trial from the ACTIVATE Network, which was a trial to evaluate response-guided interferon-based HCV therapy for participants with HCV genotypes 2/3 and recent injecting (previous 6 months) or receiving OST, prior to the availability of DAA therapy between 2012 and 2014 (Grebely THIS ISSUE). Participants received open-label directly observed peg-interferon alfa-2b and self-administered ribavirin for 12 (for those HCV RNA undetectable at week 4) or 24 weeks (for those HCV RNA detectable at week 4). Overall, 76% completed treatment, with higher treatment completion observed among those receiving 12 vs. 24 weeks of treatment (97% vs. 46%, $P < 0.001$) (Cunningham, et al., 2017). SVR12 was 66% overall, and 84% in those with undetectable HCV RNA at week 4 (12 weeks) compared to 38% in those without (24 weeks). In adjusted analysis, cirrhosis vs.

no/mild fibrosis [adjusted OR (aOR) 0.33, 95% CI 0.13, 0.86] predicted reduced SVR12, while response at week 4 was associated with increased SVR12 [aOR 8.11, 95% CI 2.73, 24.10]. Recent injecting drug use at baseline or during therapy was not associated with SVR.

Previous studies have demonstrated that reductions in injecting risk behaviours may occur in the setting of interferon-based treatment (Alavi, et al., 2015). In another paper from the ACTIVATE study, Midgard et al. evaluated trends in injecting drug use risk behaviours during and following HCV treatment (Midgard THIS ISSUE). Overall, recent injecting drug use and hazardous alcohol use decreased, while OST increased during and following HCV treatment among participants with ongoing injecting drug use. This is consistent with another paper in this issue by Artenie et al. which examined changes in injecting drug use among PWID treated for acute HCV infection (Artenie et al. THIS ISSUE). In multivariate analyses adjusting for age, gender and injection drug use at baseline, those who received interferon-based treatment [Adjusted odds ratio (AOR): 0.18; 95% Confidence interval (CI): 0.04-0.76], those who had spontaneously cleared infection (AOR: 0.34; 95% CI: 0.08-1.40), and those with contraindications to therapy (AOR: 0.24; 95% CI: 0.05-1.22) were less likely to report injection drug use at follow-up relative to those who chose not to engage in HCV care post-diagnosis. These findings may be attributed to ongoing therapeutic relationships and harm reduction education provided by physicians, nurses, counsellors and other allied health provides to patients may contribute to reductions in injecting risk behaviours. This illustrates the important role that health care in the context of HCV care can play to improve drug user health, more broadly. Further research is needed to understand whether similar reductions in injecting risk behaviours are observed in the setting of DAA therapy, where contact with healthcare providers is sometimes less frequent.

DAA therapy has improved the feasibility of HCV treatment among PWID compared to interferon-based therapies, given DAA therapies have limited psychiatric side effects, are simpler (oral, once-daily vs. weekly injections), and shorter in duration (8-12 weeks vs. 24-48 weeks). Among people receiving OST with no recent illicit drug use, post-hoc analyses of phase 2 and 3 trials of DAA therapy have demonstrated that the SVR is similar in those receiving and not receiving OST (G. J. Dore, et al., 2016; Feld, et al., 2014; Grebely, Dore, et al., 2016; J. Grebely, I. M. Jacobson, et al., 2017; Grebely, Mauss, et al., 2016; J. Grebely, et al., 2017; Puoti, et al., 2014; Zeuzem, et al., 2015). However, the majority of these trials excluded people with active drug use from participation. The first phase 3 trial to evaluate DAA therapy in people receiving OST including those with ongoing drug use was the C-EDGE CO-STAR study (G. J. Dore, et al., 2016). Overall, among people with no previous treatment experience and HCV genotypes 1, 4, or 6 and stable methadone or buprenorphine (with or without naloxone) who received elbasvir and grazoprevir for 12 weeks (n=296), treatment completion was 96%, 97% demonstrated >95% adherence, and the overall SVR was 91%.

This issue contributes substantially to the literature to provide additional data on the efficacy of DAAs among PWID treated in the real-world. In studies from Australia (Read et al. THIS ISSUE, Morris et al. THIS ISSUE), Canada (Mason et al. THIS ISSUE), the Ukraine (Mazhnaya et al. THIS ISSUE), and the United States (Norton et al. THIS ISSUE) among people with a history of injecting drug use (with and without recent drug use) an overall treatment completion of 93-100% and SVR of 80-96% was observed. Although some studies demonstrated lower SVR in intent-to-treat analyses than observed in phase 3 clinical trials, the majority of non-response occurred as a result of lost to follow-up between ETR and SVR12 and not virological failure or relapse (Read et al. THIS ISSUE, Morris et al. THIS

ISSUE, Mason et al. THIS ISSUE, Mazhnaya et al. THIS ISSUE). In modified intent-to-treat analyses excluding individuals lost to follow-up between ETR and SVR, SVR12 of 91-94% was observed (Read et al. THIS ISSUE, Morris et al. THIS ISSUE, Mason et al. THIS ISSUE, Mazhnaya et al. THIS ISSUE). These data suggest that the period between ETR and SVR12 is an important time for maintaining engagement in post-treatment care and follow-up. Importantly, drug use prior to or during therapy does not have an impact on SVR (Read et al. THIS ISSUE, Morris et al. THIS ISSUE, Mason et al. THIS ISSUE, Mazhnaya et al. THIS ISSUE, Norton et al. THIS ISSUE). However, study populations do vary with respect to the proportion with recent drug use or injecting drug use, the definitions used to define recent drug use (vary from 1-12 months), and some studies do not report information on recent drug use. In the future, studies of DAA treatment in PWID should collect standardized information about injecting risk behaviours and this information should be reported.

Among people with recent injecting drug use, there are now several studies evaluating outcomes following DAA therapy. In a study of 174 participants with injecting drug use in the last year (63% with cirrhosis, 37% with previous treatment experience, 58% genotype 1), 95% completed therapy and 93% achieved SVR (Boglione, et al., 2017). The SIMPLIFY study was the first international trial that evaluated DAA therapy in people with recent injecting drug use (J. Grebely, O. Dalgard, et al., 2017). Overall, among people with HCV genotypes 1-6 treated with sofosbuvir and velpatasvir for 12 weeks (n=103), 96% completed treatment and 94% had an SVR, with no virological failures, and one reinfection. These data provide strong support for DAA treatment among people with recent injecting drug use.

OST also provides an important opportunity to engage HCV-positive PWID into DAA-based therapy. In this issue, Panagiotoglou et al. used well-characterized data from cohorts in

Vancouver to evaluate whether OST retention could be used to inform DAA therapy initiation, thereby identifying opportunities to improve retention (Panagiotoglou et al. THIS ISSUE). Overall, among 1,427 participants with HCV/HIV, the odds of subsequent 12-week retention in OST was significantly greater in month 3 versus month 1 of OST treatment and the odds of subsequent 8-week retention in OST was significantly greater in month 2 versus month 1. Interestingly, among continuously ART-adherent individuals, the odds of subsequent twelve-week retention were not statistically significantly greater in successive months, suggesting that those engaged in ongoing HIV care may be ideal for engaging in HCV treatment. The authors suggest that this study provides indirect evidence that 12 or 8 weeks of HCV treatment should be initiated at three months or two months following stabilization on OST, respectively. However, this does not take into consideration that HCV therapy may provide an opportunity for further engagement in care and positive impact on drug dependency management. Also, the authors do not provide direct evidence to suggest that people who are stabilized on OST before initiating DAA therapy have higher responses to therapy, particularly given the high responses observed with DAA therapy among recent PWID to date (Boglione, et al., 2017; J. Grebely, O. Dalgard, et al., 2017).

There is good evidence to support that involving community-based PWID organizations in the design and implementation of programs can reduce stigma and discrimination, enhance HCV and HIV prevention and care, and lead to changes in health policies (United Nations Office on Drugs and Crime, 2017). Peer-based support and involvement is recognized as a vital component to facilitate HCV testing and treatment and a number of different models have been described (Crawford & Bath, 2013; Treloar, et al., 2015). In this issue, Bonnington and Harris explore peer education and buddy support as part of an intervention to enhance HCV diagnosis and treatment in primary care and drug treatment settings between 2014 and

2016 (Bonnington and Harris THIS ISSUE). Participants had common expectations of the peer role (to 'just be there') and its occupants' attributes (empathy, trustworthy, etc.). However, in practice, peers faced constraints on realising these expectations. A 'recovery' dominated drug treatment ethos in the UK appeared to influence the selection of 'recovery champions' as peers for the intervention. This created tensions in relations with clients, particularly when risk-adverse discourses were internalised by the peers. Peers were poorly integrated and supported within the service, affecting opportunities to relate and build trust with clients. Thus, the scope for peer support to impact on the nature and extent of clients' testing and treatment for HCV was limited. This paper highlights that the efficacy of peer involvement can be constrained by organisational structures and boundaries - especially regarding who is deemed to be 'a peer'. Peer programmes take time and care to implement and weave into wider recovery and harm reduction frameworks. Future research is needed to continue to build evidence about the importance of peer-based models of care for PWID.

Research priorities to achieve universal access to hepatitis C prevention, management and direct-acting antiviral treatment among PWID

Unfortunately, there remain gaps in knowledge that represent barriers to effective prevention and management of HCV among PWID. As part of this special issue, Grebely et al. present the outcomes of an expert round table panel to assess current research gaps and establish future research priorities for the prevention and management of HCV among PWID led by The Kirby Institute, UNSW Sydney and the International Network on Hepatitis in Substance Users (INHSU) (Grebely et al. THIS ISSUE). This round table consisted of a one-day workshop held on 6 September, 2016, in Oslo, Norway, prior to the International Symposium on Hepatitis in Substance Users (INHSU 2016). International experts in drug and alcohol, infectious diseases, and hepatology were brought together to discuss the available scientific

evidence, gaps in research, and develop research priorities. Topics for discussion included the epidemiology of injecting drug use, HCV, and HIV among PWID, HCV prevention, HCV testing, linkage to HCV care and treatment, DAA treatment for HCV infection, and reinfection following successful treatment. This paper highlights the outcomes of the roundtable discussion focused on future research priorities for enhancing HCV prevention, testing, linkage to care and DAA treatment for PWID as we strive for global elimination of HCV infection.

Conclusions

As we move towards the WHO targets to eliminate HCV infection as a global public health concern by 2030, PWID will be a key priority population for efforts to enhance prevention, increase diagnosis and treatment and reduce morbidity and mortality. This special issue contributes important data to the literature to help further guide efforts to enhance HCV prevention, linkage to care, and treatment for PWID. Although interferon-free DAA therapies provide us with important tools to achieve the WHO goals, there is still a considerable way to go with respect to improving the coverage of strategies to prevent HCV among PWID (e.g. OST and NSP), enhancing testing and diagnosis, and broadening access to DAA therapies to facilitate HCV elimination efforts among PWID. As we move forward, efforts should focus not only on improving care for HCV infection, but also improving the overall health of PWID.

References

AASLD/IDSA. Recommendations for testing, managing, and treating hepatitis C. Retrieved January 18 2015 from www.hcvguidelines.org.

Alavi, M., Raffa, J. D., Deans, G. D., Lai, C., Krajden, M., Dore, G. J., Tyndall, M. W., & Grebely, J. (2014). Continued low uptake of treatment for hepatitis C virus infection in a large community-based cohort of inner city residents. *Liver Int, 34*, 1198-1206.

Alavi, M., Spelman, T., Matthews, G. V., Haber, P. S., Day, C., van Beek, I., Walsh, N., Yeung, B., Bruneau, J., Petoumenos, K., Dolan, K., Kaldor, J. M., Dore, G. J., Hellard, M., Grebely, J., & Group, A. S. (2015). Injecting risk behaviours following treatment for hepatitis C virus infection among people who inject drugs: The Australian Trial in Acute Hepatitis C. *Int J Drug Policy, 26*, 976-983.

Asher, A. K., Portillo, C. J., Cooper, B. A., Dawson-Rose, C., Vlahov, D., & Page, K. A. (2016). Clinicians' Views of Hepatitis C Virus Treatment Candidacy With Direct-Acting Antiviral Regimens for People Who Inject Drugs. *Subst Use Misuse, 51*, 1218-1223.

Aspinall, E. J., Corson, S., Doyle, J. S., Grebely, J., Hutchinson, S. J., Dore, G. J., Goldberg, D. J., & Hellard, M. E. (2013). Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. *Clin Infect Dis, 57 Suppl 2*, S80-89.

Barua, S., Greenwald, R., Grebely, J., Dore, G. J., Swan, T., & Taylor, L. E. (2015). Restrictions for Medicaid Reimbursement of Sofosbuvir for the Treatment of Hepatitis C Virus Infection in the United States. *Ann Intern Med, 163*, 215-223.

Boglione, L., Mornese Pinna, S., De Nicolo, A., Cusato, J., Cariti, G., Di Perri, G., & D'Avolio, A. (2017). Treatment with direct-acting antiviral agents of hepatitis C virus infection in injecting drug users: A prospective study. *J Viral Hepat*.

Brener, L., Horwitz, R., von Hippel, C., Bryant, J., & Treloar, C. (2015). Discrimination by health care workers versus discrimination by others: countervailing forces on HCV treatment intentions. *Psychol Health Med, 20*, 148-153.

Bruneau, J., Roy, E., Arruda, N., Zang, G., & Jutras-Aswad, D. (2012). The rising prevalence of prescription opioid injection and its association with hepatitis C incidence among street-drug users. *Addiction, 107*, 1318-1327.

Crawford, S., & Bath, N. (2013). Peer support models for people with a history of injecting drug use undertaking assessment and treatment for hepatitis C virus infection. *Clin Infect Dis, 57 Suppl 2*, S75-79.

Cullen, W., Stanley, J., Langton, D., Kelly, Y., Staines, A., & Bury, G. (2006). Hepatitis C infection among injecting drug users in general practice: a cluster randomised controlled trial of clinical guidelines' implementation. *Br J Gen Pract, 56*, 848-856.

Cunningham, E. B., Hajarizadeh, B., Dalgard, O., Amin, J., Hellard, M., Foster, G. R., Bruggmann, P., Conway, B., Backmund, M., Robaeys, G., Swan, T., Marks, P. S., Quiene, S., Applegate, T. L., Weltman, M., Shaw, D., Dunlop, A., Bruneau, J., Midgard, H., Bourgeois, S., Thurnheer, M. C., Dore, G. J., Grebely, J., & Group, A. S. (2017). Adherence to response-guided pegylated interferon and ribavirin for people who inject drugs with hepatitis C virus genotype 2/3 infection: the ACTIVATE study. *BMC Infect Dis, 17*, 420.

de Vos, A. S., Prins, M., & Kretzschmar, M. E. (2015). Hepatitis C Virus treatment as prevention among injecting drug users: who should we cure first? *Addiction*.

Dimova, R. B., Zeremski, M., Jacobson, I. M., Hagan, H., Des Jarlais, D. C., & Talal, A. H. (2013). Determinants of hepatitis C virus treatment completion and efficacy in drug users assessed by meta-analysis. *Clin Infect Dis, 56*, 806-816.

Dore, G. J., Altice, F., Litwin, A. H., Dalgard, O., Gane, E. J., Shibolet, O., Luetkemeyer, A., Nahass, R., Peng, C., Conway, B., Grebely, J., Howe, A. Y. M., Gendrano, I. N., Chen, E., Huang, H., Dutko, F. J. P., Nickle, D. C., Nguyen, B., Wahl, J., Barr, E., Robertson, M. N., & Platt, H. L. (2016). Elbasvir/Grazoprevir to Treat HCV Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Controlled Trial (C-EDGE CO-STAR). *Ann Intern Med, In Press*.

Dore, G. J., Altice, F., Litwin, A. H., Dalgard, O., Gane, E. J., Shibolet, O., Luetkemeyer, A., Nahass, R., Peng, C. Y., Conway, B., Grebely, J., Howe, A. Y., Gendrano, I. N., Chen, E., Huang, H. C., Dutko, F. J., Nickle, D. C., Nguyen, B. Y., Wahl, J., Barr, E., Robertson, M. N., Platt, H. L., & Group, C. E. C.-S. S. (2016). Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial. *Ann Intern Med, 165*, 625-634.

Dore, G. J., & Feld, J. J. (2015). Hepatitis C virus therapeutic development: in pursuit of "perfectovir". *Clin Infect Dis, 60*, 1829-1836.

European Association for Study of, L. (2015). EASL Recommendations on Treatment of Hepatitis C 2015. *J Hepatol, 63*, 199-236.

European Union, H. C. V. C. (2017). Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study. *Lancet Gastroenterol Hepatol, 2*, 325-336.

Falade-Nwulia, O., Suarez-Cuervo, C., Nelson, D. R., Fried, M. W., Segal, J. B., & Sulkowski, M. S. (2017). Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review. *Ann Intern Med, 166*, 637-648.

Feld, J. J., Kowdley, K. V., Coakley, E., Sigal, S., Nelson, D. R., Crawford, D., Weiland, O., Aguilar, H., Xiong, J., Pilot-Matias, T., DaSilva-Tillmann, B., Larsen, L., Podsadecki, T., & Bernstein, B. (2014). Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med, 370*, 1594-1603.

Fischer, B., & Argento, E. (2012). Prescription opioid related misuse, harms, diversion and interventions in Canada: a review. *Pain Physician, 15*, ES191-203.

Foucher, J., Reiller, B., Jullien, V., Leal, F., di Cesare, E. S., Merrouche, W., Delile, J. M., & de Ledinghen, V. (2009). FibroScan used in street-based outreach for drug users is useful for hepatitis C virus screening and management: a prospective study. *J Viral Hepat, 16*, 121-131.

Gardner, E. M., McLees, M. P., Steiner, J. F., Del Rio, C., & Burman, W. J. (2011). The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clinical infectious diseases, 52*, 793-800.

Graham, S., Harrod, M. E., Iversen, J., & Simone Hocking, J. (2016). Prevalence of Hepatitis C Among Australian Aboriginal and Torres Strait Islander people: A Systematic Review and Meta-Analysis. *Hepat Mon, 16*, e38640.

Grebely, J., Dalgard, O., Conway, B., Cunningham, E., Bruggmann, P., Hajarizadeh, B., Amin, J., Marks, P., Quiene, S., Applegate, T. A., Swan, T., Byrne, J., Lacalamita, M., Dunlop, A. J., Bruneau, J., Hellard, M. E., Matthews, G. V., Powis, J., Shaw, D., Thurnheer, C. M., Weltman, M., Kronborg, I., Cooper, C., Feld, J. J., Fraser, C., Litwin, A., Dillon, J., Read, P., Gane, E., & Dore, G. J. (2017). Efficacy and safety of sofosbuvir/velpatasvir in people with chronic hepatitis C virus infection and recent injecting drug use: the SIMPLIFY study. *J Hepatol, 66*, S513.

Grebely, J., & Dore, G. J. (2011). What is killing people with hepatitis C virus infection? *Semin Liver Dis, 31*, 331-339.

Grebely, J., Dore, G. J., Zeuzem, S., Aspinall, R. J., Fox, R., Han, L., McNally, J., Osinusi, A., Brainard, D. M., Subramanian, G. M., Natha, M., Foster, G. R., Mangia, A., Sulkowski, M., & Feld, J. J. (2016). Efficacy and Safety of Sofosbuvir/Velpatasvir in

Patients With Chronic Hepatitis C Virus Infection Receiving Opioid Substitution Therapy: Analysis of Phase 3 ASTRAL Trials. *Clin Infect Dis*.

Grebely, J., Jacobson, I. M., Kayali, Z., Verna, E. C., Shiffman, M. L., Hyland, R. H., Stamm, L. M., Huang, K. C., Brainard, D. M., McHutchison, J. G., Pol, S., Chung, R. T., Bernstein, D. E., & Dore, G. J. (2017). SOF/VEL/VOX for 8 or 12 Weeks Is Well Tolerated and Results in High SVR12 Rates in Patients Receiving Opioid Substitution Therapy. *J Hepatol, 66*, S513.

Grebely, J., Lamoury, F. M. J., Hajarizadeh, B., Mowat, Y., Marshall, A. D., Bajis, S., Marks, P., Amin, J., Smith, J., Edwards, M., Gorton, C., Ezard, N., Persing, D., Kleman, M., Cunningham, P., Catlett, B., Dore, G. J., Applegate, T. L., & Live, R. S. G. (2017). Evaluation of the Xpert HCV Viral Load point-of-care assay from venepuncture-collected and finger-stick capillary whole-blood samples: a cohort study. *Lancet Gastroenterol Hepatol, 2*, 514-520.

Grebely, J., Mauss, S., Brown, A., Bronowicki, J. P., Puoti, M., Wyles, D., Natha, M., Zhu, Y., Yang, J., Kreter, B., Brainard, D. M., Yun, C., Carr, V., & Dore, G. J. (2016). Efficacy and Safety of Ledipasvir/Sofosbuvir With and Without Ribavirin in Patients With Chronic HCV Genotype 1 Infection Receiving Opioid Substitution Therapy: Analysis of Phase 3 ION Trials. *Clin Infect Dis*.

Grebely, J., Oser, M., Taylor, L. E., & Dore, G. J. (2013). Breaking down the barriers to hepatitis C virus (HCV) treatment among individuals with HCV/HIV coinfection: action required at the system, provider, and patient levels. *J Infect Dis, 207 Suppl 1*, S19-25.

Grebely, J., Puoti, M., Wedemeyer, H., Cooper, C. S., Sulkowski, M. S., Foster, G. F., Berg, T., Villa, E., Rodriguez-Perez, F., Wyles, D. L., Alami, N. N., Zhang, Z., Dumas, E., & Dore, G. J. (2017). Safety and Efficacy of Ombitasvir, Paritaprevir/Ritonavir and Dasabuvir With or Without Ribavirin in Chronic Hepati ti s C Pati ents Receiving Opioid Substi tuti on Therapy: A Pooled Analysis Across 12 Clinical Trials. *J Hepatol, 66*, S514.

Grebely, J., Robaeys, G., Bruggmann, P., Aghemo, A., Backmund, M., Bruneau, J., Byrne, J., Dalgard, O., Feld, J. J., Hellard, M., Hickman, M., Kautz, A., Litwin, A., Lloyd, A. R., Mauss, S., Prins, M., Swan, T., Schaefer, M., Taylor, L. E., Dore, G. J., & International Network for Hepatitis in Substance, U. (2015). Recommendations for the management of hepatitis C virus infection among people who inject drugs. *Int J Drug Policy, 26*, 1028-1038.

Grebely, J., & Tyndall, M. W. (2011). Management of HCV and HIV infections among people who inject drugs. *Curr Opin HIV AIDS, 6*, 501-507.

Hadland, S. E., DeBeck, K., Kerr, T., Feng, C., Montaner, J. S., & Wood, E. (2014). Prescription opioid injection and risk of hepatitis C in relation to traditional drugs of misuse in a prospective cohort of street youth. *BMJ Open, 4*, e005419.

Hagan, H., Pouget, E. R., Des Jarlais, D. C., & Lelutiu-Weinberger, C. (2008). Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. *Am J Epidemiol, 168*, 1099-1109.

Hagedorn, H., Dieperink, E., Dingmann, D., Durfee, J., Ho, S. B., Isenhart, C., Rettmann, N., & Willenbring, M. (2007). Integrating hepatitis prevention services into a substance use disorder clinic. *Journal of Substance Abuse Treatment, 32*, 391-398.

Hajarizadeh, B., Grebely, J., & Dore, G. J. (2013). Epidemiology and natural history of HCV infection. *Nat Rev Gastroenterol Hepatol, 10*, 553-562.

Hajarizadeh, B., Grebely, J., Matthews, G., Martinello, M., & Dore, G. (2016). Treatment uptake for chronic hepatitis C in Australia following universal access to interferon-

free treatments. In *Hepatology* (Vol. 63, pp. 948A-948A): WILEY-BLACKWELL 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.

Harris, M., & Rhodes, T. (2013). Hepatitis C treatment access and uptake for people who inject drugs: a review mapping the role of social factors. *Harm Reduct J, 10*, 7.

Havens, J. R., Lofwall, M. R., Frost, S. D., Oser, C. B., Leukefeld, C. G., & Crosby, R. A. (2013). Individual and network factors associated with prevalent hepatitis C infection among rural Appalachian injection drug users. *Am J Public Health, 103*, e44-52.

Havens, J. R., Walker, R., & Leukefeld, C. G. (2007). Prevalence of opioid analgesic injection among rural nonmedical opioid analgesic users. *Drug Alcohol Depend, 87*, 98-102.

Hellard, M., Rolls, D. A., Sacks-Davis, R., Robins, G., Pattison, P., Higgs, P., Aitken, C., & McBryde, E. (2014). The impact of injecting networks on hepatitis C transmission and treatment in people who inject drugs. *Hepatology, 60*, 1861-1870.

Hellard, M., Sacks-Davis, R., & Gold, J. (2009). Hepatitis C treatment for injection drug users: a review of the available evidence. *Clin Infect Dis, 49*, 561-573.

Hickman, M., McDonald, T., Judd, A., Nichols, T., Hope, V., Skidmore, S., & Parry, J. V. (2008). Increasing the uptake of hepatitis C virus testing among injecting drug users in specialist drug treatment and prison settings by using dried blood spots for diagnostic testing: a cluster randomized controlled trial. *Journal of viral hepatitis, 15*, 250-254.

Hirsch, A. A., Lawrence, R. H., Kern, E., Falck-Ytter, Y., Shumaker, D. T., & Watts, B. (2014). Implementation and evaluation of a multicomponent quality improvement intervention to improve efficiency of hepatitis C screening and diagnosis. *Jt Comm J Qual Patient Saf, 40*, 351-357.

Ho, S. B., Brau, N., Cheung, R., Liu, L., Sanchez, C., Sklar, M., Phelps, T. E., Marcus, S. G., Wasil, M. M., Tisi, A., Huynh, L., Robinson, S. K., Gifford, A. L., Asch, S. M., & Groessl, E. J. (2015). Integrated care increases treatment and improves outcomes of patients with chronic hepatitis C virus infection and psychiatric illness or substance abuse. *Clinical Gastroenterology and Hepatology, 13*, 2005-2014.e2003.

Iversen, J., Grebely, J., Topp, L., Wand, H., Dore, G., & Maher, L. (2014). Uptake of hepatitis C treatment among people who inject drugs attending Needle and Syringe Programs in Australia, 1999-2011. *J Viral Hepat, 21*, 198-207.

Jordan, A. E., Blackburn, N. A., Des Jarlais, D. C., & Hagan, H. (2017). Past-year prevalence of prescription opioid misuse among those 11 to 30years of age in the United States: A systematic review and meta-analysis. *J Subst Abuse Treat, 77*, 31-37.

Lacey, C., Ellen, S., Devlin, H., Wright, E., & Mijch, A. (2007). Hepatitis C in psychiatry inpatients: Testing rates, prevalence and risk behaviours. *Australasian Psychiatry, 15*, 315-319.

Larney, S., Grebely, J., Hickman, M., De Angelis, D., Dore, G. J., & Degenhardt, L. (2015). Defining populations and injecting parameters among people who inject drugs: Implications for the assessment of hepatitis C treatment programs. *Int J Drug Policy, 26*, 950-957.

Lelutiu-Weinberger, C., Pouget, E. R., Des Jarlais, D. D., Cooper, H. L., Scheinmann, R., Stern, R., Strauss, S. M., & Hagan, H. (2009). A meta-analysis of the hepatitis C virus distribution in diverse racial/ethnic drug injector groups. *Soc Sci Med, 68*, 579-590.

Lima, V. D., Rozada, I., Grebely, J., Hull, M., Lourenco, L., Nosyk, B., Krajden, M., Yoshida, E., Wood, E., & Montaner, J. S. (2015). Are Interferon-Free Direct-Acting Antivirals for the Treatment of HCV Enough to Control the Epidemic among People Who Inject Drugs? *PLoS One, 10*, e0143836.

Marshall, A. D., Micallef, M., Erratt, A., Telenta, J., Treloar, C., Everingham, H., Jones, S. C., Bath, N., How-Chow, D., Byrne, J., Harvey, P., Dunlop, A., Jauncey, M., Read, P., Collie, T., Dore, G. J., & Grebely, J. (2015). Liver disease knowledge and acceptability of non-invasive liver fibrosis assessment among people who inject drugs in the drug and alcohol setting: The LiveRLife Study. *Int J Drug Policy, 26*, 984-991.

Marshall, A. D., Nielsen, S., Cunningham, E. B., Aghemo, A., Alho, H., Backmund, M., Bruggmann, P., Dalgard, O., Flisiak, R., Foster, G., Gheorghe, L., Goldberg, D., Goulis, I., Hickman, M., Hoffmann, P., Jancorienė, L., Jarčuška, P., Kåberg, M., Makara, M., Maimets, M., Marinho, R., Matičič, M., Norris, S., Ólafsson, S., Øvrehus, A., Pawlotsky, J. M., Pocock, J., Robaeys, G., Roncero, C., Simonova, M., Sperl, J., Tait, M., Tolmane, I., Tomaselli, S., van der Valk, M., Vince, A., Dore, G. J., Lazarus, J. V., & Grebely, J. (2017). Restrictions for reimbursement of interferon-free direct acting antiviral therapies for HCV infection in Europe. *J Hepatol, 66*, S95–S96.

Marshall, A. D., Saeed, S., Barrett, L., Cooper, C. L., Treloar, C., Bruneau, J., Feld, J. J., Gallagher, L., Klein, M. B., Krajden, M., Shoukry, N. H., Taylor, L. E., Grebely, J., & Canadian Network on Hepatitis, C. (2016). Restrictions for reimbursement of direct-acting antiviral treatment for hepatitis C virus infection in Canada: a descriptive study. *CMAJ Open, 4*, E605-E614.

Marshall, B. D., Green, T. C., Yedinak, J. L., & Hadland, S. E. (2016). Harm reduction for young people who use prescription opioids extra-medically: Obstacles and opportunities. *Int J Drug Policy, 31*, 25-31.

Martin, N. K., Hickman, M., Hutchinson, S. J., Goldberg, D. J., & Vickerman, P. (2013). Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. *Clin Infect Dis, 57 Suppl 2*, S39-45.

Martin, N. K., Vickerman, P., Dore, G. J., Grebely, J., Miners, A., Cairns, J., Foster, G. R., Hutchinson, S. J., Goldberg, D. J., Martin, T. C., Ramsay, M., Consortium, S.-H., & Hickman, M. (2016). Prioritization of HCV treatment in the direct-acting antiviral era: An economic evaluation. *J Hepatol, 65*, 17-25.

Martin, N. K., Vickerman, P., Foster, G. R., Hutchinson, S. J., Goldberg, D. J., & Hickman, M. (2011). Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. *J Hepatol, 54*, 1137-1144.

Martin, N. K., Vickerman, P., Grebely, J., Hellard, M., Hutchinson, S. J., Lima, V. D., Foster, G. R., Dillon, J. F., Goldberg, D. J., Dore, G. J., & Hickman, M. (2013). Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology, 58*, 1598-1609.

Masson, C. L., Delucchi, K. L., McKnight, C., Hettema, J., Khalili, M., Min, A., Jordan, A. E., Pepper, N., Hall, J., & Hengl, N. S. (2013). A randomized trial of a hepatitis care coordination model in methadone maintenance treatment. *American journal of public health, 103*, e81-e88.

Merchant, R. C., Baird, J. R., Liu, T., Taylor, L. E., Montague, B. T., & Nirenberg, T. D. (2014). Brief intervention to increase emergency department uptake of combined rapid human immunodeficiency virus and hepatitis C screening among a drug misusing population. *Academic Emergency Medicine, 21*, 752-767.

Merchant, R. C., DeLong, A. K., Liu, T., & Baird, J. R. (2015). Factors influencing uptake of rapid HIV and hepatitis C screening among drug misusing adult emergency department patients: Implications for future HIV/HCV screening interventions. *Aids and Behavior, 19*, 2025-2035.

Miller, C. L., Johnston, C., Spittal, P. M., Li, K., Laliberte, N., Montaner, J. S., & Schechter, M. T. (2002). Opportunities for prevention: hepatitis C prevalence and incidence in a cohort of young injection drug users. *Hepatology, 36*, 737-742.

Moessner, B. K., Jorgensen, T. R., Skamling, M., Vyberg, M., Junker, P., Pedersen, C., & Christensen, P. B. (2011). Outreach screening of drug users for cirrhosis with transient elastography. *Addiction, 106*, 970-976.

Morris, M. D., Shiboski, S., Bruneau, J., Hahn, J. A., Hellard, M., Prins, M., Cox, A. L., Dore, G., Grebely, J., Kim, A. Y., Lauer, G. M., Lloyd, A., Rice, T., Shoukry, N., Maher, L., Page, K., International Collaboration of Incident, H. I. V., & Cohorts, H. C. V. i. I. (2017). Geographic Differences in Temporal Incidence Trends of Hepatitis C Virus Infection Among People Who Inject Drugs: The InC3 Collaboration. *Clin Infect Dis, 64*, 860-869.

Moussalli, J., Delaquaize, H., Boubilley, D., Lhomme, J. P., Ponty, J. M., Sabot, D., Kerever, A., Valleur, M., & Poynard, T. (2010). Factors to improve the management of hepatitis C in drug users: An observational sudy in an addiction centre. *Gastroenterology Research and Practice, 2010*.

Nelson, P. K., Mathers, B. M., Cowie, B., Hagan, H., Des Jarlais, D., Horyniak, D., & Degenhardt, L. (2011). Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet, 378*, 571-583.

Ooka, K., Connolly, J. J., & Lim, J. K. (2017). Medicaid Reimbursement for Oral Direct Antiviral Agents for the Treatment of Chronic Hepatitis C. *Am J Gastroenterol, 112*, 828-832.

Page, K., Morris, M. D., Hahn, J. A., Maher, L., & Prins, M. (2013). Injection drug use and hepatitis C virus infection in young adult injectors: using evidence to inform comprehensive prevention. *Clin Infect Dis, 57 Suppl 2*, S32-38.

Puoti, M., Cooper, C., Sulkowski, M. S., Foster, G. R., Berg, T., Villa, E., Rodriguez-Perez, F., Rustgi, V., Wyles, D. L., King, M., McGovern, B. H., & Wedemeyer, H. (2014). ABT-450/r/Ombitasvir plus Dasabuvir With or Without Ribavirin in HCV Genotype 1-infected Patients Receiving Stable Opioid Substitution Treatment: Pooled Analysis of Efficacy and Safety in Phase 2 and Phase 3 Trials. *Hepatology, 60*, 1135a-1136a.

Radley, A., Melville, K., Tait, J., Stephens, B., Evans, J. M., & Dillon, J. F. (2017). A quasi-experimental evaluation of dried blood spot testing through community pharmacies in the Tayside region of Scotland. *Frontline Gastroenterology*, flgastro-2016-100776.

Rosenberg, S. D., Goldberg, R. W., Dixon, L. B., Wolford, G. L., Slade, E. P., Himelhoch, S., Gallucci, G., Potts, W., Tapscott, S., & Welsh, C. J. (2010). Assessing the STIRR model of best practices for blood-borne infections of clients with severe mental illness. *Psychiatric Services, 61*, 885-891.

Roux, P., Castro, D. R., Ndiaye, K., Debrus, M., Protopopescu, C., Le Gall, J. M., Haas, A., Mora, M., Spire, B., Suzan-Monti, M., & Carrieri, P. (2016). Increased uptake of HCV testing through a community-based educational intervention in difficult-to-reach people who inject drugs: Results from the ANRS-AERLI study. *PloS one, 11*.

Roy, E., Boudreau, J. F., & Boivin, J. F. (2009). Hepatitis C virus incidence among young street-involved IDUs in relation to injection experience. *Drug Alcohol Depend, 102*, 158-161.

Scott, N., McBryde, E. S., Thompson, A., Doyle, J. S., & Hellard, M. E. (2016). Treatment scale-up to achieve global HCV incidence and mortality elimination targets: a cost-effectiveness model. *Gut*.

Stanaway, J. D., Flaxman, A. D., Naghavi, M., Fitzmaurice, C., Vos, T., Abubakar, I., Abu-Raddad, L. J., Assadi, R., Bhala, N., Cowie, B., Forouzanfour, M. H., Groeger, J., Mohd Hanafiah, K., Jacobsen, K. H., James, S. L., MacLachlan, J., Malekzadeh, R.,

Martin, N. K., Mokdad, A. A., Mokdad, A. H., Murray, C. J., Plass, D., Rana, S., Rein, D. B., Richardus, J. H., Sanabria, J., Saylan, M., Shahraz, S., So, S., Vlassov, V. V., Weiderpass, E., Wiersma, S. T., Younis, M., Yu, C., El Sayed Zaki, M., & Cooke, G. S. (2016). The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Lancet, 388*, 1081-1088.

Strike, C., Millson, M., Hopkins, S., & Smith, C. (2013). What is low threshold methadone maintenance treatment? *Int J Drug Policy, 24*, e51-56.

Swan, D., Long, J., Carr, O., Flanagan, J., Irish, H., Keating, S., Keaveney, M., Lambert, J., McCormick, P. A., McKiernan, S., Moloney, J., Perry, N., & Cullen, W. (2010). Barriers to and facilitators of hepatitis C testing, management, and treatment among current and former injecting drug users: a qualitative exploration. *AIDS Patient Care STDS, 24*, 753-762.

Tait, J. M., McIntyre, P. G., McLeod, S., Nathwani, D., & Dillon, J. F. (2010). The impact of a managed care network on attendance, follow-up and treatment at a hepatitis C specialist centre. *Journal of viral hepatitis, 17*, 698-704.

Treloar, C., Hull, P., Bryant, J., Hopwood, M., Grebely, J., & Lavis, Y. (2011). Factors associated with hepatitis C knowledge among a sample of treatment naive people who inject drugs. *Drug Alcohol Depend, 116*, 52-56.

Treloar, C., Hull, P., Dore, G. J., & Grebely, J. (2012). Knowledge and barriers associated with assessment and treatment for hepatitis C virus infection among people who inject drugs. *Drug Alcohol Rev, 31*, 918-924.

Treloar, C., Rance, J., Bath, N., Everingham, H., Micallef, M., Day, C., Hazelwood, S., Grebely, J., & Dore, G. J. (2015). Evaluation of two community-controlled peer support services for assessment and treatment of hepatitis C virus infection in opioid substitution treatment clinics: The ETHOS study, Australia. *Int J Drug Policy, 26*, 992-998.

United Nations Office on Drugs and Crime, I. N. o. P. W. U. D., Joint United Nations Programme on HIV/AIDS, United Nations Development Programme, United Nations Population Fund, World Health Organization, United States Agency for International Development. . Implementing comprehensive HIV and HCV programmes with people who inject drugs: practical guidance for collaborative interventions. . from http://www.unodc.org/documents/hiv-aids/publications/Implementing_Comprehensive_HIV_and_HCV_Programmes_with_People_Who_Inject_Drugs_PRACTICAL_GUIDANCE_FOR_COLLABORATIVE_INTERVENTIONS.pdf.

van der Meer, A. J., Wedemeyer, H., Feld, J. J., Dufour, J. F., Zeuzem, S., Hansen, B. E., & Janssen, H. L. (2014). Life expectancy in patients with chronic HCV infection and cirrhosis compared with a general population. *JAMA, 312*, 1927-1928.

WHO. (2014). Guidelines for the screening, care and treatment of persons with hepatitis C infection. In W. H. Organization (Ed.). Geneva, Switzerland.

WHO. Global health sector strategy on viral hepatitis 2016-2021. Retrieved June 5, 2017 from http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf?ua=1.

WHO. (2017b). Global Hepatitis Report 2017. . In W. H. Organization (Ed.). Geneva: World Health Organization.

Wiessing, L., Ferri, M., Grady, B., Kantzanou, M., Sperle, I., Cullen, K. J., group, E. D., Hatzakis, A., Prins, M., Vickerman, P., Lazarus, J. V., Hope, V. D., & Mathei, C. (2014). Hepatitis C virus infection epidemiology among people who inject drugs in Europe: a systematic review of data for scaling up treatment and prevention. *PLoS One, 9*, e103345.

Wolfe, D., Luhmann, N., Harris, M., Momenghalibaf, A., Albers, E., Byrne, J., & Swan, T. (2015). Human rights and access to hepatitis C treatment for people who inject drugs. *Int J Drug Policy, 26*, 1072-1080.

Yehia, B. R., Schranz, A. J., Umscheid, C. A., & Lo Re, V., 3rd. (2014). The treatment cascade for chronic hepatitis C virus infection in the United States: a systematic review and meta-analysis. *PLoS One, 9*, e101554.

Younossi, Z., & Henry, L. (2015). Systematic review: patient-reported outcomes in chronic hepatitis C--the impact of liver disease and new treatment regimens. *Aliment Pharmacol Ther, 41*, 497-520.

Zeuzem, S., Ghalib, R., Reddy, K. R., Pockros, P. J., Ben Ari, Z., Zhao, Y., Brown, D. D., Wan, S., DiNubile, M. J., Nguyen, B. Y., Robertson, M. N., Wahl, J., Barr, E., & Butterton, J. R. (2015). Grazoprevir-Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection: A Randomized Trial. *Ann Intern Med, 163*, 1-13.

Zibbell, J. E., Hart-Malloy, R., Barry, J., Fan, L., & Flanigan, C. (2014). Risk factors for HCV infection among young adults in rural New York who inject prescription opioid analgesics. *Am J Public Health, 104*, 2226-2232.