



# HHS Public Access

Author manuscript

*Int J Drug Policy*. Author manuscript; available in PMC 2018 September 10.

Published in final edited form as:

*Int J Drug Policy*. 2015 October ; 26(10): 1028–1038. doi:10.1016/j.drugpo.2015.07.005.

## Recommendations for the management of hepatitis C virus infection among people who inject drugs

Jason Grebely<sup>a,\*</sup>, Geert Robaey<sup>b,c,d</sup>, Philip Bruggmann<sup>e</sup>, Alessio Aghemo<sup>f</sup>, Markus Backmund<sup>g,h</sup>, Julie Bruneau<sup>i</sup>, Jude Byrne<sup>j</sup>, Olav Dalgard<sup>k</sup>, Jordan J. Feld<sup>l</sup>, Margaret Hellard<sup>m,n</sup>, Matthew Hickman<sup>o</sup>, Achim Kautz<sup>p</sup>, Alain Litwin<sup>q</sup>, Andrew R. Lloyd<sup>r</sup>, Stefan Mauss<sup>s</sup>, Maria Prins<sup>t,u</sup>, Tracy Swan<sup>v</sup>, Martin Schaefer<sup>w,x</sup>, Lynn E. Taylor<sup>y</sup>, and Gregory J. Dore<sup>a</sup> the International Network for Hepatitis in Substance Users

<sup>a</sup>Kirby Institute, UNSW Australia, Sydney, Australia <sup>b</sup>Department of Gastroenterology and Hepatology, Ziekenhuis Oost Limburg, Genk, Belgium <sup>c</sup>Department of Hepatology, UZ Leuven, Leuven, Belgium <sup>d</sup>Faculty of Medicine and Life Sciences, Limburg Clinical Research Program, Hasselt University, Hasselt, Belgium <sup>e</sup>Arud Centres of Addiction Medicine, Zurich, Switzerland <sup>f</sup>A.M. Migliavacca Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy <sup>g</sup>Ludwig-Maximilians-University, Munich, Germany <sup>h</sup>Praxiszentrum im Tal Munich, Munich, Germany <sup>i</sup>CRCHUM, Université de Montréal, Montréal, Canada <sup>j</sup>International Network of People who Use Drugs, Canberra, Australia <sup>k</sup>Department of Infectious Diseases, Akershus University Hospital, Lørenskog, Norway <sup>l</sup>University of Toronto, Toronto, Canada <sup>m</sup>Burnet Institute, Melbourne, Australia <sup>n</sup>Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia <sup>o</sup>School of Social & Community Medicine, University of Bristol, Bristol, United Kingdom <sup>p</sup>European Liver Patients Association, Cologne, Germany <sup>q</sup>Division of General Internal Medicine, Department of Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, United States <sup>r</sup>Inflammation and Infection Research Centre, School of Medical Sciences, UNSW Australia, Sydney, Australia <sup>s</sup>Center for HIV and Hepatogastroenterology, Düsseldorf, Germany <sup>t</sup>Department of Research, Cluster Infectious Diseases, Public Health Service of Amsterdam, Amsterdam, The Netherlands <sup>u</sup>Department of Internal Medicine, CINIMA, Academic Medical Centre, Amsterdam, The Netherlands <sup>v</sup>Treatment Action Group, New York, United States <sup>w</sup>Department of Psychiatry, Psychotherapy and Addiction Medicine, Kliniken Essen-Mitte, Essen, Germany <sup>x</sup>Department of Psychiatry and Psychotherapy-CCM, Charité – Universitätsmedizin Berlin, Berlin, Germany <sup>y</sup>Department of Medicine, Brown University, Providence, RI, United States

### Abstract

In high income countries, the majority of new and existing hepatitis C virus (HCV) infections occur among people who inject drugs (PWID). In many low and middle income countries large

\*Corresponding author at: Viral Hepatitis Clinical Research Program, The Kirby Institute, UNSW Australia, Ground Floor, CFI Building, Corner Boundary & West Streets, Darlinghurst, NSW 2010, Australia. Tel.: +61 2 9385 0900; fax: +61 2 9385 0876. jgrebely@kirby.unsw.edu.au (J. Grebely).

Conflict of interest statement: All authors have no reported conflicts relevant to the content of the manuscript.

HCV epidemics have also emerged among PWID populations. The burden of HCV-related liver disease among PWID is increasing, but treatment uptake remains extremely low. There are a number of barriers to care which should be considered and systematically addressed, but should not exclude PWID from HCV treatment. The rapid development of interferon-free direct-acting antiviral (DAA) therapy for HCV infection has brought considerable optimism to the HCV sector, with the realistic hope that therapeutic intervention will soon provide near optimal efficacy with well-tolerated, short duration, all oral regimens. Further, it has been clearly demonstrated that HCV treatment is safe and effective across a broad range of multidisciplinary healthcare settings. Given the burden of HCV-related disease among PWID, strategies to enhance HCV assessment and treatment in this group are urgently needed. These recommendations demonstrate that treatment among PWID is feasible and provide a framework for HCV assessment and

## Keywords

Drug users; Injecting; Injection; Guidelines; HCV; HIV; PWID

---

## Introduction

In high income countries, 50–80% of hepatitis C virus (HCV) infection is among people who inject drugs (PWID), and HCV epidemics have emerged among PWID in many low and middle income countries (Hajarizadeh, Grebely, & Dore, 2013). Within this population are ‘current’ or ‘recent’ PWID (Larney et al., 2015), who are at risk of transmitting and acquiring HCV infection (there are varying definitions in the literature, although one month to one year is most common (EMCDDA, 2010; WHO, 2012)). ‘Former’ PWID (people who have ceased injecting drug use) are also of importance, as a large proportion of existing HCV infections are found in this group (Larney et al., 2015). Given the relapsing nature of drug dependence, determining a cut-off to define permanent vs short-term cessation of injecting drug use (and therefore ‘current’/‘recent’ vs ‘former’ PWID) is problematic (Larney et al., 2015). These guidelines, however, are predominantly developed for clinical management of HCV in the current PWID population and the term PWID will in general relate to this population. Given a large proportion of PWID have been HCV-infected for two or more decades, many have progressed to advanced fibrosis (Grebely & Dore, 2011; Hajarizadeh et al., 2013). Rates of advanced liver disease complications, associated healthcare costs, and liver-related morbidity and mortality among PWID continue to rise (Grebely & Dore, 2011; Hajarizadeh et al., 2013).

Until recently, HCV treatment guidelines excluded PWID, due to concerns about poor adherence, adverse events and re-infection (NIH, 1997). Successful HCV treatment studies among PWID challenged this paradigm (Alvarez-Uria, Day, Nasir, Russell, & Vilar, 2009; Aspinall et al., 2013; Backmund, Meyer, Von Zielonka, & Eichenlaub, 2001; Bruggmann et al., 2008; Dalgard, 2005; Dimova et al., 2013; Dore et al., 2010; Grebely, Genoway, et al., 2007; Grebely et al., 2010; Grebely, Raffa, et al., 2007; Guadagnino et al., 2007; Hellard, Sacks-Davis, & Gold, 2009; Jack, Willott, Manners, Varnam, & Thomson, 2009; Jafferbhoy et al., 2012; Jeffrey et al., 2007; Lindenburg et al., 2011; Manolakopoulos et al., 2010; Martinez et al., 2010; Matthews, Kronborg, & Dore, 2005; Mauss, Berger, Goelz, Jacob, &

Schmutz, 2004; Melin et al., 2010; Neri et al., 2002; Papadopoulos, Gogou, Mylopoulou, & Mimidis, 2010; Robaeyts et al., 2006; Sasadeusz et al., 2011; Schaefer et al., 2003, 2007; Sylvestre, 2002; Sylvestre, Litwin, Clements, & Gourevitch, 2005; Van Thiel, Anantharaju, & Creech, 2003; Van Thiel et al., 1995; Waizmann & Ackermann, 2010; Wilkinson et al., 2009). International guidelines from the American Association for the Study of Liver Disease (AASLD)/Infectious Diseases Society of America (IDSA), the European Study for the Association of the Liver (EASL), the International Network for Hepatitis in Substance Users and the World Health Organization now all recommend treatment for HCV infection among PWID (AASLD/IDSA, 2015; European Association for Study of Liver, 2014; Robaeyts et al., 2013; WHO, 2014).

Despite revised guidelines, few PWID have received HCV treatment (Alavi et al., 2014; Grebely et al., 2009; Iversen et al., 2014; Mehta et al., 2008; NCHECR, 2009; Strathdee et al., 2005). Enhanced HCV assessment and treatment in PWID will be required to reduce future HCV-related morbidity and mortality (Hutchinson, Bird, & Goldberg, 2005b). The availability of effective, tolerable and simpler interferon-free direct acting antiviral (DAA) regimens should improve the feasibility of this approach (Dore & Feld, 2015). The International Network for Hepatitis in Substance Users (INHSU) established an expert panel to develop recommendations to enhance HCV assessment, management and treatment among PWID, with the first recommendations published in 2013 (Robaeyts et al., 2013). These recommendations have been updated to reflect the rapidly changing landscape of HCV therapy and have been updated to be in line with the methodologies used by international guidelines from AASLD and IDSA (AASLD/IDSA, 2015).

## Methods

The guidance is presented in the form of RECOMMENDATIONS. Each RECOMMENDATION is rated in terms of the level of the evidence and strength of the recommendation, using a scale developed by AASLD/IDSA (AASLD/IDSA, 2015). Recommendations are based on scientific evidence and expert opinion (Table 1). Each recommended statement includes a Roman numeral (I, II, or III) that represents the level of the evidence that supports the recommendation, and a letter (A, B, or C) that represents the strength of the recommendation.

## Epidemiology and prevention of HCV

HCV prevalence among PWID populations ranges from <20% to >80% (mid-point HCV estimate: 67% antibody positive; 50% RNA positive), with a global estimate of 10 million HCV antibody positive PWID (7.5 million with chronic HCV infection) (Hagan, Pouget, Des Jarlais, & Lelutiu-Weinberger, 2008; Nelson et al., 2011). HCV genotypes 1a, 1b, and 3a are common among PWID (Pybus, Cochrane, Holmes, & Simmonds, 2005), 4d is common among PWID in Europe (van Asten et al., 2004), and 6 in Southeast Asia (Sievert et al., 2011). HCV incidence among PWID also varies considerably from 2% to 66% per annum (Hagan et al., 2008; Page, Morris, Hahn, Maher, & Prins, 2013; Wiessing et al., 2014). Studies on time to HCV infection have demonstrated highest incidence in the initial years of injecting (Hagan et al., 2008; Roy, Boudreau, & Boivin, 2009).

High coverage of combined harm reduction programs (opioid substitution treatment [OST] and needle and syringe programs [NSP]) can reduce HCV incidence (Degenhardt et al., 2010; Hagan, Pouget, & Des Jarlais, 2011; MacArthur et al., 2014; Turner et al., 2011; van den Berg et al., 2007). Further, recent evidence has corroborated the impact of OST alone, reporting HCV transmission reductions by 50–80% (Aspinall et al., 2014; Nolan et al., 2014; Tsui, Evans, Lum, Hahn, & Page, 2014; White, Dore, Lloyd, Rawlinson, & Maher, 2014). Additional beneficial effects of OST dose–response (Nolan et al., 2014) and adjunct therapy during OST (Wang et al., 2014) have been observed.

Several modeling studies suggest that HCV treatment for PWID can lead to substantial reductions in HCV prevalence and reduce transmission (de Vos, Prins, & Kretzschmar, 2015; Hellard et al., 2014; Martin, Hickman, Hutchinson, Goldberg, & Vickerman, 2013; Martin et al., 2011; Martin, Vickerman, et al., 2013), particularly when combined with other ‘harm reduction’ interventions such as NSP and OST (Martin, Hickman, et al., 2013). Therefore, a combination prevention strategy including HCV treatment as prevention is critical for achieving reductions in HCV prevalence/transmission to very low levels, especially in settings with high existing harm reduction coverage (Williams et al., 2014). Further, given the potential prevention benefits, HCV treatment among PWID is cost-effective (Martin et al., 2012; Williams et al., 2014). As per international guidelines, given PWID are at a high risk of HCV transmission and HCV treatment may yield transmission reduction benefits, they are a high priority for treatment (AASLD/IDSA, 2015).

### Recommendations

1. PWID should be provided with appropriate access to OST and sterile drug injecting equipment as part of widespread comprehensive harm reduction programs (Class I, Level B).
2. PWID should be offered HCV treatment, given they are at elevated risk of HCV transmission and successful treatment may yield transmission reduction benefits (Class IIa, Level C).

### Natural history of HCV and effects of drugs on the liver

Chronic HCV infection develops in 75% (Grebely et al., 2014; Micallef, Kaldor, & Dore, 2006), with 10–20% developing cirrhosis over 20–30 years infection (Grebely & Dore, 2011). In a metaanalysis of cross-sectional studies of HCV-infected PWID, the 20-year cirrhosis prevalence was 15% (John-Baptiste, Krahn, Heath-cote, Laporte, & Tomlinson, 2010). In a systematic review of the progression of fibrosis among PWID with chronic HCV, the average time from HCV infection to the development of advanced liver disease (stage >F3) and cirrhosis were 29–30 years and 39–40 years, respectively (Smith et al., 2015). Factors contributing to fibrosis progression include age, moderate-heavy alcohol use, HIV, obesity and insulin resistance (reviewed in Hajarizadeh et al., 2013).

Despite prevalent misconceptions among affected populations and health care workers, no liver toxicity is reported for heroin (Rehm et al., 2005) or methadone (Kreek, Dodes, Kane, Knobler, & Martin, 1972). Buprenorphine occasionally increases transaminases (Petry,

Bickel, Piasecki, Marsch, & Badger, 2000). Methylenedioxymetamphetamine (MDMA) rarely causes acute liver failure due to direct liver toxicity (Andreu et al., 1998; Turillazzi, Riezzo, Neri, Bello, & Fineschi, 2010) and little is known about methamphetamine-related liver toxicity (Karch, Stephens, & Ho, 1999). Heavy alcohol consumption is associated with a higher risk of cirrhosis (Hutchinson, Bird, & Goldberg, 2005a). Regular cannabis use may also increase fibrosis progression (Hezode et al., 2005; Ishida et al., 2008), but other data do not support this assertion (Brunet et al., 2013).

Ageing cohorts of PWID with chronic HCV and low treatment uptake are currently leading to an increasing burden of HCV related morbidity and mortality (Grebely & Dore, 2011; Hajarizadeh et al., 2013). In several countries where PWID are the major population affected by HCV, 20–25% of deaths among HCV-infected individuals are from liver disease and 15–30% are from drug-related causes (Grebely & Dore, 2011).

## Recommendations

1. PWID should be counselled to moderate alcohol intake, or abstain if evidence of advanced liver disease (Class I, Level A).
2. Cessation of injecting is not required to limit HCV disease progression (Class IIa, Level C).

## Testing of HCV infection

Timely HCV screening, test discussion, and assessment constitute essential measures for prevention (Centers for Disease Control and Prevention, 2012). Recommendations for testing are based on the high HCV prevalence in PWID (Hagan et al., 2008; Nelson et al., 2011), the growing evidence that awareness of HCV status has sustained protective behavioural changes (e.g. injecting risk behaviours) (Aspinall et al., 2014; Bruneau et al., 2014), the potential public health benefit of reducing transmission by treating current PWID (de Vos et al., 2015; Hellard et al., 2014; Martin, Hickman, et al., 2013; Martin et al., 2011; Martin, Vickerman, et al., 2013), and the proven benefits of care and treatment in reducing HCV related morbidity and mortality (van der Meer et al., 2012, 2014). Evidence regarding the frequency of testing is limited, but due to the high incidence of HCV infection in PWID (Hagan et al., 2008; Page et al., 2013; Wiessing et al., 2014) and the benefits outlined above, at least annual HCV testing is recommended in PWID.

Successful strategies to increase HCV testing and diagnosis include interventions based on targeted case-finding (Cullen et al., 2012), risk-based assessment (Drainoni et al., 2012; Litwin et al., 2012), birth-cohort screening (Litwin et al., 2012), and motivational interviewing with case management (Masson et al., 2013). Enhanced screening could also be achieved through targeted HCV testing initiatives such as free counseling and testing, point-of-care testing, and dried blood spot testing (Meyer et al., 2015). In a systematic review of interventions incorporating dried blood spot testing in drug and alcohol clinics, prisons or NSP services, the introduction of DBS testing increased the number of tests, new diagnoses or both (Coats and Dillon, 2015).

## Recommendations

1. An anti-HCV test is recommended for HCV testing among PWID, and if the result is positive, current infection should be confirmed by a sensitive RNA test (Class I, Level B).
2. PWID who are anti-HCV negative should be routinely and voluntarily tested for HCV antibodies/RNA and if negative, every 12 months. Testing should also be offered following a high risk injecting episode (Class IIa, Level B).
3. PWID who are anti-HCV antibody positive and HCV RNA negative (through spontaneous or treatment-induced clearance) should receive regular HCV RNA testing, every 12 months or following a high risk injecting episode (Class IIa, Level B).

## Non-invasive liver fibrosis assessment

Liver biopsy is the gold standard for liver fibrosis assessment, but is invasive and logistically difficult. As per international guidelines (AASLD/IDSA, 2015; European Association for Study of Liver, 2014), non-invasive methods such as transient elastography or well-established panels of biomarkers of fibrosis are acceptable for liver disease stage assessment. Non-invasive methods have excellent utility for the identification of HCV-related cirrhosis, but lesser accuracy for earlier stages (Shaheen, Wan, & Myers, 2007) and can predict HCV-related survival (Vergniol et al., 2011). Combining multiple modalities achieves the best performance (Baranova, Lal, Binerdinc, & Younossi, 2011). Non-invasive tests are cost-effective. Among PWID, transient elastography can enhance liver disease screening (Foucher et al., 2009; Marshall et al., 2015; Moessner et al., 2011).

## Recommendations

1. Non-invasive assessments have a reduced risk and greater acceptance than liver biopsy, may enhance HCV screening and disease assessment among PWID, and should be offered, if available (Class I, Level B).
2. Combining multiple non-invasive assessments is recommended, when possible (Class I, Level B).

## Pre-therapeutic assessment

Guidelines for pre-therapeutic assessment for HCV-infected individuals are available (AASLD/IDSA, 2015; European Association for Study of Liver, 2014). However, HCV-infected PWID often have complex social, medical and psychiatric co-morbidities, complicating decisions around care (reviewed in Grebely & Tyndall, 2011). Poor knowledge and inaccurate perceptions about HCV are barriers for accessing HCV care (Doab, Treloar, & Dore, 2005; Grebely et al., 2008; Treloar et al., 2011; Treloar, Newland, Rance, & Hopwood, 2010). Factors associated with not receiving HCV treatment include older age (Kramer et al., 2011), ethnicity (Kramer et al., 2011), lack of social support (Alavi et al., 2013) (Fortier et al., 2015), lack of treatment willingness or treatment intent (Alavi et al., 2015a), ongoing or former drug use (Alavi et al., 2013, 2015a; Bini et al., 2005; Gidding et

al., 2011; Kanwal et al., 2007), ongoing alcohol use (Gidding et al., 2011; Kramer et al., 2011), advanced liver disease (Bini et al., 2005), co-morbid medical disease (Kanwal et al., 2007), psychiatric disease (Bini et al., 2005; Kramer et al., 2011) and OST (Alavi et al., 2013, 2015a; Gidding et al., 2011).

HCV peer support models have been implemented in various settings, particularly in drug and alcohol clinics (Alavi et al., 2013; Charlebois, Lee, Cooper, Mason, & Powis, 2012; Crawford & Bath, 2013; Grebely et al., 2010; Keats et al., 2015; Musgrove, 2011; Norman et al., 2008; Rance & Treloar, 2012; Roose, Cockerham-Colas, Soloway, Batchelder, & Litwin, 2014; Stein et al., 2012; Sylvestre & Zweben, 2007; Treloar et al., 2015) (Keats et al., 2015). Most models have been either service generated (provider led) (Crawford & Bath, 2013; Grebely et al., 2010; Roose et al., 2014; Stein et al., 2012; Sylvestre & Zweben, 2007) or community controlled (peer led) (Alavi et al., 2013; Charlebois et al., 2012; Crawford & Bath, 2013; Keats et al., 2015; Norman et al., 2008; Rance & Treloar, 2012; Treloar et al., 2015). Peer support models have been implemented successfully, with a range of outcomes including increased treatment uptake (Grebely et al., 2010) and improved service provision (Treloar et al., 2015) (Keats et al., 2015). Care coordination in conjunction with behavioral interventions increase the likelihood of being evaluated by a HCV specialist and initiating treatment (Evon et al., 2011; Masson et al., 2013). Finally, models of HCV care integrated within addiction treatment and primary care health centers, as well as prisons, may allow successful HCV evaluation and therapy inpatients who would not be eligible for treatment in other secondary or tertiary settings (Aspinall et al., 2013; Bruggmann & Litwin, 2013; Dimova et al., 2013; Hellard et al., 2009; Lloyd et al., 2013; Robaey et al., 2013).

## Recommendations

1. Pre-therapeutic education should include discussions of HCV transmission, risk factors for fibrosis progression, treatment, reinfection risk and harm reduction strategies (Class I, Level B).
2. Pre-therapeutic assessment should include an evaluation of housing, education, cultural issues, social functioning and support, finances, nutrition and drug and alcohol use. PWID should be linked into social support services, and peer support if available (Class I, Level B).
3. Models of HCV care integrated within addiction treatment and primary care health centers, as well as prisons, allow successful pre-therapeutic assessment (Class I, Level B).
4. Peer-driven interventions delivered within OST settings may lead to higher rates of treatment initiation and should be offered, if available (Class IIa, Level C).
5. Care coordination in conjunction with behavioural interventions can increase likelihood of PWIDs being evaluated and initiating treatment and should be offered, if available (Class I, Level B).

## Indications for treatment

The goal of HCV therapy is to prevent liver disease complications, death from HCV, other extra-hepatic manifestations, and HCV transmission in the population. SVR is associated with improved quality of life, regression of fibrosis, and reduced risk of complications in those with cirrhosis (Seeff, 2002).

According to AASLD/IDSA recommendations, successful HCV treatment results in SVR, which is tantamount to virologic cure, and as such, is expected to benefit nearly all chronically infected persons (AASLD/IDSA, 2015). Evidence clearly supports treatment in all HCV-infected persons, except those with limited life expectancy (less than 12 months) due to non-liver-related comorbid conditions (AASLD/IDSA, 2015). Urgent initiation of treatment is recommended for some patients, such as those with advanced fibrosis or compensated cirrhosis. Priorities for treatment are based on severity of disease and potential transmission reduction benefits (AASLD/IDSA, 2015). Given the rapid changes in the pace of the introduction of new HCV regimens, a regular review of the updated AASLD/IDSA and EASL recommendations for contraindications to HCV therapy is advised. Further, clinical guidance should take account of disease severity and prevention benefit.

## Recommendations

1. PWID should receive HCV assessment, with treatment decisions based on an individualised evaluation of social, lifestyle, and clinical factors (Class I, Level B).
2. Treatment is recommended for PWID with chronic HCV infection (Class I, Level A).

## PEG-IFN and DAA-based treatment: treatment recommendations

In PWID, treatment of chronic HCV is safe and effective (Alvarez-Uria et al., 2009; Backmund et al., 2001; Bruggmann et al., 2008; Dalgard, 2005; Dimova et al., 2013; Dore et al., 2010; Grebely, Genoway, et al., 2007; Grebely et al., 2010; Grebely, Raffa, et al., 2007; Guadagnino et al., 2007; Hellard et al., 2009; Jack et al., 2009; Jafferbhoy et al., 2012; Jeffrey et al., 2007; Lindenburg et al., 2011; Manolakopoulos et al., 2010; Martinez et al., 2010; Matthews et al., 2005; Mauss et al., 2004; Melin et al., 2010; Neri et al., 2002; Papadopoulos et al., 2010; Robaeyts et al., 2006; Sasadeusz et al., 2011; Schaefer et al., 2003, 2007; Sylvestre, 2002; Sylvestre et al., 2005; Van Thiel et al., 1995, 2003; Waizmann & Ackermann, 2010; Wilkinson et al., 2009) (Litwin et al., 2015; Milne et al., 2015; Mason et al., 2015; Keats et al., 2015), and has been recommended for PWID by AASLD/IDSA and EASL guidelines following individualised assessment (AASLD/IDSA, 2015; European Association for Study of Liver, 2014). Therapy has evolved rapidly, with the recent approval of novel interferon-free DAA regimens that are highly effective and much better tolerated than those containing PEG-IFN (AASLD/IDSA, 2015; European Association for Study of Liver, 2014). The four main classes of DAAs are protease inhibitors (PIs), non-structural 5A (NS5A) inhibitors and nucleoside (NI) and non-nucleoside polymerase inhibitors (NNI) (Dore & Feld, 2015). DAAs of different classes have been combined (and co-formulated in



some cases) and show very high efficacy for genotypes 1, 2, 3 and 4 with between 8 and 24 weeks of therapy (Dore & Feld, 2015). There are limited efficacy data for those infected with genotypes 5 and 6. Treatment regimens are currently genotype-specific and may require modification based on prior treatment history and the presence of cirrhosis. It is likely that future regimens will be more pan-genotypic, which will further simplify therapy. As for all individuals with HCV, treatment with interferon-free DAA therapy is preferred for PWID and should follow international treatment guidelines (AASLD/IDSA, 2015; European Association for Study of Liver, 2014).

DAA clinical development programs have excluded individuals with active drug use, but many trials have included those on OST (Jacobson et al., 2014; Lalezari et al., 2015; Mangia et al., 2013; Puoti et al., 2014). In phase II/III clinical trials, SVR is similar among people receiving OST as compared to those not receiving OST (Jacobson et al., 2014; Mangia et al., 2013; Puoti et al., 2014). Among participants with HCV genotypes 1–3 treated with sofosbuvir and ribavirin (with or without pegylated-interferon) in phase III clinical trials, rates of sustained virological response (SVR) were similar among people receiving OST as compared to those not receiving OST (Mangia et al., 2013). Among participants in phase II/III clinical trials receiving OST with HCV genotype 1, SVR was 94% in those treated with ledipasvir and sofosbuvir (with or without ribavirin) (Jacobson et al., 2014), and 96% in those treated with paritaprevir/ritonavir, ombitasvir, dasabuvir (with or without ribavirin) (Puoti et al., 2014). Similarly, in a pilot study of genotype 1 participants receiving OST (n = 38) treated with the all oral combination of paritaprevir, ritonavir, ombitasvir, and ribavirin, the overall SVR was 97% (Lalezari et al., 2015). Results from the ongoing CO-STAR study, a phase III randomized clinical trial to study the efficacy and safety of the combination regimen of MK-5172/MK-8742 in treatment-naïve participants with chronic HCV genotype 1, 4 and 6 infection who are on OST are anticipated.

HCV-protease inhibitors are generally substrates and inhibitors of cytochrome P450 A3 (CYP3A), a key enzyme in drug metabolism by the liver (Burger et al., 2013; EMA, 2012a, 2012b, 2014c; Hulskotte et al., 2015; Luo, Trevejo, van Heeswijk, Smith, & Garg, 2012; van Heeswijk et al., 2013). Paritaprevir utilises this metabolism through ritonavir-boosting, and is also a CYP3A inhibitor. Other DAA classes, in particular NS5A inhibitors, have the potential for drug-drug interactions, therefore, a thorough assessment of concomitant medication is required for all patients commencing DAA therapy (EMA, 2014a, 2014b, 2014d, 2014e). In drug-drug interaction studies of HCV protease inhibitors with methadone and buprenorphine, no clinically important interactions have been observed (Burger et al., 2013; EMA, 2012a, 2012b, 2014c, 2014e; Hulskotte et al., 2015; Luo et al., 2012; van Heeswijk et al., 2013). Amphetamine (MDMA) and ecstasy (PMA, PMMA) are metabolised by CYP3A4 and CYP2D6 and monoaminooxidases. Given that the consequences of overdose can be fatal due to hyperthermia, cardiac arrhythmia or liver failure, the concomitant use of amphetamine and ecstasy with protease inhibitors should be avoided and other drug classes of DAAs considered.

## Recommendations

1. Evaluation of safety and efficacy of interferon-free DAA regimens is required in PWID (Class I, Level C).
2. Sofosbuvir, sofosbuvir/ledipasvir, paritaprevir/ritonavir/ombi-tasvir/dasabuvir, daclatasvir, and simeprevir can be used in PWID on OST (Class I, Level B).
3. The decision to institute therapy in PWID should be based on the availability of agents locally and individual disease characteristics of infected persons. For regions without access to interferon-free DAA therapy, PWID with early liver disease should generally be advised to await access to interferon-free DAA regimens. For those with access to highly effective interferon-free DAA therapy, anyone with chronic HCV infection should be considered for therapy, taking into account social circumstances, adherence and medical and social comorbidities (Class I, Level B).
4. DAA therapy does not require specific methadone and buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be undertaken (Class I, Level B).

## Impact of drug use on adherence and SVR

Adherence to HCV therapy is often defined as receipt of >80% of scheduled PEG-IFN and ribavirin for >80% of the treatment period, but this does not distinguish between missed doses and treatment discontinuation (Weiss, Brau, Stivala, Swan, & Fishbein, 2009). However, these cut-offs may not be applicable in the interferon-free era. Suboptimal PEG-IFN exposure is mainly driven by early treatment discontinuation as compared to missed doses (Grebely, Matthews, Hellard, et al., 2011). Of note, both physicians (Marcellin et al., 2011) and individuals (Smith et al., 2007) overestimate adherence to HCV therapy. Adherence (Grebely, Matthews, Hellard, et al., 2011; Weiss et al., 2009) and treatment completion (Grebely, Matthews, Hellard, et al., 2011; Marcellin et al., 2011; Weiss et al., 2009) are associated with improved SVR, but the impact of missed doses on SVR is unclear (Grebely, Matthews, Hellard, et al., 2011; Weiss et al., 2009). Among PWID, adherence (Grebely, Matthews, Hellard, et al., 2011; Manolakopoulos et al., 2010; Sasadeusz et al., 2011; Sylvestre & Clements, 2007) and treatment completion (Grebely, Matthews, Hellard, et al., 2011) are associated with SVR. Further research is needed to characterize adherence to therapy among PWID in the DAA era.

A history of IDU does not compromise adherence (Grebely, Matthews, Hellard, et al., 2011; Lo Re et al., 2009; Marcellin et al., 2011), treatment completion (Grebely, Matthews, Hellard, et al., 2011; Hellard et al., 2009; Manolakopoulos et al., 2010; Robaey et al., 2006) or SVR (Hellard et al., 2009), although some studies have found lower treatment completion (Hellard et al., 2009). Recent drug use at treatment initiation has limited impact on adherence (Grebely, Matthews, Hellard, et al., 2011; Manolakopoulos et al., 2010; Marcellin et al., 2011; Sola et al., 2006; Sylvestre & Clements, 2007; Wilkinson et al., 2009), treatment completion (Grebely, Matthews, Hellard, et al., 2011; Hellard et al., 2009; Manolakopoulos et al., 2010; Papadopoulos et al., 2010), or SVR (Aspinall et al., 2013; Bruggmann et al.,

2008; Dore et al., 2010; Grebely, Raffa, et al., 2007; Lindenburg et al., 2011; Manolakopoulos et al., 2010; Papadopoulos et al., 2010; Sasadeusz et al., 2011; Sylvestre et al., 2005). Some studies have reported lower treatment completion in those with recent drug use at treatment initiation (Hellard et al., 2009; Jafferbhoy et al., 2012). HCV treatment does not have an impact on drug dependency treatment or increase drug use (Mauss et al., 2004; Van Thiel et al., 2003). Occasional drug use during treatment does not seem to impact adherence (Grebely, Matthews, Hellard, et al., 2011; Manolakopoulos et al., 2010; Sasadeusz et al., 2011; Sylvestre & Clements, 2007), treatment completion (Cournot et al., 2004; Grebely, Matthews, Hellard, et al., 2011; Manolakopoulos et al., 2010), or SVR (Dore et al., 2010; Manolakopoulos et al., 2010; Sasadeusz et al., 2011). However, lower adherence (Grebely, Matthews, Hellard, et al., 2011; Marcellin et al., 2011) and SVR (Grebely, Raffa, et al., 2007; Matthews et al., 2005; Sylvestre et al., 2005) has been observed in persons with frequent drug use (daily/every other day) during treatment. When discontinuation occurs, it often occurs early during therapy (Grebely, Matthews, Hellard, et al., 2011; Mauss et al., 2004). Among PWID, interferon-based HCV treatment is not associated with drug use or used needle and syringe borrowing during follow-up, and has been associated with decreased ancillary injecting equipment sharing during follow-up (Alavi et al., 2015b). In adherent PWID, alcohol use has no negative impact on SVR (Anand et al., 2006; Bruggmann, Dampz, Gerlach, Kravec, & Falcatto, 2010). However, these data on the impact of drug use on adherence and SVR are based on studies of interferon-based therapy. Further data in the interferon-free era are needed.

Factors independently associated with adherence and treatment completion among PWID, include lower education and unstable housing (Grebely, Matthews, Hellard, et al., 2011). Factors independently associated with lower SVR among PWID, include poor social functioning (Dore et al., 2010), a history of untreated depression (Alvarez-Uria et al., 2009) and ongoing drug use during treatment (Alvarez-Uria et al., 2009).

### Recommendations

1. Adherence assessments should consider missed doses and treatment discontinuation (Class I, Level B).
2. PWID should be counselled on the importance of adherence in attaining an SVR (Class I, Level A).
3. A history of IDU and recent drug use at treatment initiation are not associated with reduced SVR and decisions to treat should be made on a case-by-case basis (Class I, Level B).
4. PWID with ongoing social issues, history of psychiatric disease and those with more frequent drug use during therapy are at risk of lower adherence and SVR and need to be monitored closely during therapy (Class I, Level B).

### Impact of mental health on adherence and SVR

As reviewed in (Schaefer, Sarkar, & Diez-Quevedo, 2013), psychiatric co-morbidity is high among PWID and psychiatric symptoms such as depression may appear during antiviral

treatment even with interferon-free treatment regimens (Sulkowski et al., 2014). While interferon-free DAA therapy does not seem to have significant psychiatric side effects, antiviral treatment including PEG-IFN is associated with the development of psychiatric side effects (Schaefer et al., 2013). However, PWID do not in general have an increased risk for the development of major depression during antiviral treatment with PEG-IFN (Schaefer et al., 2013).

Although DAAs have not been shown to have psychiatric side effects, pharmacological interactions with current psychiatric medication in patients with psychiatric co-morbidity should be monitored carefully. Anticonvulsants, St. John's Wort and short acting benzodiazepines such as midazolam and triazolam are contraindicated with currently used DAAs. However, most other psychotropic medication can be combined with antivirals, but possible interactions should be evaluated on a case-by-case basis.

### Recommendations

1. Pre-treatment assessment should include an evaluation of previous or current psychiatric illness, engagement with a drug and alcohol counselor or psychiatrist and discussions around potential treatment options (Class I, Level A).
2. In cases of acute major and uncontrolled psychiatric disorders, a pre-treatment psychiatric assessment is recommended (Class IIa, Level C).
3. In case of relevant psychiatric co-morbidities with an increased risk for interferon-associated psychiatric side effects interferon-free DAA therapy should be considered (Class IIb, Level C).

### Treatment management

HCV treatment has been delivered successfully to PWID through various clinical models, including within general hospital liver disease and viral hepatitis clinics, drug detoxification clinics, opioid substitution therapy clinics, prisons and community-based clinics. As reviewed in (Bruggmann & Litwin, 2013) (Meyer et al., 2015), examples of strategies that have been successful for enhancing assessment, adherence or SVR include hospital-based and primary care-based integrated care, community-based tele-health, nurse-led education, psychoeducation, directly observed therapy, peer support groups and peer support workers. The key basis for effective HCV clinical management within all these settings is access to a multidisciplinary team, generally including clinician and nursing clinical assessment and monitoring, drug and alcohol services, psychiatric services, and social work and other social support services (including peer support, if available). Combined social interventions should target on housing, stigma reduction, criminalisation and health care delivery (Harris & Rhodes, 2013).

### Recommendations

1. HCV treatment for PWID should be considered on an individualized basis and delivered within a multidisciplinary team setting (Class I, Level A).

2. Access to harm reduction programs, social work and social support services should be a component of HCV clinical management (Class I, Level A).
3. Peer-based support should be evaluated as a means to improve HCV clinical management (Class I, Level B).

## HCV treatment in prisons

Given the close nexus between injecting drug use and imprisonment, acute and chronic HCV infections are prevalent in custodial settings worldwide (reviewed in Larney et al., 2013). Despite the substantial burden of disease in this setting, screening, assessment and treatment rates are very low (reviewed in Post, Arain, & Lloyd, 2013). Interferon-based antiviral treatment has been shown to be feasible and effective, albeit with residual concerns of reinfection and loss to follow-up upon release to freedom (Post et al., 2013). Interferon-free DAA-based treatments offered in the custodial setting have the potential for cost-effective scale-up of treatment for PWID.

### Recommendations

1. Screening and assessment for HCV should be offered to PWID in custody (Class IIa, Level C).
2. Antiviral treatment for PWID in custody is feasible and clinically effective and should be offered to PWID in custody (Class IIa, Level B).

## Reinfection following successful HCV treatment

There is still some concern that re-infection due to recurrent risk behaviours may negate potential benefits of treatment. Reported rates of reinfection following successful HCV treatment among PWID are low, with estimates generally 1–5% risk per year (reviewed in Cunningham, Applegate, Lloyd, Dore, & Grebely, 2015; Grady, Schinkel, & Dalgard, 2013). Data are needed on reinfection rates in the interferon-free DAA era and studies are needed to evaluate strategies to prevent HCV reinfection.

### Recommendations

1. PWID should not be excluded from HCV treatment on the basis of perceived risk of reinfection (Class I, Level B).
2. Harm reduction education and counselling should be provided for PWID in the context of HCV treatment to prevent HCV reinfection following successful treatment (Class I, Level B).
3. Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on PWID with ongoing risk behaviour (Class I, Level B).

## Treatment of acute HCV

Acute HCV infection refers to the period spanning the first six months following exposure to HCV (Grebely, Matthews, & Dore, 2011). Spontaneous clearance occurs in 25% (Grebely et al., 2014; Micallef et al., 2006). PEG-IFN-based SVR among HCV mono-infected PWID with acute HCV is 55–74% (reviewed in Martinello and Matthews, 2015), with treatment outcomes associated with adherence and social support, but not IDU prior to or during treatment (Dore et al., 2010). No data is available on interferon-free DAA therapy for acute HCV, although studies are underway. In settings where interferon-free DAA therapy is available for treatment of chronic HCV, including early liver disease, deferral of interferon-based acute HCV therapy for PWID to await chronic HCV is likely to be a common practice.

### Recommendations

1. PWID with acute HCV symptoms should be monitored for 12– 16 weeks (including HCV RNA levels) to allow potential spontaneous clearance (Class I, Level B).
2. PEG-IFN mono-therapy for 24 weeks may be considered for PWID with acute HCV (Class I, Level B).
3. Strategies to optimize adherence should be used in the setting of acute HCV, with consideration of directly observed PEG-IFN therapy (Class I, Level B).

## HIV/HCV co-infection

Co-infection with HIV accelerates HCV disease progression, leading to greater liver-related morbidity and mortality in HIV/HCV than in HCV mono-infected persons (Chen, Ding, Seage Iii, & Kim, 2009; Graham et al., 2001; Lo Re et al., 2014). Chronic HCV is the leading cause of non-AIDS death where combination antiretroviral therapy (cART) is accessible (Weber et al., 2006). Additional challenges with HIV/HCV include potential cART-related liver toxicity, multiple medication requirements, drug–drug interactions, higher prevalence of medical co-morbidities (reviewed in Taylor, Swan, & Matthews, 2013) and lack of access to and poor outcomes after liver transplantation (Campos-Varela, Peters, & Terrault, 2015). HIV/HCV is associated with a higher prevalence of psychiatric disorders, poverty, homelessness and incarceration (Rosenberg, Drake, Brunette, Wolford, & Marsh, 2005). Earlier antiretroviral treatment benefits all HIV-infected individuals and antiretroviral treatment should be offered to everyone with HIV (START, 2015). While interferon-based HCV treatment responses may be poorer in those with HIV/HCV, results to date indicate that SVR rates with all-oral DAA regimens in HIV/HCV co-infected patients are comparable to those of HCV mono-infected patients (Chung et al., 2004; Naggie et al., 2015; Torriani et al., 2004; Wyles et al., 2015). Achieving SVR lowers liver-related, AIDS-related and non-AIDS-related death rates among co-infected people, and may reduce rates of cART-related hepatotoxicity (Berenguer et al., 2009, 2012; Labarga et al., 2007; Limketkai et al., 2012; Mira et al., 2013). The prevalence and severity of HIV/HCV co-infection, combined with the benefits of SVR, make HCV treatment a priority for co-infected persons. Some drug–drug interactions between antiretroviral agents and DAAs may cause toxicity,

lower the likelihood of SVR, and lead to development of antiretroviral resistance (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2015).

### Recommendations

1. HCV-infected PWID should be screened for HIV (Class I, Level C).
2. The accelerated HCV disease progression in HIV/HCV should be considered in treatment decision-making; HCV treatment should be prioritized in HIV/HCV patients regardless of fibrosis stage (Class I, Level B).
3. HIV/HCV-coinfected PWID should be treated and retreated with the same DAA regimens as HCV-monoinfected persons, after recognizing and managing interactions with antiretroviral medications (Class I, Level B).
4. Early introduction of cART should be offered to all people with HIV infection (Class I, Level A).
5. Potential drug–drug interactions between HIV, HCV and OST need to be considered. Consultation with a frequently updated database/prescribing information is indicated (Class I, Level A).

### Management of hepatitis B virus (HBV) co-infection

The global prevalence of chronic HBV is 8% among PWID (Nelson et al., 2011). HBV vaccination is effective among PWID and accelerated schedules improve adherence (Hwang et al., 2010). PEG-IFN/ribavirin is effective for the treatment of HCV in those with HBV/HCV (Liu et al., 2009). As recommended by the EASL guidelines, HBV DNA detection and HBV DNA level measurement are essential for the diagnosis, decision to treat and subsequent monitoring of patients (European Association For The Study Of The Liver, 2012). There are no data concerning the use of anti-HCV direct antiviral agents in HBV/HCV coinfection (Caccamo, Saffioti, & Raimondo, 2014; Sagnelli et al., 2014). Hepatitis D virus (HDV) co infection is frequent in PWID (Kucirka et al., 2010), and PEG-IFN is the only effective drug (Rizzetto, 2013).

### Recommendations

1. PWID should be vaccinated for hepatitis A virus and HBV (Class I, Level B).(2) HBV DNA testing should be performed on all patients with evidence of chronic HBV infection (hepatitis B surface antigen positive) (Class I, Level A).(3) PWID with active HBV/HCV co-infection should be treated according to guidelines for monoinfection (for both infections) (Class IIb, Level C).

### Liver transplantation

The proportion of those with a history of IDU undergoing liver transplantation for HCV-related cirrhosis or HCC is 5–10% (De Gottardi et al., 2010; Robaeys et al., 2009). Relapse to drug use following transplantation is rare (De Gottardi et al., 2010; Robaeys et al., 2009). Selection criteria for liver transplantation include: 6–24 months of drug abstinence, controlled psychiatric disease and the presence of stable social support networks (Webb,

Shepherd, & Neuberger, 2008). OST is not a contraindication (De Gottardi et al., 2010; Kanchana et al., 2002; Webb et al., 2008). There are no data in PWID.

## Recommendations

1. Awareness should be raised that liver transplant is a therapeutic option in those with a history of IDU (Class IIa, Level B).
2. OST is not a contraindication for liver transplantation and individuals on OST should not be advised to reduce or stop therapy (Class IIa, Level B).
3. Psychiatric evaluation and follow-up should be offered to PWID undergoing liver transplantation (Class IIa, Level B).

## Conclusion

Given the burden of HCV-related disease among PWID, strategies to enhance HCV testing, linkage to care, assessment, treatment and prevention of HCV reinfection in this group are urgently needed. These recommendations demonstrate that treatment among PWID is feasible and provides a framework for HCV testing, assessment, management and treatment. However, many studies performed among PWID to date are limited, given retrospective designs, small sample sizes and lack of randomized controlled trial design. Further research is needed to evaluate strategies to enhance HCV testing, linkage to care, assessment, adherence, SVR and prevention of HCV reinfection among PWID, particularly as new interferon-free DAA regimens become available. This will be crucial in the efforts to stem the burden of HCV-related liver disease worldwide.

## References

- AASLD/IDSA. Recommendations for testing, managing, and treating hepatitis C. 2015. Retrieved from [www.hcvguidelines.org](http://www.hcvguidelines.org)
- Alavi M, Grebely J, Micallef M, Dunlop AJ, Balcomb AC, Day CA, et al. Assessment and treatment of hepatitis C virus infection among people who inject drugs in the opioid substitution setting: ETHOS study. *Clinical Infectious Diseases*. 2013; 57(Suppl. 2):S62–S69. [PubMed: 23884068]
- Alavi M, Raffa JD, Deans GD, Lai C, Krajden M, Dore GJ, et al. Continued low uptake of treatment for hepatitis C virus infection in a large community-based cohort of inner city residents. *Liver International*. 2014; 34:1198–1206. [PubMed: 24164865]
- Alavi M, Micallef M, Fortier E, Dunlop AJ, Balcomb AC, Day CA, et al. Effect of treatment willingness on specialist assessment and treatment uptake for hepatitis C virus infection among people who use drugs: The ETHOS study. *Journal of Viral Hepatitis*. 2015a May.
- Alavi M, Spelman T, Matthews GV, Haber PS, Day C, van Beek I, et al. Injecting risk behaviours following treatment for hepatitis C virus infection among people who inject drugs: The Australian Trial in Acute Hepatitis C. *International Journal of Drug Policy*. 2015b; 26(10):976–983. [PubMed: 26115881]
- Alvarez-Uria G, Day JN, Nasir AJ, Russell SK, Vilar FJ. Factors associated with treatment failure of patients with psychiatric diseases and injecting drug users in the treatment of genotype 2 or 3 hepatitis C chronic infection. *Liver International*. 2009; 29:1051–1055. [PubMed: 19580634]
- Anand BS, Currie S, Dieperink E, Bini EJ, Shen H, Ho SB, et al. Alcohol use and treatment of hepatitis C virus: Results of a national multicenter study. *Gastroenterology*. 2006; 130:1607–1616. [PubMed: 16697724]
- Andreu V, Mas A, Bruguera M, Salmeron JM, Moreno V, Nogue S, et al. Ecstasy: A common cause of severe acute hepatotoxicity. *Journal of Hepatology*. 1998; 29:394–397. [PubMed: 9764985]



- Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ, et al. Treatment of HCV infection among people who are actively injecting drugs: A systematic review and meta-analysis. *Clinical Infectious Diseases*. 2013; 57(S2):S80–S89. [PubMed: 23884071]
- Aspinall EJ, Weir A, Sacks-Davis R, Spelman T, Grebely J, Higgs P, et al. Does informing people who inject drugs of their hepatitis C status influence their injecting behaviour? Analysis of the Networks II study. *International Journal of Drug Policy*. 2014; 25:179–182. [PubMed: 24315504]
- Backmund M, Meyer K, Von Zielonka M, Eichenlaub D. Treatment of hepatitis C infection in injection drug users. *Hepatology*. 2001; 34:188–193. [PubMed: 11431750]
- Baranova A, Lal P, Biredinc A, Younossi ZM. Non-invasive markers for hepatic fibrosis. *BMC Gastroenterology*. 2011; 11:91. [PubMed: 21849046]
- Berenguer J, Alvarez-Pellicer J, Martin PM, Lopez-Aldeguer J, Von-Wichmann MA, Quereda C, et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfecting with human immunodeficiency virus and hepatitis C virus. *Hepatology*. 2009; 50:407–413. [PubMed: 19575364]
- Berenguer J, Rodriguez E, Miralles P, Von Wichmann MA, Lopez-Aldeguer J, Mallolas J, et al. Sustained virological response to interferon plus ribavirin reduces non-liver-related mortality in patients coinfecting with HIV and Hepatitis C virus. *Clinical Infectious Diseases*. 2012; 55:728–736. [PubMed: 22610932]
- Bini EJ, Brau N, Currie S, Shen H, Anand BS, Hu KQ, et al. Prospective multicenter study of eligibility for antiviral therapy among 4,084 U.S. veterans with chronic hepatitis C virus infection. *American Journal of Gastroenterology*. 2005; 100:1772–1779. [PubMed: 16086714]
- Bruggmann P, Litwin AH. Models of care for the management of hepatitis C virus among people who inject drugs: One size does not fit all. *Clinical Infectious Diseases*. 2013; 57(Suppl 2):S56–61. [PubMed: 23884067]
- Bruggmann P, Falcato L, Dober S, Helbling B, Keiser O, Negro F, et al. Active intravenous drug use during chronic hepatitis C therapy does not reduce sustained virological response rates in adherent patients. *Journal of Viral Hepatitis*. 2008; 15:747–752. [PubMed: 18637072]
- Bruggmann P, Dampz M, Gerlach T, Kravec L, Falcato L. Treatment outcome in relation to alcohol consumption during hepatitis C therapy: An analysis of the Swiss Hepatitis C Cohort Study. *Drug and Alcohol Dependence*. 2010; 110:167–171. [PubMed: 20334985]
- Bruneau J, Zang G, Abrahamowicz M, Jutras-Aswad D, Daniel M, Roy E. Sustained drug use changes after hepatitis C screening and counseling among recently infected persons who inject drugs: A longitudinal study. *Clinical Infectious Diseases*. 2014; 58:755–761. [PubMed: 24363333]
- Brunet L, Moodie EE, Rollet K, Cooper C, Walmsley S, Potter M, et al. Marijuana smoking does not accelerate progression of liver disease in HIV-hepatitis C coinfection: A longitudinal cohort analysis. *Clinical Infectious Diseases*. 2013; 57:663–670. [PubMed: 23811492]
- Burger D, Back D, Buggisch P, Buti M, Craxi A, Foster G, et al. Clinical management of drug–drug interactions in HCV therapy: Challenges and solutions. *Journal of Hepatology*. 2013; 58:792–800. [PubMed: 23137766]
- Caccamo G, Saffioti F, Raimondo G. Hepatitis B virus and hepatitis C virus dual infection. *World Journal of Gastroenterology*. 2014; 20:14559–14567. [PubMed: 25356020]
- Campos-Varela I, Peters MG, Terrault NA. Advances in therapy for HIV/hepatitis C virus-coinfecting patients in the liver transplant setting. *Clinical Infectious Diseases*. 2015; 60:108–116. [PubMed: 25228702]
- Centers for Disease Control and Prevention. Integrated prevention services for HIV infection, viral hepatitis, sexually transmitted diseases, and tuberculosis for persons who use drugs illicitly: Summary guidance from CDC and the U.S. Department of Health and Human Services. *Morbidity and Mortality Weekly Report*. 2012; 61(RR-05):1–40.
- Charlebois A, Lee L, Cooper E, Mason K, Powis J. Factors associated with HCV antiviral treatment uptake among participants of a community-based HCV programme for marginalized patients. *Journal of Viral Hepatitis*. 2012; 19:836–842. [PubMed: 23121361]
- Chen TY, Ding EL, Seage III GR, Kim AY. Meta-analysis: Increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. *Clinical Infectious Diseases*. 2009; 49:1605–1615. [PubMed: 19842982]

- Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *New England Journal of Medicine*. 2004; 351:451–459. [PubMed: 15282352]
- Coats JT, Dillon JF. The effect of introducing point-of-care or dried blood spot analysis on the uptake of hepatitis C virus testing in high-risk populations: A systematic review of the literature. *International Journal of Drug Policy*. 2015; 26(11):1050–1055. [PubMed: 26118799]
- Cournot M, Glibert A, Castel F, Druart F, Imani K, Lauwers-Cances V, et al. Management of hepatitis C in active drugs users: Experience of an addiction care hepatology unit. *Gastroenterologie Clinique et Biologique*. 2004; 28:533–539. [PubMed: 15243385]
- Crawford S, Bath N. Peer support models for people with a history of injecting drug use undertaking assessment and treatment for hepatitis C virus infection. *Clinical Infectious Diseases*. 2013; 57(Suppl 2):S75–S79. [PubMed: 23884070]
- Cullen BL, Hutchinson SJ, Cameron SO, Anderson E, Ahmed S, Spence E, et al. Identifying former injecting drug users infected with hepatitis C: An evaluation of a general practice-based case-finding intervention. *Journal of Public Health*. 2012; 34:14–23. [PubMed: 22138489]
- Cunningham EB, Applegate TL, Lloyd AR, Dore GJ, Grebely J. Mixed HCV infection and reinfection in people who inject drugs-impact on therapy. *Nature Reviews Gastroenterology and Hepatology*. 2015; 12(4):218–230. Invited Review, IF 10.43. [PubMed: 25782091]
- Dalgard O. Follow-up studies of treatment for hepatitis C virus infection among injection drug users. *Clinical Infectious Diseases*. 2005; 40(Suppl 5):S336–S338. [PubMed: 15768344]
- De Gottardi A, Hilleret MN, Gelez P, La Mura V, Guillaud O, Majno P, et al. Injection drug use before and after liver transplantation: A retrospective multicenter analysis on incidence and outcome. *Clinical Transplantation*. 2010; 24:564–571. [PubMed: 19849705]
- de Vos AS, Prins M, Kretzschmar ME. Hepatitis C Virus treatment as prevention among injecting drug users: Who should we cure first? *Addiction*. 2015 Jun; 110(6):975–983. DOI: 10.1111/add.12842 [PubMed: 25586171]
- Degenhardt L, Mathers B, Vickerman P, Rhodes T, Latkin C, Hickman M. Prevention of HIV infection for people who inject drugs: Why individual, structural, and combination approaches are needed. *Lancet*. 2010; 376:285–301. [PubMed: 20650522]
- Dimova RB, Zeremski M, Jacobson IM, Hagan H, Des Jarlais DC, Talal AH. Determinants of hepatitis C virus treatment completion and efficacy in drug users assessed by meta-analysis. *Clinical Infectious Diseases*. 2013; 56:806–816. [PubMed: 23223596]
- Doab A, Treloar C, Dore GJ. Knowledge and attitudes about treatment for hepatitis C virus infection and barriers to treatment among current injection drug users in Australia. *Clinical Infectious Diseases*. 2005; 40(Suppl. 5):S313–S320. [PubMed: 15768340]
- Dore GJ, Feld JJ. Hepatitis C virus therapeutic development: In pursuit of perfectovir. *Clinical Infectious Diseases*. 2015; 60:1829–1836. [PubMed: 25761867]
- Dore GJ, Hellard M, Matthews GV, Grebely J, Haber PS, Petoumenos K, et al. Effective treatment of injecting drug users with recently acquired hepatitis C virus infection. *Gastroenterology*. 2010; 138:123–135.e121-122. [PubMed: 19782085]
- Drainoni ML, Litwin AH, Smith BD, Koppelman EA, McKee MD, Christiansen CL, et al. Effectiveness of a risk screener in identifying hepatitis C virus in a primary care setting. *American Journal of Public Health*. 2012; 102:e115–e121. [PubMed: 22994166]
- EMA. Incivo: Summary of product characteristics. 2012a. Retrieved from [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/002313/WC500115529.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002313/WC500115529.pdf)
- EMA. Victrelis: Summary of product characteristics. 2012b. Retrieved from [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/002332/WC500109786.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002332/WC500109786.pdf)
- EMA. Daclinzia: Summary of product characteristics. 2014a. Retrieved from [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/003768/WC500172848.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003768/WC500172848.pdf)
- EMA. Harvoni: Summary of product characteristics. 2014b. Retrieved from [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/003850/WC500177995.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003850/WC500177995.pdf)

- EMA. Olysio: Summary of product characteristics. 2014c. Retrieved from [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/002777/WC500167867.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002777/WC500167867.pdf)
- EMA. Sovaldi: Summary of product characteristics. 2014d. Retrieved from [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/002798/WC500160597.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf)
- EMA. Viekirax: Summary of product characteristics. 2014e. Retrieved from [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/003839/WC500183997.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003839/WC500183997.pdf)
- EMCDDA. Trends in injecting drug use in Europe. Luxembourg: European Monitoring Centre for Drugs and Drug Addiction; 2010.
- European Association for Study of Liver. EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. *Journal of Hepatology*. 2014; 60:392–420. [PubMed: 24331294]
- European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *Journal of Hepatology*. 2012; 57:167–185. [PubMed: 22436845]
- Evon DM, Simpson K, Kixmiller S, Galanko J, Dougherty K, Golin C, et al. A randomized controlled trial of an integrated care intervention to increase eligibility for chronic hepatitis C treatment. *American Journal of Gastroenterology*. 2011; 106:1777–1786. [PubMed: 21769136]
- Fortier E, Alavi M, Micallef M, Dunlop AJ, Balcomb AC, Day CA, et al. The effect of social functioning and living arrangement on treatment intent, specialist assessment and treatment uptake for hepatitis C virus infection among people with a history of injecting drug use: The ETHOS study. *International Journal of Drug Policy*. 2015; 26(11):1094–1102. [PubMed: 26145482]
- Foucher J, Reiller B, Jullien V, Leal F, di Cesare ES, Merrouche W, et al. FibroScan used in street-based outreach for drug users is useful for hepatitis C virus screening and management: A prospective study. *Journal of Viral Hepatitis*. 2009; 16:121–131. [PubMed: 19175876]
- Gidding HF, Law MG, Amin J, Macdonald GA, Sasadeusz JJ, Jones TL, et al. Predictors of deferral of treatment for hepatitis C infection in Australian clinics. *Medical Journal of Australia*. 2011; 194:398–402. [PubMed: 21495939]
- Grady B, Schinkel J, Dalgard O. Hepatitis C virus reinfection following treatment among people who use drugs. *Clinical Infectious Diseases*. 2013; 57(S2):S105–S110. [PubMed: 23884057]
- Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: A meta-analysis. *Clinical Infectious Diseases*. 2001; 33:562–569. [PubMed: 11462196]
- Grebely J, Dore GJ. What is killing people with hepatitis C virus infection? *Seminars in Liver Disease*. 2011; 31:331–339. [PubMed: 22189973]
- Grebely J, Tyndall MW. Management of HCV and HIV infections among people who inject drugs. *Current Opinion in HIV and AIDS*. 2011; 6:501–507. [PubMed: 22001894]
- Grebely J, Genoway K, Khara M, Duncan F, Viljoen M, Elliott D, et al. Treatment uptake and outcomes among current and former injection drug users receiving directly observed therapy within a multidisciplinary group model for the treatment of hepatitis C virus infection. *International Journal of Drug Policy*. 2007; 18:437–443. [PubMed: 17854734]
- Grebely J, Raffa JD, Meagher C, Duncan F, Genoway KA, Khara M, et al. Directly observed therapy for the treatment of hepatitis C virus infection in current and former injection drug users. *Journal of Gastroenterology and Hepatology*. 2007; 22:1519–1525. [PubMed: 17645460]
- Grebely J, Genoway KA, Raffa JD, Dhadwal G, Rajan T, Showler G, et al. Barriers associated with the treatment of hepatitis C virus infection among illicit drug users. *Drug and Alcohol Dependence*. 2008; 93:141–147. [PubMed: 17997050]
- Grebely J, Raffa JD, Lai C, Krajdén M, Kerr T, Fischer B, et al. Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents. *Journal of Viral Hepatitis*. 2009; 16:352–358. [PubMed: 19226330]
- Grebely J, Knight E, Genoway KA, Viljoen M, Khara M, Elliott D, et al. Optimizing assessment and treatment for hepatitis C virus infection in illicit drug users: A novel model incorporating multidisciplinary care and peer support. *European Journal of Gastroenterology and Hepatology*. 2010; 22:270–277. [PubMed: 20425880]

- Grebely J, Matthews GV, Dore GJ. Treatment of acute HCV infection. *Nature Reviews Gastroenterology and Hepatology*. 2011; 8:265–274. [PubMed: 21423258]
- Grebely J, Matthews GV, Hellard M, Shaw D, van Beek I, Petoumenos K, et al. Adherence to treatment for recently acquired hepatitis C virus (HCV) infection among injecting drug users. *Journal of Hepatology*. 2011; 55:76–85. [PubMed: 21145855]
- Grebely J, Page K, Sacks-Davis R, Schim van der Loeff M, Rice TM, Bruneau J, et al. The effects of female sex, viral genotype and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. *Hepatology*. 2014; 59(1):109–120. [PubMed: 23908124]
- Guadagnino V, Trotta MP, Montesano F, Babudieri S, Caroleo B, Armignacco O, et al. Effectiveness of a multi-disciplinary standardized management model in the treatment of chronic hepatitis C in drug addicts engaged in detoxification programmes. *Addiction*. 2007; 102:423–431. [PubMed: 17298650]
- Hagan H, Pouget ER, Des Jarlais DC, Lelutiu-Weinberger C. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: The influence of time and place. *American Journal of Epidemiology*. 2008; 168:1099–1109. [PubMed: 18849303]
- Hagan H, Pouget ER, Des Jarlais DC. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. *Journal of Infectious Diseases*. 2011; 204:74–83. [PubMed: 21628661]
- Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. *Nature Reviews Gastroenterology and Hepatology*. 2013; 10:553–562. [PubMed: 23817321]
- Harris M, Rhodes T. Hepatitis C treatment access and uptake for people who inject drugs: A review mapping the role of social factors. *Harm Reduction Journal*. 2013; 10(7):1–11. [PubMed: 23414093]
- Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: A review of the available evidence. *Clinical Infectious Diseases*. 2009; 49:561–573. [PubMed: 19589081]
- Hellard M, Rolls DA, Sacks-Davis R, Robins G, Pattison P, Higgs P, et al. The impact of injecting networks on hepatitis C transmission and treatment in people who inject drugs. *Hepatology*. 2014; 60:1861–1870. [PubMed: 25163856]
- Hezode C, Roudot-Thoraval F, Nguyen S, Grenard P, Julien B, Zafrani ES, et al. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. *Hepatology*. 2005; 42:63–71. [PubMed: 15892090]
- Hulskotte EG, Bruce RD, Feng HP, Webster LR, Xuan F, Lin WH, et al. Pharmacokinetic interaction between HCV protease inhibitor boceprevir and methadone or buprenorphine in subjects on stable maintenance therapy. *European Journal of Clinical Pharmacology*. 2015; 71:303–311. [PubMed: 25666027]
- Hutchinson SJ, Bird SM, Goldberg DJ. Influence of alcohol on the progression of hepatitis C virus infection: A meta-analysis. *Clinical Gastroenterology and Hepatology*. 2005a; 3:1150–1159. [PubMed: 16271348]
- Hutchinson SJ, Bird SM, Goldberg DJ. Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. *Hepatology*. 2005b; 42:711–723. [PubMed: 16116637]
- Hwang LY, Grimes CZ, Tran TQ, Clark A, Xia R, Lai D, et al. Accelerated hepatitis B vaccination schedule among drug users: A randomized controlled trial. *Journal of Infectious Diseases*. 2010; 202:1500–1509. [PubMed: 20936979]
- Ishida JH, Peters MG, Jin C, Louie K, Tan V, Bacchetti P, et al. Influence of cannabis use on severity of hepatitis C disease. *Clinical Gastroenterology and Hepatology*. 2008; 6:69–75. [PubMed: 18166478]
- Iversen J, Grebely J, Topp L, Wand H, Dore G, Maher L. Uptake of hepatitis C treatment among people who inject drugs attending Needle and Syringe Programs in Australia, 1999–2011. *Journal of Viral Hepatitis*. 2014; 21:198–207. [PubMed: 24438681]
- Jack K, Willott S, Manners J, Varnam MA, Thomson BJ. Clinical trial: A primary-care-based model for the delivery of anti-viral treatment to injecting drug users infected with hepatitis C. *Alimentary Pharmacology and Therapeutics*. 2009; 29:38–45. [PubMed: 18945252]
- Jacobson IM, Kwo PY, Kowdley KV, Yang JC, Zhu Y, Hyland RH, et al. Virologic response rates to all oral fixed-dose combination ledipasvir/sofosbuvir regimens are similar in patients with and

without traditional negative predictive factors in phase 3 clinical trials. Boston, MA: AASLD: The Liver Meeting®; 2014.

- Jafferbhoy H, Miller MH, Dunbar JK, Tait J, McLeod S, Dillon JF. Intravenous drug use: Not a barrier to achieving a sustained virological response in HCV infection. *Journal of Viral Hepatitis*. 2012; 19:112–119. [PubMed: 22239500]
- Jeffrey GP, MacQuillan G, Chua F, Galhenage S, Bull J, Young E, et al. Hepatitis C virus eradication in intravenous drug users maintained with subcutaneous naltrexone implants. *Hepatology*. 2007; 45:111–117. [PubMed: 17187435]
- John-Baptiste A, Krahn M, Heathcote J, Laporte A, Tomlinson G. The natural history of hepatitis C infection acquired through injection drug use: Meta-analysis and meta-regression. *Journal of Hepatology*. 2010; 53:245–251. [PubMed: 20537752]
- Kanchana TP, Kaul V, Manzarbeitia C, Reich DJ, Hails KC, Munoz SJ, et al. Liver transplantation for patients on methadone maintenance. *Liver Transplantation*. 2002; 8:778–782. [PubMed: 12200777]
- Kanwal F, Hoang T, Spiegel BM, Eisen S, Dominitz JA, Gifford A, et al. Predictors of treatment in patients with chronic hepatitis C infection – Role of patient versus nonpatient factors. *Hepatology*. 2007; 46:1741–1749. [PubMed: 18046707]
- Karch SB, Stephens BG, Ho CH. Methamphetamine-related deaths in San Francisco: Demographic, pathologic, and toxicologic profiles. *Journal of Forensic Sciences*. 1999; 44:359–368. [PubMed: 10097363]
- Keats J, Micallef M, Grebely J, Hazelwood S, Everingham H, Shrestha N, et al. Assessment and delivery of treatment for hepatitis C virus infection in the opioid substitution treatment setting with integrated peer-based support. *International Journal of Drug Policy*. 2015; 26(10):999–1006. [PubMed: 26275578]
- Kramer JR, Kanwal F, Richardson P, Giordano TP, Petersen LA, El-Serag HB. Importance of patient, provider, and facility predictors of hepatitis C virus treatment in veterans: A national study. *American Journal of Gastroenterology*. 2011; 106:483–491. [PubMed: 21063393]
- Kreek MJ, Dodes L, Kane S, Knobler J, Martin R. Long-term methadone maintenance therapy: Effects on liver function. *Annals of Internal Medicine*. 1972; 77:598–602. [PubMed: 4629927]
- Kucirka LM, Farzadegan H, Feld JJ, Mehta SH, Winters M, Glenn JS, et al. Prevalence, correlates, and viral dynamics of hepatitis delta among injection drug users. *Journal of Infectious Diseases*. 2010; 202:845–852. [PubMed: 20701536]
- Labarga P, Soriano V, Vispo ME, Pinilla J, Martin-Carbonero L, Castellares C, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. *Journal of Infectious Diseases*. 2007; 196:670–676. [PubMed: 17674307]
- Lalezari J, Sullivan JG, Varunok P, Galen E, Kowdley KV, Rustgi V, et al. Ombitasvir/paritaprevir/r and dasabuvir plus ribavirin in HCV genotype 1-infected patients on methadone or buprenorphine. *Journal of Hepatology*. 2015; 63:364–369. [PubMed: 25839406]
- Larney S, Kopinski H, Beckwith CG, Zaller ND, Jarlais DD, Hagan H, et al. Incidence and prevalence of hepatitis C in prisons and other closed settings: Results of a systematic review and meta-analysis. *Hepatology*. 2013; 58:1215–1224. [PubMed: 23504650]
- Larney S, Grebely J, Hickman M, De Angelis D, Dore GJ, Degenhardt L. Defining populations and injecting parameters among people who inject drugs: Implications for the assessment of hepatitis C treatment programs. *International Journal of Drug Policy*. 2015; 26(10):950–957. [PubMed: 26297564]
- Limketkai BN, Mehta SH, Sutcliffe CG, Higgins YM, Torbenson MS, Brinkley SC, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfecting with HIV/HCV. *JAMA*. 2012; 308:370–378. [PubMed: 22820790]
- Lindenburg CE, Lambers FA, Urbanus AT, Schinkel J, Jansen PL, Krol A, et al. Hepatitis C testing and treatment among active drug users in Amsterdam: Results from the DUTCH-C project. *European Journal of Gastroenterology and Hepatology*. 2011; 23:23–31. [PubMed: 21042221]
- Litwin AH, Smith BD, Drainoni ML, McKee D, Gifford AL, Koppelman E, et al. Primary care-based interventions are associated with increases in hepatitis C virus testing for patients at risk. *Digestive and Liver Disease*. 2012; 44:497–503. [PubMed: 22342471]

- Litwin AH, Soloway IJ, Cockerham-Colas L, Reynoso S, Heo M, Tenore C. Successful treatment of chronic hepatitis C with triple therapy in an opioid agonist treatment program. *International Journal of Drug Policy*. 2015; 26(10):1014–1019. [PubMed: 26341685]
- Liu CJ, Chuang WL, Lee CM, Yu ML, Lu SN, Wu SS, et al. Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. *Gastroenterology*. 2009; 136:496–504.e493. [PubMed: 19084016]
- Lloyd AR, Clegg J, Lange J, Stevenson A, Post JJ, Lloyd D, et al. Safety and effectiveness of a nurse-led outreach program for assessment and treatment of chronic hepatitis C in the custodial setting. *Clinical Infectious Diseases*. 2013; 56:1078–1084. [PubMed: 23362288]
- Lo Re V 3rd, Amorosa VK, Localio AR, O’Flynn R, Teal V, Dorey-Stein Z, et al. Adherence to hepatitis C virus therapy and early virologic outcomes. *Clinical Infectious Diseases*. 2009; 48:186–193. [PubMed: 19086908]
- Lo Re V 3rd, Kallan MJ, Tate JP, Localio AR, Lim JK, Goetz MB, et al. Hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus-monoinfected patients: A cohort study. *Annals of Internal Medicine*. 2014; 160:369–379. [PubMed: 24723077]
- Luo X, Trevejo J, van Heeswijk RP, Smith F, Garg V. Effect of telaprevir on the pharmacokinetics of buprenorphine in volunteers on stable buprenorphine/naloxone maintenance therapy. *Antimicrobial Agents and Chemotherapy*. 2012; 56:3641–3647. [PubMed: 22564847]
- MacArthur GJ, van Velzen E, Palmateer N, Kimber J, Pharris A, Hope V, et al. Interventions to prevent HIV and Hepatitis C in people who inject drugs: A review of reviews to assess evidence of effectiveness. *International Journal of Drug Policy*. 2014; 25:34–52. [PubMed: 23973009]
- Mangia A, Kugelmas M, Everson GT, Hineostrova F, Ma J, McNally J, et al. Virologic response rates to sofosbuvir-containing regimens are similar in patients with and without traditional negative predictive factors: A retrospective analysis of phase 3 data. *Hepatology*. 2013; 58:752A. [PubMed: 23468040]
- Manolakopoulos S, Deutsch MJ, Anagnostou O, Karatapanis S, Tiniakou E, Papatheo-doridis GV, et al. Substitution treatment or active intravenous drug use should not be contraindications for antiviral treatment in drug users with chronic hepatitis C. *Liver International*. 2010; 30:1454–1460. [PubMed: 20846344]
- Marcellin P, Chousterman M, Fontanges T, Ouzan D, Rotily M, Varastet M, et al. Adherence to treatment and quality of life during hepatitis C therapy: A prospective, real-life, observational study. *Liver International*. 2011; 31:516–524. [PubMed: 21382162]
- Marshall AD, Micallef M, Erratt A, Telenta J, Jones SC, Bath N, et al. 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. *International Journal of Drug Policy*. 2015; 26(10):984–991. [PubMed: 26256938]
- Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. *Journal of Hepatology*. 2011; 54:1137–1144. [PubMed: 21145810]
- Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg DJ, et al. Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. *Hepatology*. 2012; 55:49–57. [PubMed: 21898506]
- Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, Vickerman P. 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. *Clinical Infectious Diseases*. 2013; 57(Suppl 2):S39–S45. [PubMed: 23884064]
- Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology*. 2013; 58:1598–1609. [PubMed: 23553643]
- Martinello M, Matthews GV. Enhancing the detection and management of acute hepatitis C virus infection. *International Journal of Drug Policy*. 2015; 26(10):899–910. [PubMed: 26254495]

- Martinez AD, Dimova R, Marks KM, Beeder AB, Zeremski M, Kreek MJ, et al. Integrated internist – addiction medicine – hepatology model for hepatitis C management for individuals on methadone maintenance. *Journal of Viral Hepatitis*. 2010; 19:47–54. [PubMed: 21129131]
- Mason K, Dodd Z, Sockalingam S, Altenberg J, Meaney C, Millson P, et al. Beyond viral response: A prospective evaluation of a community-based, multi-disciplinary, peer-driven model of HCV treatment and support. *International Journal of Drug Policy*. 2015; 26(10):1007–1013. [PubMed: 26005037]
- Masson CL, Delucchi KL, McKnight C, Hetteema J, Khalili M, Min A, et al. A randomized trial of a hepatitis care coordination model in methadone maintenance treatment. *American Journal of Public Health*. 2013; 103:e81–e88.
- Matthews G, Kronborg IJ, Dore GJ. Treatment for hepatitis C virus infection among current injection drug users in Australia. *Clinical Infectious Diseases*. 2005; 40(Suppl 5):S325–S329. [PubMed: 15768342]
- Mauss S, Berger F, Goelz J, Jacob B, Schmutz G. A prospective controlled study of interferon-based therapy of chronic hepatitis C in patients on methadone maintenance. *Hepatology*. 2004; 40:120–124. [PubMed: 15239094]
- Mehta SH, Genberg BL, Astemborski J, Kavasery R, Kirk GD, Vlahov D, et al. Limited uptake of hepatitis C treatment among injection drug users. *Journal of Community Health*. 2008; 33:126–133. [PubMed: 18165889]
- Melin P, Chousterman M, Fontanges T, Ouzan D, Rotily M, Lang JP, et al. Effectiveness of chronic hepatitis C treatment in drug users in routine clinical practice: Results of a prospective cohort study. *European Journal of Gastroenterology and Hepatology*. 2010; 22:1050–1057. [PubMed: 20351554]
- Meyer JP, Moghimi Y, Marcus R, Lim JK, Litwin AH, Altice FL. Evidence-based interventions to enhance assessment, treatment, and adherence in the chronic Hepatitis C care continuum. *International Journal of Drug Policy*. 2015; 26(10):922–935. [PubMed: 26077144]
- Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: A systematic review of longitudinal studies. *Journal of Viral Hepatitis*. 2006; 13:34–41. [PubMed: 16364080]
- Milne R, Price M, Wallace B, Drost A, Haigh-Gidora I, Nezil FA, et al. From principles to practice: Description of a novel equity-based HCV primary care treatment model for PWID. *International Journal of Drug Policy*. 2015; 26(10):1020–1027. [PubMed: 26277611]
- Mira JA, Rivero-Juarez A, Lopez-Cortes LF, Giron-Gonzalez JA, Tellez F, de los Santos-Gil I, et al. Benefits from sustained virologic response to pegylated interferon plus ribavirin in HIV/hepatitis C virus-coinfected patients with compensated cirrhosis. *Clinical Infectious Diseases*. 2013; 56:1646–1653. [PubMed: 23429381]
- Moessner BK, Jorgensen TR, Skamling M, Vyberg M, Junker P, Pedersen C, et al. Outreach screening of drug users for cirrhosis with transient elastography. *Addiction*. 2011; 106:970–976. [PubMed: 21182552]
- Musgrove SM. NUAAs ETHOS Projects: The story of a Hep C peer support worker & his clinic. 2nd international symposium on hepatitis in substance users. 2011
- Naggie S, Cooper C, Saag M, Stamm LM, Yang JC, Pang PS, et al. Ledipasvir/sofosbuvir for 12 weeks in patients coinfecting with HCV and hiv-1: ION-4. 22nd conference on retroviruses and opportunistic infections. 2015
- NCHECR. HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2009. Sydney, NSW: NCHCER, The University of New South Wales; 2009.
- Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: Results of systematic reviews. *Lancet*. 2011; 378:571–583. [PubMed: 21802134]
- Neri S, Bruno CM, Abate G, Ierna D, Mauceri B, Cilio D, et al. Controlled clinical trial to assess the response of recent heroin abusers with chronic hepatitis C virus infection to treatment with interferon alpha-n2b. *Clinical Therapeutics*. 2002; 24:1627–1635. [PubMed: 12462291]
- NIH. National Institutes of Health Consensus Development Conference Panel statement: Management of hepatitis C. *Hepatology*. 1997; 26:2S–10S. [PubMed: 9305656]

- Nolan S, Dias Lima V, Fairbairn N, Kerr T, Montaner J, Grebely J, et al. The impact of methadone maintenance therapy on hepatitis C incidence among illicit drug users. *Addiction*. 2014; 109:2053–2059. [PubMed: 25041346]
- Norman J, Walsh NM, Mugavin J, Stooze MA, Kelsall J, Austin K, et al. The acceptability and feasibility of peer worker support role in community based HCV treatment for injecting drug users. *Harm Reduction Journal*. 2008; 5:8. [PubMed: 18298862]
- Page K, Morris MD, Hahn JA, Maher L, Prins M. Injection drug use and hepatitis C virus infection in young adult injectors: Using evidence to inform comprehensive prevention. *Clinical Infectious Diseases*. 2013; 57(Suppl 2):S32–S38. [PubMed: 23884063]
- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services; 2015. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf> [Accessed 26.07.15]
- Papadopoulos V, Gogou A, Mylopoulou T, Mimidis K. Should active injecting drug users receive treatment for chronic hepatitis C? *Arquivos de Gastroenterologia*. 2010; 47:238–241. [PubMed: 21140082]
- Petry NM, Bickel WK, Piasecki D, Marsch LA, Badger GJ. Elevated liver enzyme levels in opioid-dependent patients with hepatitis treated with buprenorphine. *American Journal on Addictions*. 2000; 9:265–269. [PubMed: 11000922]
- Post JJ, Arain A, Lloyd AR. Enhancing assessment and treatment of hepatitis C in the custodial setting. *Clinical Infectious Diseases*. 2013; 57(Suppl 2):S70–S74. [PubMed: 23884069]
- Puoti M, Cooper C, Sulkowski M, Foster GR, Berg T, Villa E, et al. ABT-450/r/ombitasvir + 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. Boston, MA: AASLD: The Liver Meeting®; 2014.
- Pybus OG, Cochrane A, Holmes EC, Simmonds P. The hepatitis C virus epidemic among injecting drug users. *Infection, Genetics and Evolution*. 2005; 5:131–139.
- Rance J, Treloar C. Integrating treatment: Key findings from a qualitative evaluation of the Enhancing Treatment of Hepatitis C in Opiate Substitution Settings (ETHOS) study. Sydney: National Centre in HIV Social Research; 2012.
- Rehm J, Frick U, Hartwig C, Gutzwiller F, Gschwend P, Uchtenhagen A. Mortality in heroin-assisted treatment in Switzerland 1994–2000. *Drug and Alcohol Dependence*. 2005; 79:137–143. [PubMed: 16002023]
- Rizzetto M. Current management of delta hepatitis. *Liver International*. 2013; 33(Suppl 1):195–197. [PubMed: 23286865]
- Robaey G, Van Vlierberghe H, Mathei C, Van Ranst M, Bruckers L, Buntinx F. Similar compliance and effect of treatment in chronic hepatitis C resulting from intravenous drug use in comparison with other infection causes. *European Journal of Gastroenterology and Hepatology*. 2006; 18:159–166. [PubMed: 16394797]
- Robaey G, Nevens F, Starkel P, Colle I, Van Eyken P, Bruckers L, et al. Previous intravenous substance use and outcome of liver transplantation in patients with chronic hepatitis C infection. *Transplantation Proceedings*. 2009; 41:589–594. [PubMed: 19328933]
- Robaey G, Grebely J, Mauss S, Bruggmann P, Moussalli J, De Gottardi A, et al. Recommendations for the management of hepatitis C virus infection among people who inject drugs. *Clinical Infectious Diseases*. 2013; 57(Suppl 2):S129–S137. [PubMed: 23884061]
- Roose RJ, Cockerham-Colas L, Soloway I, Batchelder A, Litwin AH. Reducing barriers to hepatitis C treatment among drug users: An integrated hepatitis C peer education and support program. *Journal of Health Care for the Poor and Underserved*. 2014; 25:652–662. [PubMed: 24858874]
- Rosenberg SD, Drake RE, Brunette MF, Wolford GL, Marsh BJ. Hepatitis C virus and HIV co-infection in people with severe mental illness and substance use disorders. *AIDS*. 2005; 19(Suppl 3):S26–S33. [PubMed: 16251824]
- Roy E, Boudreau JF, Boivin JF. Hepatitis C virus incidence among young street-involved IDUs in relation to injection experience. *Drug and Alcohol Dependence*. 2009; 102:158–161. [PubMed: 19251382]



- Sagnelli E, Pisaturo M, Martini S, Sagnelli C, Filippini P, Coppola N. Advances in the treatment of hepatitis B virus/hepatitis C virus coinfection. *Expert Opinion on Pharmacotherapy*. 2014; 15:1337–1349. [PubMed: 24773464]
- Sasadeusz JJ, Dore G, Kronborg I, Barton D, Yoshihara M, Weltman M. Clinical experience with the treatment of hepatitis C infection in patients on opioid pharmacotherapy. *Addiction*. 2011; 106:977–984. [PubMed: 21205057]
- Schaefer M, Schmidt F, Folwaczny C, Lorenz R, Martin G, Schindlbeck N, et al. Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. *Hepatology*. 2003; 37:443–451. [PubMed: 12540795]
- Schaefer M, Hinzpeter A, Mohmand A, Janssen G, Pich M, Schwaiger M, et al. Hepatitis C treatment in difficult-to-treat psychiatric patients with pegylated inter-feron-alpha and ribavirin: Response and psychiatric side effects. *Hepatology*. 2007; 46:991–998. [PubMed: 17668880]
- Schaefer M, Sarkar R, Diez-Quevedo C. Management of mental health problems prior to and during treatment of HCV infection in patients with drug addiction. *Clinical Infectious Diseases*. 2013; 57(Suppl. 2):S111–S117. [PubMed: 23884058]
- Seeff LB. Natural history of chronic hepatitis C. *Hepatology*. 2002; 36:S35–S46. [PubMed: 12407575]
- Shaheen AA, Wan AF, Myers RP. FibroTest and Fibro Scan for the prediction of hepatitis C-related fibrosis: A systematic review of diagnostic test accuracy. *American Journal of Gastroenterology*. 2007; 102:2589–2600. [PubMed: 17850410]
- Sievert W, Altraif I, Razavi HA, Abdo A, Ahmed EA, Alomair A, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. *Liver International*. 2011; 31(Suppl 2):61–80. [PubMed: 21651703]
- Smith SR, Wahed AS, Kelley SS, Conjeevaram HS, Robuck PR, Fried MW. Assessing the validity of self-reported medication adherence in hepatitis C treatment. *Annals of Pharmacotherapy*. 2007; 41:1116–1123. [PubMed: 17519299]
- Smith DJ, Combellick J, Jordan AE, Hagan H. Hepatitis C virus (HCV) disease progression in people who inject drugs (PWID): A systematic review and meta-analysis. *International Journal of Drug Policy*. 2015; 26(10):911–921. [PubMed: 26298331]
- Sola R, Galeras JA, Montoliu S, Tural C, Force L, Torra S, et al. Poor response to hepatitis C virus (HCV) therapy in HIV- and HCV-coinfected patients is not due to lower adherence to treatment. *AIDS Research and Human Retroviruses*. 2006; 22:393–400. [PubMed: 16706615]
- START. Starting Antiretroviral Treatment Early Improves Outcomes for HIV-Infected Individuals. 2015
- Stein MR, Soloway IJ, Jefferson KS, Roose RJ, Arnsten JH, Litwin AH. Concurrent group treatment for hepatitis C: Implementation and outcomes in a methadone maintenance treatment program. *Journal of Substance Abuse Treatment*. 2012; 43:424–432. [PubMed: 23036920]
- Strathdee SA, Latka M, Campbell J, O'Driscoll PT, Golub ET, Kapadia F, et al. Factors associated with interest in initiating treatment for hepatitis C Virus (HCV) infection among young HCV-infected injection drug users. *Clinical Infectious Diseases*. 2005; 40(Suppl 5):S304–S312. [PubMed: 15768339]
- Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *New England Journal of Medicine*. 2014; 370:211–221. [PubMed: 24428467]
- Sylvestre DL. Treating hepatitis C in methadone maintenance patients: An interim analysis. *Drug and Alcohol Dependence*. 2002; 67:117–123. [PubMed: 12095661]
- Sylvestre DL, Clements BJ. Adherence to hepatitis C treatment in recovering heroin users maintained on methadone. *European Journal of Gastroenterology and Hepatology*. 2007; 19:741–747. [PubMed: 17700258]
- Sylvestre DL, Zweben JE. Integrating HCV services for drug users: A model to improve engagement and outcomes. *International Journal of Drug Policy*. 2007; 18:406–410. [PubMed: 17854729]
- Sylvestre DL, Litwin AH, Clements BJ, Gourevitch MN. The impact of barriers to hepatitis C virus treatment in recovering heroin users maintained on methadone. *Journal of Substance Abuse Treatment*. 2005; 29:159–165. [PubMed: 16183464]

- Taylor LE, Swan T, Matthews GV. Management of HCV/HIV coinfection among people who use drugs in the era of direct-acting antiviral-based therapy. *Clinical Infectious Diseases*. 2013; 57(Suppl. 2):S118–S124. [PubMed: 23884059]
- Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *New England Journal of Medicine*. 2004; 351:438–450. [PubMed: 15282351]
- Treloar C, Newland J, Rance J, Hopwood M. Uptake and delivery of hepatitis C treatment in opiate substitution treatment: Perceptions of clients and health professionals. *Journal of Viral Hepatitis*. 2010; 17:839–844. [PubMed: 20070504]
- Treloar C, Hull P, Bryant J, Hopwood M, Grebely J, Lavis Y. Factors associated with hepatitis C knowledge among a sample of treatment naive people who inject drugs. *Drug and Alcohol Dependence*. 2011; 116(1–3):52–56. [PubMed: 21194852]
- Treloar C, Rance J, Bath N, Everingham H, Micallef M, Day C, et al. 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. *International Journal of Drug Policy*. 2015; 26(10):992–998. [PubMed: 25697089]
- Tsui JI, Evans JL, Lum PJ, Hahn JA, Page K. Association of opioid agonist therapy with lower incidence of hepatitis C virus infection in young adult injection drug users. *JAMA Internal Medicine*. 2014; 174:1974–1981. [PubMed: 25347412]
- Turillazzi E, Riezzo I, Neri M, Bello S, Fineschi V. MDMA toxicity and pathological consequences: A review about experimental data and autopsy findings. *Current Pharmaceutical Biotechnology*. 2010; 11:500–509. [PubMed: 20420577]
- Turner KM, Hutchinson S, Vickerman P, Hope V, Craine N, Palmateer N, et al. The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: Pooling of UK evidence. *Addiction*. 2011; 106:1978–1988. [PubMed: 21615585]
- van Asten L, Verhaest I, Lamzira S, Hernandez-Aguado I, Zangerle R, Boufassa F, et al. Spread of hepatitis C virus among European injection drug users infected with HIV: A phylogenetic analysis. *Journal of Infectious Diseases*. 2004; 189:292–302. [PubMed: 14722895]
- van den Berg CH, Smit C, Bakker M, Geskus RB, Berkhout B, Jurriaans S, et al. Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. *European Journal of Epidemiology*. 2007; 22:183–193. [PubMed: 17334821]
- van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA*. 2012; 308:2584–2593. [PubMed: 23268517]
- van der Meer AJ, Wedemeyer H, Feld JJ, Dufour JF, Zeuzem S, Hansen BE, et al. Life expectancy inpatients with chronic HCV infection and cirrhosis compared with a general population. *JAMA*. 2014; 312:1927–1928. [PubMed: 25387192]
- van Heeswijk R, Verboven P, Vandevoorde A, Vinck P, Snoeys J, Boogaerts G, et al. Pharmacokinetic interaction between telaprevir and methadone. *Antimicrobial Agents and Chemotherapy*. 2013; 57:2304–2309. [PubMed: 23478952]
- Van Thiel DH, Molloy PJ, Friedlander L, Kania RJ, Fagioli S, Caraceni P, et al. Interferon alpha treatment of chronic hepatitis C in patients with evidence for co-existent autoimmune dysregulation. *Hepato-Gastroenterology*. 1995; 42:900–906. [PubMed: 8847043]
- Van Thiel DH, Anantharaju A, Creech S. Response to treatment of hepatitis C in individuals with a recent history of intravenous drug abuse. *American Journal of Gastroenterology*. 2003; 98:2281–2288. [PubMed: 14572580]
- Vergniol J, Foucher J, Terreboune E, Bernard PH, le Bail B, Merrouche W, et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. *Gastroenterology*. 2011; 140:1970–1979. 1979.e1971–e1973. [PubMed: 21376047]
- Waizmann M, Ackermann G. High rates of sustained virological response in hepatitis C virus-infected injection drug users receiving directly observed therapy with peginterferon alpha-2a (40KD) (PEGASYS) and once-daily ribavirin. *Journal of Substance Abuse Treatment*. 2010; 38:338–345. [PubMed: 20362408]

- Wang L, Wei X, Wang X, Li J, Li H, Jia W. Long-term effects of methadone maintenance treatment with different psychosocial intervention models. *PLOS ONE*. 2014; 9:e87931. [PubMed: 24498406]
- Webb K, Shepherd L, Neuberger J. Illicit drug use and liver transplantation: Is there a problem and what is the solution? *Transplant International*. 2008; 21:923–929. [PubMed: 18657088]
- Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: The D:A:D study. *Archives of Internal Medicine*. 2006; 166:1632–1641. [PubMed: 16908797]
- Weiss JJ, Brau N, Stivala A, Swan T, Fishbein D. Review article: Adherence to medication for chronic hepatitis C – Building on the model of human immunodeficiency virus antiretroviral adherence research. *Alimentary Pharmacology and Therapeutics*. 2009; 30:14–27. [PubMed: 19416131]
- White B, Dore GJ, Lloyd AR, Rawlinson WD, Maher L. Opioid substitution therapy protects against hepatitis C virus acquisition in people who inject drugs: The HITS-c study. *Medical Journal of Australia*. 2014; 201:326–329. [PubMed: 25222455]
- WHO. WHO, UNODC, UNAIDS technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users – 2012 revision. Geneva: World Health Organization; 2012.
- WHO. Guidelines for the screening, care and treatment of persons with hepatitis C infection. Geneva, Switzerland: World Health Organization; 2014.
- Wiessing L, Ferri M, Grady B, Kantzanou M, Sperle I, Cullen KJ, et al. 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*. 2014; 9:e103345. [PubMed: 25068274]
- Wilkinson M, Crawford V, Tippet A, Jolly F, Turton J, Sims E, et al. Community-based treatment for chronic hepatitis C in drug users: High rates of compliance with therapy despite ongoing drug use. *Alimentary Pharmacology and Therapeutics*. 2009; 29:29–37. [PubMed: 18752631]
- Williams R, Aspinall R, Bellis M, Camps-Walsh G, Cramp M, Dhawan A, et al. Addressing liver disease in the UK: A blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. *Lancet*. 2014; 384:1953–1997. [PubMed: 25433429]
- Wyles DL, Ruane P, Sulkowski M, Dieterich D, Luetkemeyer AF, Morgan TR, et al. Daclatasvir in combination with sofosbuvir for HIV/HCV coinfection: ALLY-2 study; 22nd conference on retroviruses and opportunistic infections; 2015.

**Table 1**

Grading system used to rate the level of the evidence and strength of the recommendation for each recommendation (using the recommendations system developed by the American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA) (AASLD/IDSA, 2015)).

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence and/or opinion is in favor of usefulness and efficacy
Class IIb	Usefulness and efficacy are less well established by evidence and/or opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful
Level of Evidence	Description
Level A <sup>a</sup>	Data derived from multiple randomized clinical trials, meta-analyses, or equivalent
Level B <sup>a</sup>	Data derived from a single randomized trial, nonrandomized studies, or equivalent
Level C	Consensus opinion of experts, case studies, or standard of care

<sup>a</sup>In some situations, such as for IFN-sparing HCV treatments, randomized clinical trials with an existing standard-of-care arm cannot ethically or practicably be conducted. The US Food and Drug Administration (FDA) has suggested alternative study designs, including historical controls or immediate vs deferred, placebo-controlled trials. For additional examples and definitions see FDA link: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225333.pdf>. In those instances for which there was a single predetermined, FDA-approved equivalency established, panel members considered the evidence as equivalent to a randomized controlled trial for levels A or B (AASLD/IDSA, 2015).