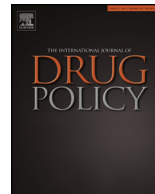




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Review

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

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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 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

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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 care. Further research is needed to evaluate strategies to enhance testing, linkage to care, treatment, adherence, viral cure, and prevent HCV reinfection among PWID, particularly as new interferon-free DAA treatments for HCV infection become available.

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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;

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 ^a	Data derived from multiple randomized clinical trials, meta-analyses, or equivalent
Level B ^a	Data derived from a single randomized trial, nonrandomized studies, or equivalent
Level C	Consensus opinion of experts, case studies, or standard of care

^a 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 pre-determined, FDA-approved equivalency established, panel members considered the evidence as equivalent to a randomized controlled trial for levels A or B (AASLD/IDSA, 2015).

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 meta-analysis of cross-sectional studies of HCV-infected PWID, the 20-year cirrhosis prevalence was 15% (John-Baptiste, Krahn,

Heathcote, 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 \geq F3) and cirrhosis were 29–30 years and 39–40 years, respectively (Smith, 2015, this issue). Factors contributing to fibrosis progression include age, moderate-heavy alcohol use, HIV, obesity and insulin resistance (reviewed in Hajarzadeh 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; Hajarzadeh 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, 2015, this issue). 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, 2015, this issue).

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, Birerdinc, & 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, 2015, this issue), lack of treatment willingness or treatment intent (Alavi et al., 2015), ongoing or former drug use (Alavi et al., 2013, 2015; 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), comorbid medical disease (Kanwal et al., 2007), psychiatric disease (Bini et al., 2005; Kramer et al., 2011) and OST (Alavi et al., 2013, 2015; 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, 2015, this issue). 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, 2015, this issue). 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 in patients 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

contra-indications 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, 2015, this issue; Milne, 2015, this issue; Mason, 2015, this issue; Keats, 2015, this issue), 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 CYP450 3A4 and CYP450 2D6 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/ombitasvir/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 $\geq 80\%$ of scheduled PEG-IFN and ribavirin for $\geq 80\%$ 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., 2015, this issue). In adherent PWID, alcohol use has no negative impact on SVR (Anand et al., 2006; Bruggmann, Dampz, Gerlach, Kravec, & Falcato, 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, 2015, this issue), examples of strategies that have been successful for enhancing assessment, adherence or SVR include hospital-based and primary care-based integrated care, community-based telehealth, 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, 2015](#), this issue), 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 mono-infection (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; Robaey et al., 2009). Relapse to drug use following transplantation is rare (De Gottardi et al., 2010; Robaey 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.

Conflict of interest statement

All authors have no reported conflicts relevant to the content of the manuscript.

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