

Recommendations for the Management of Hepatitis C Virus Infection Among People Who Inject Drugs

Geert Robaey^{1,2,3,a} Jason Grebely^{4,a} Stefan Mauss⁵ Philip Bruggmann⁶ Joseph Moussalli^{7,8} Andrea De Gottardi⁹ Tracy Swan¹⁰ Amber Arain^{1,3} Achim Kautz¹¹ Heino Stöver¹² Heiner Wedemeyer¹³ Martin Schaefer^{14,15} Lynn Taylor¹⁶ Markus Backmund^{17,18} Olav Dalgard¹⁹ Maria Prins^{20,21} and Gregory J. Dore^{4,22} on behalf of the International Network on Hepatitis in Substance Users

¹Department of Gastroenterology and Hepatology, Ziekenhuis Oost Limburg, Genk, ²Department of Hepatology UZ Leuven, and ³Faculty of Medicine and Life Sciences, Limburg Clinical Research Program, Hasselt University, Belgium; ⁴Kirby Institute, University of New South Wales, Sydney, Australia; ⁵Center for HIV and Hepatogastroenterology, Düsseldorf, Germany; ⁶Arud Centres of Addiction Medicine, Zurich, Switzerland; ⁷Hôpital Pitié-Salpêtrière, and ⁸Université Pierre et Marie Curie, Paris VI, Paris, France; ⁹Hepatology, Clinic of Visceral Surgery and Medicine, Inselspital, Berne, Switzerland; ¹⁰Treatment Action Group, New York, New York; ¹¹European Liver Patients Association, Cologne, ¹²Institute of Addiction Research, University of Applied Sciences, Frankfurt am Main, ¹³Department of Gastroenterology, Hepatology and Endocrinology, University of Hannover; ¹⁴Department of Psychiatry, Psychotherapy and Addiction Medicine, Kliniken Essen-Mitte, Essen, and ¹⁵Department of Psychiatry and Psychotherapy—CCM, Charité—Universitätsmedizin Berlin, Germany; ¹⁶Department of Medicine, Brown University, Providence, Rhode Island; ¹⁷Ludwig-Maximilians-University, and ¹⁸Praxiszentrum im Tal Munich, Munich, Germany; ¹⁹Department of Infectious Diseases, Akershus University Hospital, Lørenskog, Norway; ²⁰Department of Research, Cluster Infectious Diseases, Public Health Service of Amsterdam, and ²¹Department of Internal Medicine, Center for Infection and Immunity Amsterdam, Academic Medical Centre, Amsterdam, the Netherlands; and ²²HIV/Immunology/Infectious Diseases Clinical Services Unit, St Vincent's Hospital, Sydney, Australia

In the developed world, the majority of new and existing hepatitis C virus (HCV) infections occur among people who inject drugs (PWID). The burden of HCV-related liver disease in this group is increasing, but treatment uptake among PWID remains low. Among PWID, there are a number of barriers to care that should be considered and systematically addressed, but these barriers should not exclude PWID from HCV treatment. Furthermore, 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 provides a framework for HCV assessment, management, and treatment. Further research is needed to evaluate strategies to enhance assessment, adherence, and SVR among PWID, particularly as new treatments for HCV infection become available.

Keywords. drug users; injecting; injection; guidelines; HCV; HIV.

In the developed world, 50%–80% of hepatitis C virus (HCV) infection is among people who inject drugs (PWID) [1]. Hereafter, “PWID” will refer to people with current or “active” injection drug use (IDU),

which is generally defined as use in the past 6 months, and to former injectors who are still active non-injection drug users and/or on opioid substitution therapy (OST). The natural history of HCV (increase in liver cirrhosis after 15–20 years), and an aging cohort of PWID, means that a large burden of advanced liver disease is anticipated in the next decade [2].

Until recently, HCV treatment guidelines excluded PWID, due to concerns about poor adherence, adverse events, and reinfection [3]. Successful HCV treatment studies among PWID challenged this paradigm [4–35], and guidelines have been revised to consider HCV treatment among PWID on a “case-by-case” basis [36–38].

^aG. R. and J. G. contributed equally to this work.

Correspondence: Geert Robaey, MD, PhD, Professor of Medicine and Life Sciences, Department of Gastroenterology and Hepatology, Ziekenhuis Oost Limburg, Schiepse Bos 6, B 3600 Genk, Belgium (geert.robaey@zol.be).

Clinical Infectious Diseases 2013;57(S2):S129–37

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DOI: 10.1093/cid/cit302

Despite revised guidelines, few PWID have received HCV treatment [39–42]. Enhanced HCV assessment and treatment in PWID will be required to reduce future HCV-related morbidity and mortality [43]. The availability of effective, tolerable, and simpler direct-acting antivirals (DAAs) should improve the feasibility of this approach. The International Network of Hepatitis in Substance Users established an expert panel to develop recommendations to enhance HCV assessment, management, and treatment among PWID.

METHODS

The recommendations have been graded according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, [38]. The strength of recommendations reflects the quality of underlying evidence (Table 1). The quality of the evidence has been classified in 1 of 3 levels: high (A), moderate (B), or low (C). The GRADE system offers 2 grades of recommendation: strong (1) or weak (2).

Epidemiology and Prevention of HCV

Prevalence of HCV among PWID is 65% [44] and >80% among long-term PWID [45]. HCV genotypes 1a, 1b, and 3a are common among PWID [46]. Genotype 4d is common among PWID in Europe [47], and 6 in Southeast Asia [48]. Incidence of HCV in PWID is 2%–45% per annum [45]. High coverage of combined harm reduction programs (opioid substitution treatment [OST] and needle exchange programs) can reduce HCV incidence [49–51]. Modeling studies suggest that HCV treatment for PWID could reduce transmission [52].

Recommendations

1. PWID should be routinely and voluntarily tested for HCV antibodies/RNA and if negative, every 6–12 months (B1).
2. PWID should be provided with clean drug injecting equipment and access to OST as part of widespread comprehensive harm reduction programs, including in prisons (B1).

Natural History of HCV and Effects of Drugs on the Liver

Chronic HCV infection develops in 75% [53], with 10%–20% developing cirrhosis over 20–30 years of infection [2]. In a meta-analysis of HCV-infected PWID, the 20-year cirrhosis prevalence was 15% [54]. Despite slow HCV disease progression over the initial 20 years of infection, factors contributing to fibrosis progression include age, continued moderate to heavy alcohol use, human immunodeficiency virus (HIV) infection, obesity, and insulin resistance (reviewed in [2]).

Despite misconceptions among affected populations and healthcare workers, no liver toxicity is reported for heroin [55] or methadone [56]. Buprenorphine occasionally increases transaminases [57]. Methylenedioxymethamphetamine rarely

Table 1. Evidence Grading (Adapted From the GRADE System)

Evidence	Notes	Quality of Evidence/Grade
High quality	Further research is very unlikely to change our confidence in the estimate of effect.	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	B
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain.	C
Recommendation Notes		
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.	1
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost, or resource consumption.	2

causes acute liver failure due to direct liver toxicity [58, 59], and little is known about methamphetamine-related liver toxicity [60]. Heavy alcohol consumption is associated with a higher risk of cirrhosis [61]. Tobacco [62] and daily cannabis [63, 64] smoking may increase fibrosis progression, but further studies are needed. Coffee consumption is associated with lower necroinflammatory activity and less-advanced fibrosis [65, 66].

Aging cohorts of PWID with chronic HCV and low treatment uptake are currently leading to an increasing burden of HCV-related morbidity and mortality [2]. 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 [2].

Recommendations

1. PWID should be counseled to moderate alcohol intake, or abstain if there is evidence of advanced liver disease (A1).
2. PWID should be counseled to moderate cannabis use, or abstain if there is evidence of advanced liver disease (B2).
3. Cessation of injecting is not required to limit HCV disease progression (B2).
4. The potential impact of drug use on the liver should be discussed with PWID (C2).

Noninvasive Liver Fibrosis Assessment

Liver biopsy is the gold standard for liver fibrosis assessment, but it is invasive and logistically difficult. As per international guidelines [37, 38], noninvasive methods such as transient elastography or well-established panels of biomarkers of fibrosis are acceptable for liver disease assessment. Noninvasive methods have excellent utility for the identification of HCV-related cirrhosis, but lesser accuracy for earlier stages [67], and can predict HCV-related survival [68]. Combining multiple modalities achieves the best performance [69]. Noninvasive tests are cost-effective [70]. Among PWID, transient elastography can enhance liver disease screening [71, 72].

Recommendations

1. Noninvasive 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 (B1).
2. Combining multiple noninvasive assessments is recommended, when possible (B1).

Pretherapeutic Assessment

Guidelines for pretherapeutic assessment for those with HCV are available [37, 38]. However, HCV-infected PWID have complex social, medical, and psychiatric comorbidities, complicating decisions around care (reviewed in [73]). Poor HCV knowledge and inaccurate perceptions are barriers for accessing care [74–77]. Factors associated with not receiving HCV treatment include older age [78], minority ethnicity [78], ongoing or former drug use [79–81], ongoing alcohol use [78, 79], advanced liver disease [80], comorbid diseases [78, 81], psychiatric disease [78, 80], and OST [79].

Recommendations

1. Pretherapeutic education should include discussions of HCV transmission, risk factors for fibrosis progression, treatment, reinfection risk, and harm reduction strategies (B1).
2. Pretherapeutic 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 to social support services and peer support, if available (A1).

Indications for Treatment

The goal of HCV therapy is to prevent liver disease complications and death from HCV. The end point is sustained virologic response (SVR), which equates to cure in >99% of patients. SVR is associated with improved quality of life, regression of fibrosis, and reduced risk of complications in patients with cirrhosis [82].

According to international guidelines [37, 38], individuals with chronic HCV and absolute contraindications to standard of care should not receive therapy.

Recommendations

1. PWID should receive HCV assessment, with treatment decisions based on an individualized evaluation of social, lifestyle, and clinical factors (B1).
2. PWID with absolute contraindications to standard of care should not receive HCV therapy (B1).

Peginterferon and DAA-Based Treatment

In PWID, treatment of chronic HCV with pegylated interferon alfa (peg-IFN)/ribavirin (RBV) is safe and effective [4–35], and has been recommended for PWID by international guidelines following individualized assessment [37, 38]. DAA therapy, when added to peg-IFN/RBV, enhances treatment response for chronic HCV genotype 1 [83–86]. Future DAAs in combination with peg-IFN/RBV should provide improved efficacy, tolerability, dosing schedules, and therapy duration [87]. Evidence suggests that IFN-free DAA-based regimens are likely to be curative in a high proportion of individuals with chronic HCV genotype 2/3 [88, 89] and 1 [90–92] infections.

DAA clinical development programs have excluded individuals with active drug use, but many trials have included those on OST. DAA-based safety and treatment outcome data have not been presented on clinical trial subpopulations of individuals on OST. Drug–drug interaction studies have been undertaken on telaprevir and boceprevir with methadone [93, 94] and buprenorphine [94, 95], with no clinically important interactions observed.

Recommendations

1. Evaluation of safety and efficacy of telaprevir and boceprevir, in combination with peg-IFN/RBV, is required in PWID with chronic HCV genotype 1 (C1).
2. Telaprevir and boceprevir can be used in PWID on OST (B1).
3. Telaprevir and boceprevir do not require specific methadone and buprenorphine dose adjustment, but patients should be monitored for signs of opioid toxicity or withdrawal (B1).
4. Consideration of telaprevir and boceprevir use in PWID should be undertaken on an individualized basis, but those with early liver disease should generally be advised to await further data and/or potential development of improved DAA-based therapies (B1).

Impact of Drug Use on Adherence and SVR

Adherence to HCV therapy is often defined as receipt of $\geq 80\%$ of scheduled peg-IFN/RBV for $\geq 80\%$ of the treatment period, but this does not distinguish between missed doses and treatment discontinuation [96]. Suboptimal peg-IFN exposure is

driven by early treatment discontinuation as compared to missed doses [97]. Both physicians [98] and individuals [99] overestimate adherence to HCV therapy. Adherence [96, 97] and treatment completion [96–98] are associated with SVR, but the impact of missed doses on SVR is unclear [96, 97]. Among PWID, adherence [29, 35, 97, 100] and treatment completion [97] are associated with SVR.

Peg-IFN/RBV is safe and effective among those with a history of IDU [4, 6–9, 11–35] and among active PWID [101], with SVR of 54%–56% [4, 34, 101]. PWID often have characteristics associated with favorable HCV treatment response, including younger age, HCV genotype 3, and mild liver disease [9]. A history of IDU does not compromise adherence [97, 98, 102], treatment completion [4, 21, 29, 97], or SVR [4], although some studies have found lower treatment completion [4]. Recent drug use at treatment initiation has limited impact on adherence [29, 30, 97, 98, 100, 103], treatment completion [4, 28, 29, 97], or SVR [6, 7, 20, 24, 27–29, 35, 101]. Some studies have reported lower treatment completion in patients with recent drug use at treatment completion [4, 32]. HCV treatment does not have an impact on drug dependency treatment or increase drug use [17, 18]. Occasional drug use during treatment does not seem to impact adherence [29, 35, 97, 100], treatment completion [29, 97, 104], or SVR [7, 29, 35]. However, lower adherence [97, 98] and SVR [19, 20, 24] have been observed in persons with frequent drug use (daily/every other day) during treatment. When discontinuation occurs, it often occurs early during therapy [18, 97]. In adherent PWID, alcohol use does not impact SVR [105, 106].

Factors independently associated with adherence and treatment completion among PWID include lower education and unstable housing [97]. Factors independently associated with lower SVR among PWID include poor social functioning [7], a history of untreated depression [33], and ongoing drug use during treatment [33].

Recommendations

1. Adherence should consider missed doses and treatment discontinuation (B1).
2. PWID should be counseled on the importance of adherence in attaining SVR (A1).
3. HCV treatment can be considered for PWID, provided they wish to receive treatment and are able and willing to maintain regular appointments (A1).
4. A history of IDU and recent drug use at treatment initiation are not associated with reduced SVR, and decisions to treat must be made on a case-by-case basis (B1).
5. PWID with ongoing social issues or 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 (B1).

Impact of Mental Health on Adherence and SVR

As reviewed in [107], psychiatric comorbidity is high among PWID. However, PWID do not have an increased risk for the development of major depression during peg-IFN treatment. Poorer social functioning is associated with new-onset depression during peg-IFN treatment [108]. Psychiatric comorbidity is not associated with lower adherence, treatment completion, SVR, or depression during peg-IFN treatment [26, 108–113].

As reviewed in [107], psychiatric contraindications to HCV therapy include acute major and uncontrolled psychiatric disorders. Although data are conflicting, studies show that prophylactic antidepressants can reduce IFN-induced depression, particularly in patients with previous or ongoing depression [107]. Depression-specific symptoms are responsive to serotonergic antidepressants [107]. Psychiatric adverse events related to peg-IFN can be managed without dose adjustment or discontinuation.

Recommendations

1. Pretreatment 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 (A1).
2. If psychiatric comorbidities are present, decisions to treat with peg-IFN must be made on a case-by-case basis (A1).
3. In cases of acute major and uncontrolled psychiatric disorders, a pretreatment psychiatric assessment is recommended (C2).
4. Prophylactic antidepressants are recommended in cases of a history of IFN-induced depression and with depressive symptoms at baseline (B1).

Treatment Management

HCV treatment has been delivered successfully to PWID through various models, including within hospital-based clinics, drug detoxification clinics, OST clinics, prisons, and community-based clinics. As reviewed in [114], 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 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).

Recommendations

1. HCV treatment for PWID should be considered on an individualized basis and delivered within a multidisciplinary team setting (B1).

2. Access to harm reduction programs, social work, and social support services should be a component of HCV clinical management (B2).

3. Peer-based support should be evaluated as a means to improve HCV clinical management (B2).

Reinfection Following Successful HCV Treatment

There is still some concern that reinfection due to recurrent risk behaviors 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 [115]).

Recommendations

1. PWID should not be excluded from HCV treatment on the basis of perceived risk of reinfection (B1).

2. Harm reduction education and counseling should be provided for PWID in the context of HCV treatment (B1).

3. Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on PWID with ongoing risk behavior (B2).

Treatment of Acute HCV

Acute HCV infection refers to the period spanning the first 6 months following exposure to HCV [116]. Spontaneous clearance occurs in 25% [53]. Peg-IFN–based SVR among HCV-monoinfected PWID with acute HCV is 55%–74% (reviewed in [116]), with treatment outcomes associated with adherence and social support, but not IDU prior to or during treatment [7].

Recommendations

1. PWID with acute HCV symptoms should be monitored for 12–16 weeks (including HCV RNA levels) to allow potential spontaneous clearance (A1).

2. Peg-IFN monotherapy for 24 weeks should be considered for PWID with acute HCV (B1).

3. Strategies to optimize adherence should be used in the setting of acute HCV, with consideration of directly observed peg-IFN therapy (B2).

HIV/HCV Coinfection

Prevalence of HCV among HIV-infected PWID is high (>80%) [117]. Chronic HCV is the leading cause of non-AIDS death where combination antiretroviral therapy (cART) is accessible [118]. Challenges with HIV/HCV include accelerated HCV disease progression, potential cART-related liver toxicity, multiple medication requirements, drug–drug interactions, and medical comorbidities (reviewed in [119]). HIV/HCV is associated with a higher prevalence of psychiatric disorders, poverty, homelessness, and incarceration [120]. HCV treatment responses may be poorer in those with HIV/HCV [121, 122].

Recommendations

1. HCV-infected PWID should be screened for HIV (B1).
2. The accelerated HCV disease progression in HIV/HCV should be considered in treatment decision making (B2).
3. Potential drug–drug interactions between HIV, HCV, and OST need to be considered (A1).
4. Early introduction of cART should be considered (B1).

Management of Hepatitis B Virus Coinfection

The global prevalence of chronic hepatitis B virus (HBV) is 8% among PWID [44]. HBV vaccination is effective among PWID, and accelerated schedules improve adherence [123]. Peg-IFN/RBV is effective for the treatment of HCV in persons with HBV/HCV [124]. Hepatitis D virus coinfection is frequent in PWID [125]. Peg-IFN is the only effective drug [126].

Recommendations

1. PWID should be vaccinated for hepatitis A virus and HBV (A1).
2. PWID with active HBV/HCV coinfection should be considered for peg-IFN/RBV therapy (B1).

Liver Transplantation

The proportion of people with a history of IDU undergoing liver transplant for HCV-related cirrhosis or hepatocellular carcinoma is 5%–10% [127, 128]. Relapse to drug use following transplant is rare [127, 128]. Selection criteria for liver transplantation include 6–24 months of drug abstinence, controlled psychiatric disease, and the presence of stable social support networks [129]. OST is not a contraindication [127, 129, 130]. 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 (B2).
2. OST is not a contraindication for liver transplantation, and individuals on OST should not be advised to reduce or stop therapy (A1).
3. Psychiatric evaluation and follow-up should be offered to PWID undergoing liver transplant (B1).

CONCLUSIONS

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 provides a framework for HCV 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 assessment, adherence, and SVR among PWID, particularly as new DAAs become available. This will be crucial in the efforts to stem the burden of HCV-related liver disease worldwide.

Notes

Supplement sponsorship. This article was published as part of a supplement entitled "Prevention and Management of Hepatitis C Virus Among People Who Inject Drugs: Moving the Agenda Forward," sponsored by an unrestricted grant from the International Network on Hepatitis in Substance Users (INHSU), The Kirby Institute (University of New South Wales), Abbvie, Gilead Sciences, Janssen-Cilag, and Merck.

Potential conflicts of interest. All authors: No reported conflicts.

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

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