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TOPIC HIGHLIGHT

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Eligibility of persons who inject drugs for treatment of hepatitis C virus infection

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Abstract

In this decade, an increase is expected in end-stage liver disease and hepatocellular carcinoma, most commonly caused by hepatitis C virus (HCV) infection. Although people who inject drugs (PWID) are the major source for HCV infection, they were excluded from antiviral treatments until recently. Nowadays there is incontrovertible evidence in favor of treating these patients, and substitution therapy and active substance use are no longer contraindications for antiviral treatment. The viral clearance in PWID after HCV antiviral treatment with interferon or pegylated interferon combined with ribavirin is comparable to the viral clearance in non-substance users. Furthermore, multidisciplinary approaches to delivering treatment to PWID are advised, and their treatment should be considered on an individualized basis. To prevent the spread of HCV in the PWID community, recent active PWID are eligible for treatment in combination with needle exchange programs and substitution therapy. As the rate of HCV reinfection is low after HCV antiviral treatment, there is no need to withhold HCV treatment due to concerns about reinfection alone. Despite the advances in treatment efficacies and data supporting their success, HCV assessment of PWID and initiation of antiviral treatment remains low. However, the proportion of PWID assessed and treated for HCV is increasing, which can be further enhanced by understanding the barriers to and facilitators of HCV care. Removing stigmatization and implementing peer support and group treatment strategies, in conjunction with greater involvement by nurse educators/practitioners, will promote greater treatment seeking and adherence by PWID. Moreover, screening can be facilitated by noninvasive methods for detecting HCV antibodies and assessing liver fibrosis stages. Recently, HCV clearance has become a major endpoint in the war against drugs for the Global Commission on Drug Policy. This review highlights the most recent evidence concerning HCV infection and treatment strategies in PWID.

Key words: Hepatitis C virus; Persons who inject drugs; Methadone; Sustained viral response; Adherence

Core tip: People who inject drugs are considered to be the main reservoir for hepatitis C virus (HCV) infection. Accumulating evidence indicates that HCV-infected injection drug users can be successfully treated, and the earlier they are treated, the better the outcome. Therefore, in the future, the barriers for antiviral treatment for these individuals must be overcome. This topic highlight presents the most recent data concerning HCV infection and treatment of injection drug users.

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INTRODUCTION

At the end of the nineties (1997) substance users were excluded from antiviral therapy against hepatitis C virus (HCV) infection[1]. However, a great deal of evidence, accumulated between 2000 and 2005, showed a favorable outcome of HCV antiviral therapy in persons who inject drugs (PWID), and by 2009, they were no longer excluded from antiviral therapy in the American Association for the Study of Liver Diseases guidelines[2]. Since then, the International Network on Hepatitis in Substance Users (www.inhsu.com) has organized forums at three international symposia distributing substantial information on the epidemiology and management of substance users infected with HCV, portions of which have been published in a supplemental issue of *Clinical Infectious Diseases*[3,4]. Indeed, international recommendations for the treatment of HCV infection in PWID have recently been published[5] and are being integrated into the European guidelines for HCV management[6]. In addition, the eradication of HCV has become an actionable, evidence-based recommendation for constructive legal and policy reform of the Global Commission on Drug Policy[7]. In view of the recent changes, this article aims to review and highlight new aspects concerning HCV infection in PWID.

HCV INFECTION AMONG PWID

HCV infection is one of the leading causes of chronic liver disease, and the prevalence of liver cirrhosis is increasing[8,9]. In developed countries, 50%-80% of HCV infection occurs in current and former PWID[5,10]. The prevalence of HCV among PWID is approximately 65%, and can reach as high as 80% in long-term users[11,12]. There are multiple strains of HCV, and PWID are generally infected with genotypes 1a, 1b and 3a[13], though genotype 4d is common among PWID in Europe[14,15], and genotype 6 is found in those from Southeast Asia[5,16,17]. Factors associated with HCV infection in PWID include sex (female)[18], ethnicity[19,20], unstable housing[21], frequent injection of cocaine[18,22-24], imprisonment[24], presence of injecting social-networks[25,26] and sharing of injection equipment[5,23,27].

Disease progression and diagnosis

Progression to chronic HCV (CHC) infection occurs in 75% of cases, with cirrhosis developing over two to three decades in 10%-20%[28-30]. HCV disease progression is slow and depends on the presence of several cofactors such as age[9], continued moderate to heavy alcohol consumption[31-33], HIV[34-37], obesity[38,39], insulin resistance[40,41], daily cannabis[42-44] and daily tobacco use[45]. However, coffee consumption is associated with lower necro-inflammatory activity and less advanced fibrosis[46-49]. There have been no reports of liver toxicity with heroin[50] or methadone[51], though buprenorphine occasionally increases transaminases[52], and methylenedioxymetamphetamine rarely causes acute liver failure due to direct liver toxicity[53-56].

The ageing population of PWID with CHC infection combined with low treatment uptake are leading to an increase in the burden of HCV related morbidity and mortality[37,57-59]. In many countries where PWID are the largest population affected by HCV, 15%-30% of deaths are from drug-related causes, 20%-25% of deaths are from liver disease[9], and liver failure, which increases over time, becomes the most common cause of death by the end of follow-up[5,9,60-63].

There are various techniques available to assess liver disease progression and liver fibrosis, though the gold standard is diagnosis from liver biopsy[2]. However, non-invasive methods have a greater acceptance among patients, including transient elastography (Fibroscan), which has been shown to enhance liver disease screening among PWID[64,65] and acoustic radiation force impulse imaging.

HCV TREATMENT

Treatment of PWID

A treatment for HCV infection combines pegylated interferon (Peg-IFN) and ribavirin (RBV), which is safe and effective in PWID[66-96] and has been recommended by international guidelines[2,5,6]. In CHC treatment trials, the median sustained virologic response (SVR) rate among PWID is 54.3%, and is comparable to rates among non-PWID[66]. In CHC patients infected with genotype 1, therapy with direct acting agents (DAA) combined with Peg-IFN and RBV enhances treatment response[97-100], though the first cohort studies on the outcome of DAA therapy in substance users are underway. Studies evaluating drug interactions, including combinations of telaprevir and boceprevir with methadone[101] and buprenorphine[102], found no clinically important interactions[49]. Furthermore, there is currently no indication that history of substance use, substitution therapy or active substance use influences SVR[103-105].

It is important to note that PWID are typically younger[82], are infected with genotype 3 and have mild liver disease[71] compared to non-substance users, which are characteristics associated with favorable HCV treatment outcome[5]. However, treatment of HCV-infected PWID is complicated by their complex social, medical and psychiatric comorbidities[106], lack of HCV knowledge and inaccurate perceptions of patients[107-110]. Other factors that may prevent HCV-infected PWID from seeking treatment include age[111], being of an ethnic minority[111], former or ongoing drug[112-114] and alcohol use[111,112], advanced liver disease[113], comorbid diseases[111-114], psychiatric disease[111-113] and opioid substitution treatment[5,112]. In order to overcome these barriers, recent guidelines

recommend linking PWID to social support services and peer support by providing pre-therapeutic education and counseling about the impact of alcohol, cannabis, tobacco and drug use on their life[5]. HCV treatment for PWID should be considered on an individualized basis and delivered within a multidisciplinary team setting[5].

Treatment of active PWID

Acceptable treatment outcomes, with a low rate of re-infection (2.4 per 100 patient years), can be achieved in actively injecting PWID, as they show high adherence to treatment (82%)[115]. The first randomized controlled trial among active PWID reported that the delivery of directly observed therapy (DOT) with Peg-IFN and self-administered (SA) RBV within multidisciplinary community health centers was an effective strategy for the treatment of HCV with a low reinfection rate[116]. In this trial nearly 80% completed treatment, two-thirds responded to therapy, and drug use at the time of treatment initiation was not associated with reduced SVR. Additional studies have confirmed that SVR rates are not affected, with an SVR rate of 55.5% among treated PWID that is comparable to rates of 54% and 56% recorded in Peg-IFN plus RBV registration trials[117,118].

Treatment completion and adherence among PWID

Recently, a meta-analysis of 32 studies by Dimova *et al*[95] found that the treatment completion rate among PWID was 83.4%. Moreover, it has been shown that there is no difference between PWID and non-PWID with respect to treatment adherence[71,88]. However, among studies that compared addiction-treated and untreated PWID during HCV therapy, the higher the proportion of addiction-treated patients, the higher the HCV treatment completion rate. Thus, the assessment of a patient's social circumstances and the availability of support (in addition to injection behavior) are important aspects to consider when starting HCV treatment.

Review of the literature shows that seven studies have evaluated antiviral treatment adherence in patients with a history of drug use[90,91,96,119-122]. These studies defined adherence differently, and do not present a consensus regarding what adequate treatment adherence is. These studies defined adherence as receiving ≥ 80% of expected Peg-IFN and RBV dosage for ≥ 80% of the expected therapy duration[91,96,119,120], presentation at ≥ 80% of visitation dates[122], fulfillment of the treatment schedule and 6-mo follow-up[90], or being > 80% compliant with the planned cumulative doses of Peg-IFN, RBV and the prescribed duration of treatment[121]. One study reported that patients attending 80% of addiction care sessions demonstrated an adherence of more than 80%[91]. In this study, the consumption of crack and heroin was significantly associated with reduced compliance, with users being five times more likely not to comply. Three of the reports studied adherence in PWID on opioid substitution therapy[96,119,121]. Adherence rates of 68%[119] and 85%[96] were reported for the total population. However, when DOT and SA groups were compared, 67 and 63% of patients were > 80% compliant with Peg-IFN treatment, 50 and 54% were > 80% compliant with RBV treatment, and 67 and 63% were > 80% compliant with the prescribed duration of treatment, respectively[121]. Former drug users also demonstrate an excellent adherence to therapy[120]. In a study evaluating adherence in patients with a history of intravenous drug use, 65% of the 175 patients were considered to be adherent to therapy, as they completed the recommended treatment schedule and attended the follow-up period[90]. An adherence rate of 92% was reported in patients on heroin maintenance[122]. Only three[90,96,119] of these seven studies evaluated the relationship between adherence and the response to treatment and found that SVR rates were significantly higher in adherent patients compared to non-adherent patients. In conclusion, adherence during the antiviral treatment is associated with better treatment outcome.

Barriers for HCV antiviral management in PWID

There are barriers for HCV care and management that are present at multiple levels. At the level of government, competing national priorities can impede the healthcare system, and promote a lack of awareness of HCV infection. At the level of the clinical management team, there is often a lack of experience and collaborative networking. There is also a paucity of treatment settings adapted for the needs of PWID[123,124]. The lack of HCV knowledge and the limited infrastructure for treatment in addiction and primary care centers prevents them from treating PWID[106,125,126]. Finally, the patients themselves are an obstacle, and they may not seek treatment because of insufficient awareness of HCV, competing life priorities, fear of side effects, anxieties of being stigmatized, *etc*.[107,110,127-131].

The stigmatization of HCV patients is an important barrier to receiving HCV care, a topic which has been discussed in great detail by Treloar *et al*[132]. Patients are stigmatized because of their drug use and their HCV infection. Stigmas perceived by PWID can persist even after reducing or ceasing drug use[133], and can have a negative effect on their mental and physical health[134-138]. The stigma associated with HCV infection negatively impacts the prevention of transmission, the seeking of and adherence to treatment and the overall quality of life[137-141]. Patients can be stigmatized by family members or partners[138], the public[142] and most commonly by healthcare settings[132]. However, trust in healthcare professionals can impact health-related patient behavior, and improving this trust may reduce the associated stigmas and create a willingness to use health services and adherence to treatment[132,143].

STRATEGIES AND TREATMENT MODELS TO IMPROVE HCV CARE IN PWID

The HCV care of patients can be improved by treating comorbidities, side effects and providing all the necessary

support. A multidisciplinary approach to HCV treatment can be provided by utilizing community-based and hospital-based clinics, as well as opioid substitution treatment and drug detoxification centers[67,92,144-147]. For example, the placement of an internist addiction medicine specialist from an opioid substitution program in a hepatitis clinic proved to be an effective and efficient way to deliver HCV evaluation and treatment to patients in opioid substitution therapy[72]. A meta-analysis by Dimova *et al*[95] identified "treatment of addiction during HCV therapy" as a parameter leading to higher treatment completion[95]. Integrating HCV care into both primary addiction care and into general practices has also proved to be effective[145,148-150].

An overview on management of mental health problems in HCV patients with drug addictions by Schaefer *et al*[151] indicated that PWID do not have an increased risk of developing major or severe depression during HCV antiviral treatment with IFN. However, it is recommended to make case-by-case decisions and provide antidepressant treatment when needed, especially for patients who are depressed or have a history of depression. It was also shown that the integration of psychologist-led interventions into a hepatology unit increased HCV treatment eligibility in an underserved population with mental health and substance abuse comorbidities[152]. This trial by Evon *et al*[152] enrolled 101 HCV patients who were deferred from antiviral therapy owing to mental health or substance abuse. The integrated care intervention group received counseling and case management, including monthly phone and in-person intervention sessions with the hepatology psychologist for up to nine months. In an intent-to-treat analysis, 42% of intervention group participants became eligible for therapy compared to 18% of standard care participants. Additionally, a study by Reimer *et al*[153] found that CHC patients (infected with genotype 1/4) who attended at least five psychoeducation sessions showed significantly higher SVR rates.

The involvement of nurse educators/practitioners can greatly improve HCV management. Systematic consultations with a nurse after each medical visit enhanced treatment adherence (74.0% *vs* 62.8%) and increased SVR rates (38.2% *vs* 24.8%) compared to a conventional follow-up[154]. Psychotherapy provided by a psychiatric nurse along with administration of psychopharmacological medication in an HCV clinic can significantly improve assessment and treatment uptake[155]. A nurse-led model of HCV assessment and treatment developed by Lloyd *et al*[156] involved a substantial task transfer from specialist physicians to trained nurses. In this two-year study, 108 patients were treated, including 85 (79%) triaged for specialist review conducted by telemedicine only. Antiviral treatment delivery was found to be both safe (7% treatment discontinuations, 12% serious adverse events) and efficacious (69% SVR for those with completed datasets and 44% by intention-to-treat analysis).

Opioid substitution clinics, which provide substance abuse treatment, have begun to integrate DOT of Peg-IFN and/or RBV in collaboration with a secondary or tertiary setting that is providing the HCV care with favorable results[70,86]. Grebely *et al*[86] observed an end of treatment response in 67% of the subjects despite ongoing drug use in 75% of patients during treatment with an SVR rate of 55%[85]. An SVR rate of 98% was reported in a similar study evaluating the efficacy and tolerability of DOT with Peg-IFN and RBV in 49 opioid-addicted injection drug users[70].

Other models of HCV treatment incorporating peer support and group treatment are very effective. In these models, peers stimulate each other in developing positive and healthy behaviors, and have been shown to increase the assessment and treatment of HCV[67,157-161]. The group treatment model used by Stein *et al*[157] was found to be acceptable by all patients, and no patient expressed discomfort with receiving medical care in a group setting. Of the first 27 patients who initiated the group treatment, 42% achieved an SVR. Results from the nonprofit community clinic OASIS indicate that the peer-based model is successful at engaging, educating and treating a diverse spectrum of chaotic drug users[161]. This model allowed for successful treatment of more challenging HCV patients, including those with active drug use, mental illness and psychosocial instability. In a clinic with only one physician and one or two physician assistants, almost 3500 people were tested and several hundred were treated. The peer-based models show encouraging results not only in assessment and treatment but also in the prevention of HCV[162-164].

Current knowledge suggests that as no one model meets all the needs of a heterogeneous patient population, offering a range of various settings is the best way to reach the greatest needs of PWID. Close collaboration of all involved health professionals is crucial for every model to be successful. Furthermore, acceptance of the individual circumstances of PWID will determine the level of success of any model of HCV management, rather than rigid exclusion criteria[158].

COST-EFFECTIVENESS OF HCV MANAGEMENT IN PWID

As the majority of new HCV infections occur in PWID, successful screening and treatment of this population will prevent new cases and lower costs associated with disease progression[165-167]. Martin *et al*[167] determined that HCV case finding among PWID by offering dried blood spot testing in specialist addiction services or prisons as compared to using venipuncture was cost-effective. However, the cost-effectiveness of prison case-finding interventions depends on adequate continuity of care with the community after release from prison. Another modeling study by this group explored the feasibility of DAA-based HCV treatment as prevention and indicated that scaling-up treatment could lead to substantial reductions in HCV prevalence[166]. However, the cost of treatment may limit its scaling-up, thus, treatment cost also needs to

be addressed.

HCV IN CORRECTIONAL SETTINGS

The prevalence of HCV is much higher in prison inmates than in the general population, ranging from 30%-40%[168]. Furthermore, there is a clear association between the HCV prevalence and inmate history of injection drug use, sex (female) and tattooing[169]. Thus, prisons may be important settings for health intervention such as screening, diagnosis, prevention and treatment of HCV infection. Screening rates could be improved in correctional settings with the introduction of dried blood spot testing[170]. SVR rates for prison patients treated with a combination therapy are comparable to those observed in non-inmate patients, therefore, antiviral treatment in prison may be cost-effective[171]. Prevention and treatment could also be improved if more programs were developed to ensure continuity of care and follow-up upon release or transfer from prisons[172].

REINFECTION AFTER SUCCESSFUL HCV TREATMENT

Frequent testing and viral sequencing are necessary to discriminate between relapse and reinfection in high-risk populations. Guidelines recommend monitoring for HCV reinfection with annual HCV RNA assessments in PWID with ongoing risk behaviors[5]. As ongoing injection drug use after treatment is common, harm reduction and counseling about the risk of reinfection is important[173]. However, rates of HCV reinfection among PWID is low, at approximately 1%-5%[173], even among persons who continue injection drug use during and after treatment. A recent meta-analysis by Aspinall *et al*[115] reported that the pooled HCV reinfection risk was 2.4 per 100 person-years, suggesting that HCV treatment should not be withheld due to concerns about reinfection alone. Moreover, HCV reinfection after treatment may clear spontaneously[173].

PREVENTION OF HCV TRANSMISSION

HCV prevention strategies in PWID have been described in detail by Page *et al*[174] who state that it is essential to promote access to sterile injection materials (increased needle/syringe distribution) in combination with strategies to encourage injection cessation, opioid substitution treatment, interventions to reduce risk behaviors, rapid and accurate HCV testing and diagnosis and increased access and initiation of HCV treatment. The impact and feasibility of treatment as a prevention strategy could be substantially increased by future IFN-free DAA treatment regimes with enhanced efficacy (> 90%), once-daily oral-only dosing, reduced toxicity and shortened treatment duration (about 12 wk)[175].

IMPROVEMENTS IN HCV CARE FOR THE FUTURE

There are several changes that can be made to improve the treatment and management of HCV care. Firstly, patients should be treated irrespective of their liver fibrosis stage, which is not the case at this moment in many countries, as a fibrosis stage of at least F2 is a prerequisite to obtain antiviral treatment. Secondly, the risk of reinfection should be an indication for treatment, as people at risk of reinfection are also the ones most likely to further spread the virus. Thirdly, treatment could be increased among PWID by decriminalizing drug use and reducing other barriers to HCV care, such as high treatment costs[176].

Only five countries offer systematic annual screening for infectious diseases to all PWID according to the European Liver Patients Association, and only two countries have governmental funding for a national hepatitis strategy[177]. Thus, systematic screening for HCV infection in PWID needs to be developed. Oral IFN-free regimens are approaching 100% efficacy, but real world effectiveness will remain very low without fundamental change in health care delivery[177]. An increase in instrumental support provided by healthcare professionals is needed. As suggested by the Global Commission on Drug Policy, the war against drugs must be substituted with "drug policy success measurement" indicators that have real meaning in communities, such as reduced rates of HCV infection, fewer overdose deaths, reduced drug market violence, fewer individuals incarcerated and lowered rates of problematic substance abuse[7].

CONCLUSION

PWID are the major reservoir for infectious HCV, and as a result, an increase is expected in compensated and decompensated liver disease and hepatocellular carcinoma in this population. At the end of the nineties, PWID were excluded from antiviral therapy in official guidelines, but nowadays there is incontrovertible evidence supporting treatment of these patients. The guidelines recommend that these patients be considered on an individualized basis for antiviral therapy and that therapy should be provided within a multidisciplinary team setting. Indeed, HCV clearance has recently become a major endpoint in the war against drugs for the Global Commission on Drug Policy.

Although the outcome of antiviral treatment and treatment compliance in PWID is comparable to non-PWID, there are still several barriers to accessing care. By understanding the barriers to and facilitators of HCV care, the proportion of PWID assessed and treated for HCV is being increased. HCV screening has been facilitated by noninvasive methods for detecting HCV antibodies and stage of liver fibrosis. Treatment has been

facilitated by implementing various strategies and models of HCV care that include the integration of psychologist-led interventions, involvement of nurse practitioners and DOT and peer support models. Despite the high prevalence of HCV-infected patients and the favorable outcome of antiviral treatment in custodial settings, the uptake for HCV management needs to be increased substantively. Eligibility of recently active PWID for treatment in combination with needle exchange programs and substitution therapy can help to prevent the spread of HCV in the PWID community. Although HCV screening and treatment in PWID is shown to be cost-effective, the assessment of PWID for antiviral treatment remains low. Despite the irrefutable evidence in favor of treating PWID, the management of their care has yet to be initiated in some countries, and optimized in many others.

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