

Factors associated with uptake, adherence, and efficacy of hepatitis C treatment in people who inject drugs: a literature review

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Introduction and methods: Hepatitis C virus (HCV) infections are highly prevalent amongst people who inject drugs (PWID). Despite well documented evidence of its effectiveness, suggested cost-effectiveness, and potential to reduce HCV prevalence rates, the uptake of antiviral HCV treatment by PWID is low. This nonsystematic literature review describes factors associated with the uptake, adherence, and efficacy of HCV treatment among PWID and discusses strategies to increase their uptake of treatment.

Results: Low HCV treatment uptake among PWID is associated with a number of patient-related and provider-related barriers. Beliefs and fears about low efficacy and adverse effects on the patient's part are common. A substantial number of factors are associated with the chaotic lifestyle and altered social functioning of PWID, which are often associated with decompensation or relapsing into drug addiction. This may lead to perceived low adherence with treatment and low efficacy on the provider's part too, where lack of support, inadequate management of addiction, and other drug-related problems and poor treatment of side effects have been described. Practical issues such as the accessibility of treatment and finances also play a role. Strategies to improve the HCV treatment rate among PWID involve pretreatment management and assessment, a multidisciplinary approach, management of side effects, and enhanced education and counseling.

Conclusion: Specific factors are associated with poorer treatment outcomes in PWID on the side of both the patient and the treatment system. However, given that PWID can achieve treatment adherence and sustained virologic response rates comparable with those in nondrug users, drug use per se should not be considered a criterion for exclusion from treatment. Further development of measures leading to higher uptake of treatment and adherence in PWID and appropriate adaptation of HCV treatment guidelines represent important tools in this regard.

Keywords: hepatitis C virus, people who inject drugs, treatment uptake, adherence, efficacy

Introduction

With more than 185 million people infected worldwide, hepatitis C is a global public health concern.¹⁻³ While iatrogenic exposure, such as unsafe therapeutic injecting practices, is responsible for the majority of hepatitis C virus (HCV) transmissions in developing countries, injecting drug use is the predominant risk factor in Western industrialized cultures.⁴⁻⁷ The prevalence of HCV antibodies among people who inject drugs (PWID) varies between countries, with the rates being from 40% to 90%.⁸⁻¹⁰ Worldwide, between 6 and 15 million PWID are infected with the virus,⁹ and with around 350,000 deaths per year, HCV is an increasing cause of morbidity and mortality.¹¹

Despite the fact that PWID represent the majority of HCV-infected individuals in developed countries, their uptake of treatment is generally considered to be low.¹²⁻¹⁵

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This nonsystematic literature review focuses on uptake of HCV treatment, as well as adherence with it and efficacy of treatment in PWID, and identification of associated factors. Following that, strategies for augmenting the uptake of HCV treatment are reviewed and discussed.

Clinical aspects and natural course of HCV infection

The course of acute HCV infection is variable and in most cases asymptomatic. As a result of the mainly unspecific, often fatigue-like or flu-like symptoms, early detection and assessment of HCV infection remains a challenge, especially given that not all patients show elevated transaminases. In acute infection, spontaneous eradication of the virus is possible; clearance is reported for 20%–50% of those who are infected.^{16–18} A number of host and virus factors have been described as predictors of spontaneous HCV clearance, such as host genetics (IL28B genotype, HLA type), female sex, nonblack ethnic origin, an innate and adaptive robust immune response, virus-specific neutralizing antibodies, HCV genotype, chronic hepatitis B virus (co)infection, and human immunodeficiency virus-negative status.¹⁹

In the absence of spontaneous clearance within 6 months, HCV infection is considered to be chronic, leading to liver cirrhosis in 8%–45% of infected individuals.^{20,21} Similar rates have been found in a recent meta-analysis of 47 published papers, in which the estimated rate of progression to cirrhosis in PWID was 8.1 per 1,000 person-years, which corresponds to a mean estimate of 14.8% in 20 years.²² Cirrhosis can result in hepatic decompensation and liver cancer, with a peak incidence at around 30 years after infection.^{11,21,23} This signifies that individuals who were infected with HCV in the 1970s and 1980s are now at high risk of HCV-related liver disease and mortality.²⁴ It is therefore of vital importance to increase treatment uptake in order to reduce the number of liver disease-related deaths.

HCV prevention and treatment options

To begin, we review the options for HCV prevention and how these are relevant to treatment uptake and efficacy. There is a very high genetic variability of HCV, with six main genotypes and 80 subtypes. This variability is the main reason for the difficulties encountered in development of a vaccine, because it must be effective in all genotypes. The genetic variability is of clinical significance regarding treatment efficacy. Rates of sustained virologic response, assessed 6 months after the end of treatment, range between 45% and 54% in

HCV genotype 1 and between 65% and 82% in genotypes 2 and 3, with a slightly higher sustained virologic response in genotype 2.^{25–28} This has led to different durations of treatment depending on the virus genotype, ie, 24 weeks for genotypes 2 and 3, and 48 weeks for genotypes 1 and 4.^{6,29,30} Shorter or longer treatment regimens adjusted to the patient's individual viral response can be used.^{31–33} Thus, greater treatment efficacy can be achieved through the individualization of treatment regimes. The most reliable predictor of the efficacy of treatment is measurement of viral kinetics in the first 12–24 weeks of treatment. Negative HCV-RNA in week 4 indicates a high chance of a sustained virologic response. On the contrary, if the decrease in HCV-RNA in week 12 (early virologic response) is lower than $2\log(10)$, the probability of a sustained virologic response is only 0%–3%.^{34,35} Other important predictors of the efficacy of treatment, besides HCV genotype, are genetic polymorphism in IL28B and the stage of liver fibrosis.^{28,36}

There is substantial evidence that opiate substitution treatment reduces the risk of HCV transmission among PWID,^{37,38} and a further risk reduction can be achieved by simultaneous participation in needle and syringe programs and opiate substitution treatment.^{39,40} Nonetheless, data on the effectiveness of opiate substitution treatment and needle and syringe programs for primary prevention of hepatitis C infection and subsequent modeling show that these interventions do not necessarily lead to substantial reductions in HCV prevalence. Statistical modeling for both interventions (40% baseline chronic HCV prevalence) shows that they are unlikely to considerably reduce chronic HCV prevalence after 10 years unless the intervention coverage is increased by over half, being up to 80% in opiate substitution treatment and 100% in needle and syringe programs.^{41,42}

Interestingly, recent modeling analyses show a strong preventive potential of HCV treatment in PWID, since the risk of HCV transmission decreases with lower HCV prevalence.^{43,44} This primary prevention effect of HCV treatment is larger in populations with a lower baseline HCV prevalence.^{45,46} Even for low treatment rates, a large reduction in HCV at the population level can be achieved.⁴⁷ In addition, statistical modeling suggests that HCV treatment of active injecting drug users is the most cost-effective policy option when chronic HCV prevalence among PWID is below 60% (about 80% antibody prevalence). This effect remains stable even if the sustained virologic response in active injecting drug users is half of that found in non/ex-users.⁴⁸ Furthermore, it has been estimated that HCV treatment in all infected patients in 2010 could

reduce the risk of cirrhosis, liver decompensation, cancer-related, and liver-related deaths by 16%, 42%, 31%, and 36% in the course of 20 years, respectively.²¹ In conclusion, the evidence suggests that increasing treatment uptake by active users may be an effective method of reducing the carrier pool and preventing spread of the virus.

Treatment uptake and barriers

In order to increase treatment uptake, it is important to understand the current barriers to recruitment into treatment. They can be categorized as system-related, patient-related, and provider-related factors.

Different studies point towards a higher potential for treatment uptake within specific referral settings. These are considered system-related factors. A high HCV treatment uptake rate of approximately 20%–30% was found among active PWID referred to an HCV treatment clinic, who were receiving opioid replacement treatment, peer support, and/or multidisciplinary care.^{49–52} An even greater uptake of HCV treatment (76%) was reported among PWID to whom HCV treatment was offered and who were eligible on the basis of positive HCV RNA.⁵³ On the other hand, when PWID are systematically excluded from HCV treatment because of active or recent drug use, uptake is low. This is evident in Budapest, Hungary, and Bratislava, Slovakia, where abstinence stipulated as a prerequisite for HCV treatment in national guidelines or health insurance schemes represented a considerable barrier to uptake of treatment.^{54,55} Nevertheless, studies show that the uptake and success of treatment can be achieved in spite of active or recent drug use. In an Amsterdam-based cohort, 30% of HCV-infected drug users started treatment, although almost all had used illicit drugs 6 months before treatment, 19% were actively injecting, 62% used alcohol, and 41% suffered from psychiatric comorbidity. From the 58 patients recruited into treatment, 57 had sufficient adherence and 37 (65%) achieved a sustained virologic response.⁵⁰ Similarly, a Canadian study reported a high treatment uptake rate (51%) and a high sustained virologic response rate (67%) despite ongoing drug use during treatment in 75% of the patients.⁵⁶ Clinicians can adopt a harm reduction approach and tolerate illicit drug use during treatment as long as the therapeutic regime is adhered to.⁵⁷ Thus, treatment of active drug users is possible, and active drug users can achieve high levels of uptake of treatment, as well as adherence with it. On the other hand, external factors that stigmatize, discriminate against, or even police drug users represent substantial barriers to uptake of treatment and adherence with it.^{58,59}

HCV treatment uptake is further affected by patient-related factors, ie, barriers to treatment as experienced by PWID. The low treatment uptake rate (6%) among HCV-infected drug users in Baltimore, MD, USA, was associated with treatment-related perceptions and a low perceived need for treatment.¹² A lack of motivation may also be responsible for a low treatment uptake rate.⁵⁵ Human immunodeficiency virus coinfection can reduce the uptake of treatment and adherence with it, as well as the efficacy of treatment.^{60,61} Adverse effects of HCV treatment may also hamper uptake and adherence, although new medication increases the efficacy of treatment. The current standard treatment for chronic HCV infection is a combination of pegylated interferon α (PEG-IFN) and ribavirin. In 2011, two directly acting antivirals, ie, the protease inhibitors telaprevir and boceprevir, were introduced for the treatment of HCV genotype 1 in combination with PEG-IFN and ribavirin. Adding either of these medications to PEG-IFN and ribavirin leads to higher sustained virologic response rates compared with standard dual treatment (up to 75%), although with a possible higher rate of adverse effects, such as rash or anemia, and with higher treatment costs. Moreover, new directly acting antivirals administered in interferon-free regimens for a shorter duration and show higher efficacy, better tolerance, and fewer side effects, should be available in the near future.^{62–64} Interestingly, in this context, a positive effect of modest cannabis use in reduction of side effects of HCV treatment, higher adherence, and a higher sustained virologic response has been reported.^{57,65}

Finally, providers are often reluctant to provide HCV treatment to active injecting drug users.^{66,67} One of the clinician-related barriers to treating PWID is fear of relapse into drug injecting and consequent HCV reinfection after successful HCV treatment. For example, 75% of clinicians treating HCV in the Czech Republic preferred nonusers to active drug users for inclusion in treatment, which was even more relevant when financial limitations on treatment were reported by 60% of treatment centers.⁶⁸ However, a persistent, sustained, virologic response rate and a low reinfection rate of 3%–5% were found, even in those who continued or relapsed into drug injecting.^{69,70} These findings support the assumption of a low reinfection rate in PWID after a sustained virologic response, even if they continue to inject drugs.⁷¹

Treatment adherence and efficacy

One of the most important reasons for low HCV treatment uptake in PWID is the assumption of reduced adherence with the treatment regimen leading to poorer treatment outcomes, although the relationship between adherence and outcome

seems to be complex.⁷² Nonadherence in HCV treatment may refer to both dose reduction and early discontinuation of treatment, with the latter probably having a stronger impact on reduced sustained virologic response.^{73,74} Contrary to expectations, PWID do not differ from nondrug users in their adherence to treatment (eg, for tuberculosis, acquired immune deficiency syndrome, and hepatitis B virus vaccination), with rates ranging between 30% and nearly 100%. In programs specifically designed for drug users, adherence often exceeds 80%.⁷¹ The following studies exemplify that PWID can attain high treatment adherence, treatment completion, and sustained virologic response in spite of a number of factors typically associated with low adherence and discontinuation of treatment.

A cohort study of treatment-naïve patients in Belgium and the Netherlands reported comparable high HCV treatment completion rates in both drug users (91.8%) and nondrug users (93.2%). Sustained virologic response rates in PWID/noninjecting drug users were around 40% and did not differ significantly after adjustment for HCV genotype.⁷⁵ Likewise, a French cohort study demonstrated a similar sustained virologic response in active drug users and patients on opioid substitution treatment (58%) as compared with former (51%) and nondrug users (49%), despite a more chaotic lifestyle and higher rate of psychiatric comorbidity.⁷⁶ Moreover, in a prospective study comparing sustained virologic response rates in four groups (patients without a history of psychiatric disorders or drug abuse, psychiatric patients, opioid-substituted patients, former drug users), an overall sustained virologic response rate of 58.6% was found. Sustained virologic response was only associated with genotype and not with patient group, psychiatric diagnosis, depression, antidepressant treatment, sex, or liver enzymes before treatment.⁷⁷ In addition, a high sustained virologic response (86% in genotype 1 and 100% in genotype 3) in former drug users has been associated with excellent adherence, young age of the patient, early start of HCV treatment, and with a low stage of liver fibrosis.⁷⁸ Perhaps most significantly, high completion (92%) and sustained virologic response rates (69%), comparable with those in nondrug-user populations, were also achieved in a well defined sample of comorbid severely opioid-dependent subjects on heroin maintenance treatment. This stresses that, within a needs-adapted treatment setting, HCV treatment may even be extended to difficult-to-treat opioid-dependent patients.⁷⁹ The findings of these individual studies are confirmed by recent systematic reviews. Sustained virologic response in drug users (mean rate 54.3%; range 18.1%–94.1%) was

found to be comparable with that among non/ex-users (54%–63%), although the efficacy of treatment was found to be lower in drug users with acute HCV, ie, sustained virologic response in drug users of 68.5% versus 81.5% in nonusers.⁸⁰ Similarly, a high pooled sustained virologic response rate among drug users of 55.5% (95% confidence interval 50.6%–60.3%) was found in another review, together with a high completion rate of 83.4% (95% confidence interval 77.1%–88.9%), which was higher in addiction-treated patients and in those receiving support services during antiviral therapy.⁸¹

In contrast, some findings indicate lower treatment adherence and efficacy in drug users as compared with former or nondrug users. This is often associated with altered social functioning, a chaotic lifestyle, and continuation or relapse into drug use. For example, in an Australian sample that consisted predominantly of PWID with recently acquired HCV infection, sustained virologic response (overall 55% by intention-to-treat) was negatively associated with reduced social functioning, current opiate pharmacotherapy, and lower adherence, ie, 29% in nonadherent versus 63% in adherent with 80% or more PEG-IFN doses in 80% of the treatment duration.^{53,82} In San Francisco, CA, USA, although 68% adherence with HCV treatment was observed in drug users on methadone maintenance treatment, the adherence rate was associated with a sustained virologic response (42% in adherent versus 4% in nonadherent patients). Moreover, adherence was lower in patients without a period of abstinence before starting HCV treatment and in those who relapsed into drug use during treatment.⁸³ HCV treatment failure has also been associated with liver cirrhosis, depression, and active injecting drug use.³⁶

From this abundance of studies, it is evident that a large number of factors can affect treatment adherence and efficacy in PWID. These findings support the suggestion that the decision regarding inclusion or exclusion of PWID from HCV treatment should be taken on an individual basis for each patient.⁷¹ Factors that are potentially associated with lower uptake, adherence, and efficacy of treatment in PWID on the patient's side, as well as on the side of treatment professionals and the treatment system, are described in Table 1.

Strategies to overcome barriers to HCV treatment

Treatment guidelines play a crucial role in initiation of therapy, because they define the current standard of care and provide recommendations on financial coverage by health insurance schemes. In 2005, a systematic literature review of HCV

Table 1 Patient-related, provider-related, and system-related factors associated with lower uptake, adherence, and efficacy of HCV treatment in PWID

Patient-related factors ^{12,53,61,89,90,104,105}	Provider-related factors ^{56,87,89,90,104}	System-related factors ^{12,54–56,58,59,68,87,89}
<ul style="list-style-type: none"> • Chaotic lifestyle and altered social functioning • Psychiatric comorbidity and depression • HIV coinfection and parallel antiretroviral treatment • Decompensating and relapse into illicit drug use • Lack of information on HCV infection and treatment • Perceived low efficacy of HCV treatment • Fear of diagnosis, treatment procedures and side effects • Financial problems and problems with transportation to visits 	<ul style="list-style-type: none"> • Presumption of low adherence • Concerns regarding relapse and reinfection • Lack of information and counseling for drug users • HCV treatment not regarded as “core business” of drug services • Lack of multidisciplinary approach and team composition • Poor management of side effects 	<ul style="list-style-type: none"> • Lack of integration of addiction treatment and HCV treatment • Formal high-threshold criteria for treatment • Referral-associated delays • Gaps in health insurance schemes and budgetary limits of care • Stigmatizing and discrimination against drug users

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; PWID, people who inject drugs.

treatment guidelines in the “old” European Union countries and Norway was performed with regard to criteria for inclusion of drug users into treatment.⁸⁴ The authors found considerable differences between countries, ranging from clear disapproval of treatment or the absence of any specific guidelines to recommendations for treatment under specific conditions (eg, a specified period of abstinence from drug use). Only the guidelines in France clearly stressed treatment of active drug users. Given that this review is 8 years old, one might assume that the inclusion criteria in national recommendations have been developed further in the meantime.⁸⁴ However, the current European guidelines still appear rather inconclusive in terms of active drug users.^{28,85} Given the strong evidence in support of the benefits and effectiveness of treating HCV-infected PWID, clear recommendations that tolerate drug use rather than excluding PWID from treatment should be followed.⁸⁶

Naturally, not all HCV-infected PWID are suited to treatment. Pretreatment management and assessment of patients is often used as a measure to manage factors that influence adherence, such as depression, and is also used to test for compliance and clinic attendance.^{68,77} As previously discussed, a wide range of patient-related factors can have an impact on adherence with treatment and its efficacy. Several of these have been associated with sustained virologic response in some studies but not in others. Because of the complexity of factors related to adherence and the efficacy of treatment, clinicians should decide about recruitment into treatment on an individual basis. A future challenge will be to provide guidelines and standardized scales to help clinicians make these individualized assessments more effectively.

With a multidisciplinary approach, potential barriers to recruitment and follow-up of treatment can be addressed

effectively. Multidisciplinary teams may consist of addiction specialists, infectious diseases specialists, primary care physicians, nurses, counselors, researchers, and other health or social workers and, if necessary, referral to other professionals outside the treatment center team can be offered.^{12,50,56,68,87–89} A multidisciplinary approach is best applied in a “one-stop-shop” model where various treatments and counseling services are offered in one center. Integrating drug treatment and treatment of HCV (and eventually also human immunodeficiency virus or tuberculosis) in the same center can increase uptake and adherence with therapy.^{56,90–93} HCV counseling, testing, and treatment interventions may be incorporated into drug treatment services with inpatient treatment and opioid substitution programs, because they are more likely to offer HCV services than outpatient and drug-free programs.^{94–96} As different treatments are offered together, clinicians should take into consideration the interactions between therapies for hepatitis C and other medication.

Offering medical and mental health services in addition to drug and HCV treatment can help manage the adverse effects of HCV treatment, thereby lowering the barriers to uptake and adherence. A multidisciplinary team may address psychologic side effects, such as depression and emotional lability, or somatic complications, such as hemolytic anemia.⁹⁷ Thus, the success of HCV treatment will depend on the collaboration of experts from various fields to create treatment programs specifically designed for drug users.

Finally, a crucial strategy in overcoming barriers to uptake of HCV treatment is education. Public campaigns, such as the one run for acquired immune deficiency syndrome in the 1990s, are essential to improve knowledge and eliminate

misconceptions regarding HCV on both the patient's and the provider's side. Australia set an example in this regard. In 2000, a mass media campaign was run and successfully increased public knowledge about the means of transmission of HCV.⁹⁸ Furthermore, it is important to educate people about the availability of HCV screening and treatment and to make these and other services widely available. For instance, research shows that when sterile syringes are easily accessible, PWID readily make use of them.^{99–101} Education could thus also increase HCV screening for individuals with acute HCV. Early treatment uptake is important because the spontaneous clearance rate is limited and, in contrast with chronic HCV, treatment of acute HCV leads to much higher clearance rates¹⁰² within a shorter period of time.^{17,103} This also applies to PWID.⁸² If drug users were aware of this advantage, they might be more likely and more frequently willing to get tested and thus enable detection of HCV infection at an early stage.

Conclusion

HCV infection is an important cause of morbidity, mortality, and related social costs. In developed countries, injecting drug use represents the main route of HCV transmission and yet treatment uptake is low among drug users. HCV treatment has been shown to be efficient in terms of viral clearance and with regard to its potential to prevent further HCV transmissions in the population. The uptake and efficacy of treatment are therefore an important public health issue. Factors associated with poorer treatment outcomes in PWID have been identified on the part of patients, providers, and treatment systems. However, the literature suggests that PWID can achieve treatment adherence and sustained virologic response rates comparable with those of nondrug users. Therefore, drug use per se should not be considered a criterion for exclusion and treatment should be initiated on the basis of an individual assessment of each drug user. Further development of measures leading to higher uptake of treatment and adherence with it, along with appropriate adaptation of treatment guidelines, represent important tools in this regard.

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Author contributions

VM and BS contributed to the concept and design of the review. VM, BS, LS, JS, VB, TG, and JR participated in

identification of the data sources and analysis and interpretation of the findings. VM, BS, LS, JS, VB, TG, and JR contributed to drafting the manuscript. All the authors read and approved the final manuscript.

Disclosure

The authors have no competing interests in this work.

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