

# Treatment for hepatitis C virus and cannabis use in illicit drug user patients: implications and questions

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**Illicit drug users are the primary risk group for HCV transmission, and will form the largest HCV treatment population for years to come. Sylvestre *et al.*'s study suggests that cannabis use may benefit treatment retention and outcomes in illicit drug users undergoing HCV treatment. In fact, there is substantial evidence that cannabis use may help address key challenges faced by drug users in HCV treatment (e.g., nausea, depression), especially when such treatment occurs in the context of methadone maintenance treatment which may amplify these consequences. While further research is required on the biological and clinical aspects of the benefits of cannabis use for HCV treatment, and the effectiveness of cannabis use for HCV treatment needs to be explored in larger study populations, we advocate that in the interim existing barriers to cannabis use are removed for drug users undergoing HCV treatment until the conclusive**

Sylvestre and colleagues [1] present a small yet highly interesting prospective observational study of a sample of hepatitis C virus (HCV)-infected substance users undergoing interferon/ribavirin combination treatment in the context of methadone maintenance treatment (MMT). Their analyses showed that those patients who used cannabis during the course of treatment were significantly more likely to indicate adherence to HCV treatment and, consequently were more likely to achieve a sustained virological response than cannabis non-users in the sample.

Clearly, a multi-variate analyses would have strengthened Sylvestre *et al.*'s [1] inquiry, and allowed for a rigorous examination of the specific contribution of cannabis use to the observed treatment effects. While the small sample size did not allow for a simultaneous control of all potentially influencing factors, it would have allowed for the inclusion of possible key determinants (e.g. HCV genotype, which was unequally distributed in the sample). Despite this methodological limitation, the positive findings of this study as presented raise a number of important questions and possible implications for HCV treatment practice and policy as these currently unfold across established market economies. Overall, numerous modeling exercises have projected that the burden of HCV morbidity and mortality consequences will continue to rise over the next 20 years in North

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America, Australia and elsewhere [2–4]. Today, the majority of HCV-infected individuals in these jurisdictions are former or active drug users; more importantly, drug use-related risk behavior is causally responsible for the majority of new cases of HCV transmission [5,6]. For example, most recent data from British Columbia, Canada, indicate that more than four out of five incident HCV transmissions are illicit drug use related [7]. In other words, the future reduction of HCV-related burden of disease – besides more effective prevention – will need to include effective and adequate HCV treatment provision to former or current drug users [8,9]. As amply discussed, this poses a number of distinct challenges regarding the specific behaviors and needs of this specific patient population, with key implications for treatment delivery and practice.

Until a few years ago, treatment guidelines categorically excluded active illicit drug users from consideration for HCV treatment [10,11]. The main reasons for this approach were that drug users' lives were considered too unstable to comply with the lengthy and demanding HCV treatment regimen because of high susceptibility to the potential severe side effects of treatment (e.g. depression) and potentially ongoing drug use as too large a risk for re-infection with HCV. Partly on the basis of a number of HCV treatment studies with drug user patients [12,13] – indicating good treatment

feasibility and outcomes comparable to general community samples – these categorical norms have been gradually softened and revised in many jurisdictions. As a result of the high costs of, and the limited resources for, HCV treatment, however, the drug user patient pool is only slowly and sporadically being embraced by HCV treatment providers [8,9]. This status quo provides a timely opportunity to empirically explore the specific means and approaches facilitating best possible HCV treatment courses and outcomes for this specific target population.

So how might cannabis use specifically be helpful in facilitating HCV treatment delivery and outcomes in illicit drug user populations? A number of possible reasons and effect points exist, some of which may lie behind the results of Sylvestre *et al.* [1]. Of primary importance is the fact that interferon-based HCV treatment in many instances brings with itself a variety of intensive and severe side effects, the main ones including nausea/vomiting, weight loss, sleeplessness and depressive symptoms [14–19]. These side effects are the rule rather than the exception of HCV treatment patient populations, and contribute to the fact that patients in HCV treatment typically indicate significantly lowered Quality of Life scores compared with general populations, or even with HCV-infected individuals before commencing therapy [20,21]. Furthermore, these side effects are a main reason for compromised compliance with the HCV treatment regimen – for example, expressed by patients refusing to take their medications – or even a premature termination of treatment. Importantly, however, several distinct factors may amplify the severity and impact of the described side effects of HCV treatment, specifically in illicit drug user patients. Most users present generally and chronically compromised physical health conditions, and specifically struggle with problems such as nausea, malnutrition and/or insomnia as effects related to their drug use or withdrawal [22–24]. In addition, the prevalence of depressive symptoms in illicit drug user populations is – even without the influence of HCV or its treatment – highly elevated: for example, 40–60% of illicit opioid user populations indicate such mental health symptoms, rendering them highly susceptible to an aggravation of these problems once undergoing interferon therapy [25,26].

Although often described as ‘anecdotal’ or ‘inconclusive’, a fairly large body of research, nevertheless, has provided substantial evidence that the so-called ‘medicinal properties’ of cannabis may offer considerable utility in providing coping, supportive or therapeutic effects for the above-listed side effects of HCV treatment [27–29]. For example, a series of studies have resulted in the conclusion that cannabis is an ‘effective anti-emetic’ substance ([30]: p. 107), an effect that is primarily used in countering the effects of chemotherapy for cancer

patients. Further studies have indicated that ‘smoking marijuana inhibits nausea, improves appetite, reduces anxiety, relieves aches and pains [and] improves sleep’, especially in AIDS patients struggling with the side effects of highly active anti-retroviral therapy (HAART) treatment – which in many respects are very similar to interferon therapy for HCV – and that it ‘may have anti-depressant properties’ ([30]: p. 110). Specific studies on the role of cannabis use on adherence to HAART have hence concluded that medicinal cannabis use is ‘very effective’ in countering these undesirable effects and in facilitating treatment adherence ([31]: p. 1919). These observed benefits have been the reason why – besides terminal cancer patients – AIDS patients have become the other main patient group that is permitted access to government sponsored medical cannabis provision in jurisdictions where such programs exist [32].

Several recent studies have suggested that a pragmatic and beneficial way to deliver HCV treatment to illicit (e.g. opioid) drug users may be to ‘embed’ this therapy into MMT or other forms of opioid maintenance treatment [9,12,33]. The benefits of this are on the one hand related to the mechanics of ‘one-stop-shopping’: that is, patients receiving their HCV drugs when picking up their daily methadone dose – akin to a directly observed therapy setup – while at the same time utilizing MMT’s effect of reducing risky drug use and possible HCV re-exposure if the virus is cleared [34,35]. While MMT structure and routine may aid HCV treatment adherence, an often-ignored fact is that for many opioid users, the experiences of methadone are very similar to the undesirable side effects of interferon intake: Qualitative studies with MMT patients have described the effects of methadone as numbness, bone aches, loss of energy and drive, and depression [36–38]. While embedding HCV treatment care into MMT may help to ‘anchor’ HCV patients in treatment care routines, the distinct pharmacological effects of methadone may add to or intensify the – already rather unpleasant – side effects of interferon treatment. Hence, the described possible therapeutic effects of cannabis use providing relief for these symptoms may be of principal importance and benefit for the distinct needs of illicit drug users undergoing HCV treatment care in the particular context of MMT. Overall, cannabis use may thus even offer dual benefits, in facilitating adherence to both MMT and HCV treatment in the HCV-infected drug user, and thus contribute to public health benefits related to both these interventions.

Of course, concerns do exist about the possible risks and harmful effects that cannabis use may have on the drug user patient undergoing HCV treatment care. The main negative effects of long-term regular cannabis use are its potential pulmonary (carcinogenic) effects, a possible amplification of psychiatric episodes (i.e. schizophrenia),

dependence and psychomotor functions impairment (e.g. for driving) [39,40]. It can, however, be assumed that most patients undergoing HCV treatment and conjointly using cannabis will have been cannabis users before commencing HCV therapy, and hence are not initiating such use as a complementary activity. Yet even if this was the case for some patients, the potential benefits of a higher likelihood of treatment success appear to outweigh the risks, especially given the already high-risk profile of the target population.

Another relevant consideration is that cannabis use can influence cellular and humoral immunity. Most available data on this issue, however, originate from animal and in-vitro experiments, leaving questions about the implications for humans unanswered. On the one hand, immuno-depressive effects have been attributed to cannabis, which might be amplified by immuno-depressive effects of interferon- $\alpha$ , thereby possibly compromising adherence to HCV-treatment [41]. These effects are of a most critical concern in HCV/HIV co-infected individuals, where the immune system may be heavily destabilized. On the other hand, the antiviral action of interferon- $\alpha$  might be boosted by antiviral activity of cannabis, which could result in the favorable sustained virological response rates in cannabis users as observed in the studies by Brassard *et al.* [42] and Grotenhermen [43]. Finally, there should perhaps be a word of caution about the potential consequences of intensive marijuana use in individuals with chronic hepatitis C. A recent – although retrospective – study suggests that regular long-term marijuana use may promote hepatic fibrosis [44]. Indeed, drugs that block cannabinoid receptors are now being evaluated for their effect on reducing hepatic fibrosis [45].

Considering the evolving epidemiology of HCV – with illicit drug use being the increasingly main causal factor of new transmissions – the need to effectively attract HCV-infected drug users into treatment and the potential role of cannabis use in facilitating treatment adherence and hence aiding in producing successful HCV treatment outcomes, we make two major recommendations. First, larger and optimally rigorous (e.g. randomized controlled or matched) clinical trials need to be conducted to empirically ascertain the specific role of cannabis use on impeding or facilitating the ‘dynamic, complex and multi-dimensional’ process ([31]: p. 1906) of adherence specifically to HCV therapy, as well as to assess possible interactive effects. Secondly, even before such effects are conclusively established, those HCV treatment patients – and this should not be limited to those with an illicit drug use history – desiring to aid their treatment adherence by cannabis use should be legally permitted in doing so. This suggestion is particularly relevant as it is challenging for jurisdictions where the personal use of cannabis is currently prohibited by (criminal) law; for

example, the United States and Canada. While Canada and 11 US states have active medicinal marijuana access programs, receiving legally sanctioned permission to use marijuana under these programs’ auspices is a rather difficult and bureaucratic venture, and limited to relatively small numbers of patients. Equally important, medicinal marijuana access programs to date have principally specified AIDS (i.e. wasting) and cancer treatment (i.e. chemotherapy) symptoms as acknowledged medical indications for program eligibility, and predominantly ignored HCV, underscoring HCV’s continued existence as a ‘stepchild’ in the shadows of other diseases. To illustrate, Canada’s medicinal marijuana access program explicitly only lists AIDS and cancer as eligibility indications [46], whereas among the US programs, only two (Rhode Island and Washington) list HCV as a possible indication for program access [47,48].

Furthermore, given that the number of HCV treatment patients with an illicit drug history or in active opiate maintenance therapy will likely substantially rise in the next few years, these restrictive circumstances need to be remedied. It may in fact be an ironical truth that those persons who contracted HCV through a form of illicit drug use may be aided in ridding themselves of this, potentially fatal, virus by the use of another drug in addition to their HCV therapy. Unless we can conclusively and empirically falsify this proposition, the opportunity to do so should be actively facilitated and provided where desired.

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