Management of HCV and HIV infections among people who inject drugs

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Purpose of review

Despite a high burden of hepatitis C virus (HCV) and HIV infection among IDUs and the advent of effective therapies, assessment and treatment remain limited. The current review focuses on the management of HCV and HIV among IDUs, focusing particularly on recent strategies to enhance assessment, uptake and response to HCV and HIV treatment.

Recent findings

There are compelling data demonstrating that with the appropriate programs, treatment for HIV and HCV among IDUs is successful. However, assessment and treatment for HCV and HIV lags far behind the numbers of IDUs who could benefit from therapy, related to systems, provider and patient-related barriers to care. Strategies for enhancing assessment and treatment for HCV and HIV have been developed, including novel models integrating HCV/HIV care within existing community-based and drug and alcohol clinics, innovative methods for education delivery (including peer-support models) and directly observed therapy.

Summary

As we move forward, research must move beyond demonstrating that HCV and HIV infections can be successfully treated among IDUs. There is clear evidence that this is both feasible and effective. Novel strategies to enhance assessment, uptake and response to treatment should be evaluated among IDUs to elucidate mechanisms to enhance care for this underserved population.

Keywords

assessment, barriers, care, hepatitis C virus, treatment

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Introduction

Globally, HIV and hepatitis C virus (HCV) infections have spread rapidly among IDUs. Pharmacologic advances have led to the development of effective therapies for HIV [1] and HCV [2]. For those individuals with access to HIV and HCV therapies, this has resulted in dramatic reductions in morbidity and mortality [1,2]. However, the impact among IDUs has been less pronounced, especially with regards to HCV treatment in which access and uptake remain limited. Inadequate HIV and HCV assessment and treatment among IDUs is due to patient, provider and systems-level barriers, complicating the management of these infections.

As we move forward, research must move beyond the demonstration that IDUs can be successfully treated for HCV and HIV, as this has been clearly demonstrated. The focus must be on the evaluation of strategies to enhance engagement in assessment and treatment; and strategies to improve therapy outcome among IDUs. This review summarizes recent progress in the management of HIV and HCV among IDUs with an emphasis on strategies to enhance assessment and treatment.

Management of HCV infection in IDUs with HIV/HCV

The majority of HCV-infected individuals develop chronic infection and will be at risk of developing cirrhosis and hepatocellular carcinoma [3]. Treatment success has increased from 10% with interferon in the mid-1990s, to 55–85% (depending on HCV genotype) with pegylated-interferon (PEG-IFN) and ribavirin [2]. Successful treatment is associated with viral eradication, normalization of liver enzymes, regression of hepatic fibrosis, improvement in quality of life, reduced risk of advanced liver disease complications and improved survival [3].

Among long-term IDUs (injecting >6 years), HCV prevalence is high (64–94%) [4]. A large proportion of IDUs

are above 40 years old, most of whom will have had HCV for 15–25 years. The natural history of chronic HCV (cirrhosis risk escalates after 15–20 years) [5] and the ageing cohort effect in this population means that over the next decade a large burden of advanced liver disease is anticipated. In a study of inner city residents from Vancouver, a high rate of mortality was observed, with those above 50 years of age at significant risk of liver-related mortality [6]. Given that many communities of IDUs were infected with HCV in the 1970s and 1980s, there will inevitably be greater incidence of liver disease over the next decade.

Until recently, HCV treatment guidelines excluded IDUs from consideration, citing concerns about adherence, increased susceptibility to side effects (e.g. depression) and re-infection [7]. Successful HCV treatment studies among IDUs have challenged this paradigm [8•,9,10,11••, 12•,13,14] and guidelines have been revised to consider HCV treatment among IDUs on a 'case-by-case' basis [15–19].

There is compelling evidence that PEG-IFN/ribavirin is well tolerated and effective among IDUs [8•,20–35]. In a systematic review of studies evaluating HCV treatment among IDUs, 71% completed treatment and 54% achieved an sustained virological responses (SVR) [8•]. In addition, HCV treatment does not seem to have a major impact on drug dependency treatment or increase drug use [26,27]. Injecting drug use in the 6 months preceding the initiation of therapy is not associated with poorer response to HCV therapy [11••,29,33]. Further, HCV treatment can be successful even for persons who continue to inject drugs, although more frequent use is correlated with less success [28,29,33]. Social functioning may be a better indicator of treatment outcome, given that it is independently associated with SVR, after adjusting for drug use [11••]. Decisions around whether or not to treat HCV should be made around broader issues such as social functioning (e.g. housing, employment, etc.) and medical comorbidities (e.g. mental health, HIV, etc.) and not drug use alone.

Despite an emerging burden of HCV-related liver disease, changes to clinical guidelines and improved therapeutic outcomes, very few IDUs have ever been offered HCV treatment. In Australia, Canada and the USA, only 1–9% of current IDUs have received HCV treatment [36–39]. Among inner city residents in Vancouver, Canada, only 1% (15 of 1360) of HCV antibody-positive individuals received HCV treatment between 2000 and 2004 (Fig. 1) and the rate of HCV infection was 25 times higher than the rate of HCV treatment uptake [38]. Given that the future burden of HCV will be driven by IDUs, any efforts to curtail the long-term consequences of HCV will require enhancing HCV assessment and treatment in this population.

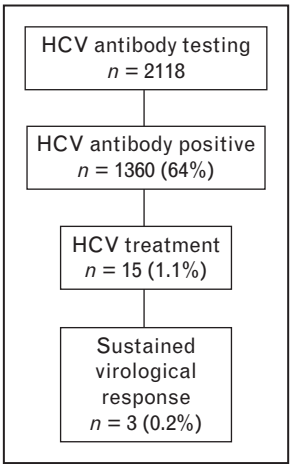
Key points

- Treatment for hepatitis C virus (HCV) and HIV infections is successful among IDUs, particularly when integrated into multidisciplinary models of care.
- Uptake of treatment for HCV and HIV infections remain unacceptably low, in part due to a number of barriers at the level of the system, practitioner and patient.
- A number of novel models have recently been developed to enhance engagement in HCV and HIV care services, serving to increase the proportion of patients assessed and treated for these infections.
- It is crucial that research moves beyond the demonstration that IDUs can successfully be treated for HCV and HIV infections as there is clear evidence for this now.
- There is a need for further research investigating novel strategies to enhance assessment of liver disease, improve engagement in HCV care and improve therapeutic outcomes.

Although there is a perception by some practitioners that IDUs are not interested in receiving HCV treatment, 53–86% of IDUs report a willingness to initiate HCV treatment [39–44]. Impaired access to therapy often results from the combination of multiple barriers to therapy present at the levels of the system, practitioner and patient [45].

At the systems level, there is limited infrastructure for the provision of HCV assessment and treatment among

Figure 1 The shrinking effect of hepatitis C virus treatment among drug users



HCV treatment uptake and sustained virological response among individuals having receiving HCV antibody testing in a large, community-based cohort of inner city residents in Vancouver. HCV, hepatitis C virus. Data from [38].

IDUs, particularly in the drug and alcohol setting. Patients have cited a limited knowledge of testing locations [46•], limited accessibility of testing, results and treatment [47] and long waiting lists for treatment [40] as barriers to care. In many countries, treatment is simply not available due to the high cost of PEG-IFN/ribavirin.

At the provider level, practitioners cite concerns of adherence, ongoing drug use, relapse to drug use, risk of exacerbation of comorbid psychiatric disease and re-infection as reasons for not assessing or treating HCV among IDUs [45]. In a study of Canadian specialists, only 20% would consider providing treatment to current IDUs regularly using a needle exchange service [48]. For primary care doctors, who may have the most access to drug using populations, the supports and expertise required to initiate and sustain HCV treatment are often lacking. The decision to treat IDUs with HIV co-infection is an additional deterrent to HCV therapy complicated by issues of the timing of combination antiretroviral therapy (cART) and the severity of HIV disease [49]. Patients report that patient–provider relationships have an important influence on whether they even discuss HCV and treatment with their doctor [46•,50•].

At the patient level, poor knowledge and inaccurate perceptions about HCV are significant barriers for accessing HCV care. Patients report not seeking HCV treatment due to a lack of knowledge of HCV and its treatment [44,46•,47,50•,51–53], the absence of noticeable symptoms [40,46•,52], perceptions around HCV being a benign disease [46•] and fears of liver biopsy and treatment side effects [40,46•,52,54]. Patient perceptions are influenced by the 'horror stories' of negative experiences of liver biopsies and HCV treatment propagated within peer networks [46•]. Also, the importance of HCV at a particular time in someone's life may be superseded by other 'life' priorities such as ongoing drug and alcohol use [40,44,46•,52,53,55,56], prioritization of obtaining drugs [47], employment [46•], unstable housing [50•] and parental responsibilities [50•]. This situation may lead to forgotten appointments [46•] and poor adherence with the HCV assessment and treatment process [55]. Facilitators for seeking HCV care include an interest in promoting one's health [47], having symptomatic infection [46•], having physical health problems [44] and knowing someone who has died from HCV [52].

Strategies to improve engagement with HCV services have been explored. A model to enhance access to HCV care for underserved populations focused on the integration of community-based health centers in New Mexico used state-of-the-art telehealth technology to provide training and support for primary care providers to deliver best-practice HCV care [57••]. This model was effective, with similar responses to HCV treatment observed among community-based clinics as compared to a university-based hospital [57••]. In San Francisco, one hospital assessed the impact of targeted, formal patient education sessions (two hour education seminar facilitated by a nurse practitioner) on HCV knowledge and assessment [58]. Test scores increased by 14% compared with preintervention and there was a higher compliance with HCV assessment as compared with historical controls (64 vs. 39%, $P < 0.0001$). Peer support may be important, given data suggesting that engagement in HCV care may be facilitated by the influence of peers who completed treatment [46•]. In Oakland, a peer-support group model has been developed in which peer educators and medical practitioners co-facilitate groups of 5–20 IDUs, encouraging peer-led discussion around HCV [59,60]. One program at a community health center in Vancouver has built on this model, demonstrating that among 204 IDUs attending their support group, HCV assessment occurred in 53%, HCV treatment in 28% and the first 4 weeks of group attendance predicted successful assessment [9]. In Melbourne, a successful model was based on the integration of a peer-support worker into a community-based liver clinic who facilitated referrals to the service and provided support to people considering and undergoing treatment [61].

Strategies to enhance screening for liver disease among IDUs using noninvasive transient elastography (e.g. FibroScan) may be effective [62•,63]. FibroScan-based assessment utilizes an ultrasound-based technique to measure liver stiffness, having good diagnostic accuracy for distinguishing cirrhosis from mild disease. In Denmark [62•] and France [63], FibroScan-based liver assessment at addiction clinics was a feasible strategy to screen for liver disease and HCV.

Despite a high adherence reported among IDUs receiving HCV treatment [64,65•], poor adherence is associated with reduced response to therapy [11••,64,65•]. One strategy to enhance adherence and response to HCV therapy among IDUs is directly observed therapy (DOT) of weekly PEG-IFN and self-administered ribavirin [33]. Further, once-daily ribavirin (concomitantly as daily DOT with methadone/buprenorphine and citalopram) may be an alternative strategy for improving adherence [12•]. Strategies to enhance adherence to HCV therapies will remain important, particularly in the new era of directly acting antiviral (DAA) agents. The two most advanced agents, telaprevir and boceprevir, both are taken as pills three times a day and require strict adherence to minimize the likelihood of resistance [66,67].

An additional consideration is the interaction of DAAs with opioid substitution therapy (e.g. methadone and buprenorphine). Telaprevir has been shown to reduce

exposure to R-methadone (active form), but this is not associated with opioid withdrawal, suggesting that no a-priori adjustment of methadone is required when initiating telaprevir [68]. There are no data on interactions between boceprevir and methadone or buprenorphine.

Treatment of HIV infection in IDUs with HIV/HCV

For people with access to cART, HIV has become a chronic and manageable infection [1]. The introduction of once-daily treatment options and fixed-dose combination pills have simplified treatment, removing the complexities of multiple drug 'cocktails' that once created obstacles to initiating treatment. Based upon recent clinical evidence, a CD4 cell count of 350–500 copies/μl is the recommended level for initiating cART [69]. However, this CD4 level will continue to increase as HIV treatment becomes better tolerated, more convenient and has less short/long-term adverse effects. Overall, improvements in cART have increased the number of people eligible for therapy and the challenge is to provide treatment to those who need it. Whereas much of the global focus has been on the provision of cART to people living in resource-poor settings, there are serious discrepancies in access to cART between IDUs and other HIV-infected people in all countries [70,71•]. In Baltimore, a study looking at trends in cART initiation among IDUs between 1996 and 2008 failed to show a substantial improvement in cART initiation despite the great strides in treatment during that period [72•]. This occurred for a variety of reasons, including lack of engagement with healthcare, poorly managed addiction and mental health disorders, concurrent illnesses and a range of structural barriers to care [73•].

Perhaps the most challenging aspect of providing HIV care and treatment to IDUs is engagement into any consistent medical care. Even untreated HIV infection becomes a secondary concern when confronted with the day-to-day social and health challenges faced by drug users. In addition, IDUs are highly stigmatized in most societies and can become separated from basic services, including healthcare. Added to this situation is the use of criminal enforcement as a deterrent to drug use that often results in repeated arrests and incarceration [74,75]. In addition to the obvious disruptions in medical care, the disconnection from family and support networks makes re-engagement even more difficult. Alternate strategies in dealing with drug users that include both individual and structural approaches are urgently needed to engage IDUs into healthcare and improve health outcomes [76].

Although studies have shown that IDUs can have similar therapeutic outcomes when compared to non-IDUs once on cART [77], the supports necessary to ensure these outcomes are not the same. The most successful programs for HIV-infected IDUs offer a comprehensive approach to HIV care with close monitoring of medication dispensing and social supports [78]. To enhance adherence, DOT programs have been successfully instituted [79]. These programs not only enhance the uptake and adherence to cART, they come with numerous health and social benefits [80]. In cities where these programs exist, they are generally at a demonstration phase only and large scale-ups of these comprehensive programs are needed. In some countries there are essentially no support programs and drug users remain completely outside of HIV care and many die of their HIV infection without ever receiving treatment [81].

There continues to be concerns among healthcare providers around adherence and the potential for antiretroviral resistance if cART is not taken consistently. This has delayed treatment initiation until such time that patients are deemed 'stable' and ready to start therapy. For many IDUs this may never happen, leading to indefinite delays in treatment initiation or cART starts that may occur very late in the course of infection. This is largely unfounded. Although preparing an individual for the initiation of cART is an important component of HIV care, delaying therapy because of adherence concerns is not justified. A recent meta-analysis showed no difference in the rates of antiretroviral resistance between IDU and non-IDU patients in a large provincial database [82•].

HCV/HIV co-infection is another reason to initiate cART early. The natural history of HCV is accelerated in untreated HIV infection, whereas recent studies have shown that treating HIV can restore immune function and slow HCV progression [83]. If treatment for both infections is being considered, in most cases, cART should be initiated first with the goal of reaching an undetectable HIV plasma viral load before HCV treatment is started. Once stable on an HIV treatment plan, the focus of support can be placed on HCV treatment. Although there may be overlap, the supports needed for HCV treatment are generally more intensive than for HIV therapy.

For people wanting to reduce or discontinue opiate use, methadone or buprenorphine substitution therapy is effective. The initiation of substitution therapy can also increase the uptake of other medications including cART [84•]. Daily dispensing programs that provide methadone and cART at the same location increase adherence to both therapies and allow closer monitoring and support [85]. The use of buprenorphine/naloxone in a multidisciplinary clinic also has shown high retention in HIV treatment [86]. Unfortunately, substitution therapy is not available for stimulant users (i.e. cocaine,

methamphetamine) who make up the majority of drug users in some regions. Other forms of addiction treatment and supports are certainly necessary as part of the cART dispensing in these environments although there is a critical lack of proven interventions.

The co-administration of cART with opiate substitution therapy may require dosing changes due to drug–drug interactions. Although many drug–drug interactions have been described, the most clinically relevant interaction involves non-nucleoside reverse transcriptase inhibitors (NNRTIs), specifically efavirenz and nevirapine, with methadone. It has been shown that methadone area under the curve decreases approximately 50% due to CYP450 induction with the concurrent use of NNRTIs [87]. This administration can induce withdrawal symptoms in some patients who were on stable methadone dosing and up to half of patients will require an upward adjustment of their methadone [88]. There does not appear to be a clinically relevant interaction between NNRTIs and buprenorphine although the data are limited.

In addition to the clear health benefits of cART among those initiating treatment, increasing attention has been focused on the public health benefits of therapy through the reduction in HIV transmission when community plasma viral loads are lowered [89•]. Although reductions in HIV transmission have not been empirically shown with needle/syringe sharing exposures as with sexual exposures, it is likely that the same principles hold and that individuals with undetectable plasma viral loads are not as infectious.

Conclusion

As we move forward, further research into strategies to enhance assessment of liver disease, improve engagement in HCV care and improve therapeutic outcomes through the introduction of new and better therapies are the necessary pieces to a complex puzzle of how to best manage HCV in IDUs.

The provision of HIV testing, care and treatment for IDUs is often neglected despite the high burden of disease and the indisputable benefits of treatment. This is even more pressing as co-infection with HCV is essentially universal among HIV-positive IDUs. Although HIV treatment outcomes can be excellent, even in the face of continued drug use, innovative programs and interventions are necessary to ensure that HIV treatment is both initiated and sustained.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 568–569).

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