Injection Drug Use and the Hepatitis C Virus: Considerations for a Targeted Treatment Approach—The Case Study of Canada

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ABSTRACT *Infection with the hepatitis C virus (HCV) is a major public health burden in Canada and globally. The literature shows that injection drug use is currently the primary transmission route for HCV, and that a majority of injection drug users (IDUs) are currently infected with HCV in Canada. This article first reviews the burden of HCV within IDU populations and the transmission risks and the treatment implications specific to IDUs. Traditionally, IDUs have been excluded from HCV treatment unless abstaining from illicit drug use. However, recent research suggests that categorical exclusion is not medically necessary. A series of key questions about the feasibility of offering HCV treatment to IDUs in the specific Canadian context are considered, including concerns related to the motivation of treatment for IDUs, treatment delivery, treatment side effects, HCV reinfection, and the social environment. The article concludes that treatment of HCV-infected illicit drug users is both feasible and may be necessary to reduce transmission and adverse outcomes in this high-risk population.*

KEYWORDS *Canada, Hepatitis C, Injection drug use, Prevention, Treatment.*

INTRODUCTION

Infection with the hepatitis C virus (HCV) and related disease consequences constitute a major health burden in Canada as well as globally.^{1–3} This situation is aggravated by the fact that the major health consequences of HCV infection—including liver cirrhosis and hepatocellular carcinoma—do not, in many cases, materialize until years or decades after infection. Among the various risk factors for HCV in Canada, injection drug use has emerged as the primary transmission route. Furthermore, the majority of injection drug users (IDUs) appear to be infected with HCV, and the majority of new HCV infections can be attributed to injection drug use.^{4,5}

In this article, we first give a brief overview of HCV risk and epidemiology as it relates to IDUs in the Canadian context. We then outline HCV transmission risk factors within populations of IDUs, followed by a discussion of treatment implications and barriers. Finally, we outline a set of questions and challenges specific to the

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target population of IDUs that will need to be addressed to facilitate much-needed targeted HCV treatment options.

THE HEPATITIS C VIRUS BURDEN

General Population

About 170 million persons worldwide (3% of the global population) are infected with the HCV.⁶ If not treated, the infection becomes chronic in 50% to 85% of individuals; 10% to 20% of infected persons develop liver cirrhosis within 10–20 years of infection, and 5% to 10% of those with cirrhosis develop hepatocellular carcinoma.^{7,8}

In Canada, it is estimated that 0.8%–1.0% of the total population, or 250,000–315,000 persons, are HCV infected.^{1,9} Regional variations exist, with peak HCV prevalence rates in the three largest provinces (British Columbia, Ontario, Quebec).¹ Prediction models of the future HCV-related burden of illness in Canada suggest that approximately 4,000 new HCV infection cases are expected each year.¹⁰ Estimates propose that the number of patients with HCV-related cirrhosis, liver failure, and hepatocellular carcinoma will likely double by the year 2008; simultaneously, it is expected that the number of HCV-related liver deaths would more than double in that period.^{1,9,10} The HCV-related health care costs have been estimated at \$500 million per annum in Canada to date; by 2010, this cost burden is expected to reach \$1 billion (M. Krajden, personal communication, 2002). Similar proportions of the burden of illness related to HCV exists for the United States, where 2.7 million persons have chronic HCV infection; for the period 2010–2019, estimates predict 165,000 deaths from liver disease, 27,000 deaths from hepatocellular carcinoma, \$10.7 billion in direct medical expenditures, and societal costs of \$75.5 billion in lost productivity related to HCV.¹¹

Injection Drug User Populations

IDUs are at particular risk of HCV exposure and infection, related in large part to the method of drug administration that defines the population. For the purposes of this article, injection drug use refers to the injection of any illicit drug, mainly opiates, cocaine, crack, and amphetamines, although IDUs can employ variable routes of drug administration.¹² Although the drugs used by IDUs may be different, there are certain HCV transmission-related risks and characteristics that appear regardless of the drug injected.

The two major transmission routes responsible for the majority of previous and existing HCV infections in Canada have been therapeutic blood receipt and injection drug use.⁴ As detection of HCV infection in donated blood and tissue samples has improved substantially and prevention measures have been established, injection drug use remains the single major risk factor for HCV transmission. Between one half and two thirds of HCV infections in Canada are thought to be caused by injection drug use.^{4,5} A small proportion of the remaining cases of HCV transmission are thought to be attributable to sexual transmission, needle-stick accidents, and tattooing.^{3,13,14} Although discussion of drug use as a risk for HCV transmission is usually limited to “injection,” other forms of drug administration involving the exchange of blood (intranasal cocaine use and crack smoking) have been identified as possible transmission routes.^{13–16} Even in light of the evidence pointing toward injection drug use as the primary risk factor for HCV transmission, IDUs remain a relatively understudied population of those with chronic HCV infection.¹⁷

Within the high-risk population of IDUs in other Western countries, numerous studies¹⁸ have demonstrated anti-HCV positivity rates of 60% to 95%. One of the

strongest predictors of anti-HCV positivity is the duration of injection drug use.^{19–28} In an ongoing cohort study of untreated illicit opiate users in five cities across Canada, saliva tests indicated 61% anti-HCV positivity.²⁹ Other evidence of the high rates of anti-HCV comes from specific Canadian cities. For example, a cohort of 1,345 injection drug users in Vancouver (Vancouver cohort study of IDUs, VIDUS) demonstrated that 81.6% were anti-HCV positive at recruitment; over a 3-year follow-up period (1996–1999), the originally seronegative cases demonstrated an incidence rate of over 16 per 100 person-years.³⁰ An open cohort of IDUs in Montreal indicated a 70% anti-HCV prevalence rate,³¹ and a Toronto cohort of untreated illicit opiate users self-reported a 56% anti-HCV positivity rate.³² A cohort of drug injecting youth in Vancouver indicated 46% anti-HCV prevalence at baseline,³³ and injection drug user populations in Calgary and Winnipeg have indicated anti-HCV prevalence rates of 56% and 60%, respectively.³⁴

INJECTION DRUG USERS AS A DISTINCT HIGH-RISK GROUP FOR HEPATITIS C VIRUS

Direct and indirect characteristics and determinants render IDUs a distinct population from the perspective of HCV transmission risk and treatment implications. The determinants related to the high risk of HCV transmission for IDUs are presented in the next section. This is followed by a review of injection drug use-specific HCV treatment challenges. Canadian data are reported if applicable and/or available.

Hepatitis C Virus Transmission Risk

Overall, IDUs are a distinct risk population for HCV because they have chronic exposure to the virus, are engaged in specific risk behaviors facilitating HCV transmission, and are in a particular social context that increases risk of transmission.

Drug Use and Injection Risks Because blood-to-blood contact is the main mode of transmission for HCV infection, a variety of distinct risk factors exists for IDUs in relation to the route of drug administration: injection. The main risk factor for HCV transmission has been shown to be the sharing of contaminated needles and other drug use paraphernalia; front- and backloading, communal mixing and drawing into syringes from the same bags, as well as “booting” and “jacking” (drawing blood into a syringe before injecting) also increase the possibility of blood-to-blood contact.^{2,3,35–38} HCV may be transmitted more efficiently than human immunodeficiency virus (HIV) as it exhibits higher infectivity,³⁹ increasing the risks of sharing contaminated injection equipment.^{37,40}

Although not all IDUs share needles, the practice is quite common; in one study, 33% of untreated illicit opiate users in Toronto reported having shared needles, and 41% of respondents had shared other works in the last year.³² In VIDUS, of 776 participants who reported active injection drug use in the 6 months before the most recent follow-up, during the period January 1999 to October 2000, there were 27% who reported sharing needles during the 6-month period.⁴¹

Daily injection, sharing needles, cocaine injection (which is typically more frequent), and a history of drug treatment have been shown to be significantly correlated with anti-HCV positivity.⁴² Sharing of injection equipment other than needles is also an important risk factor because blood particles are contained in both syringes and other injection paraphernalia.²⁷ One study found that 54% of HCV infections in IDUs who did not share needles were attributable to cooker/cotton sharing.²⁷

Skin infections related to injection, including abscesses and other open wounds, are also common in IDUs.¹² Open wounds on the skin may enhance the transmission of HCV through direct contact with infected blood. Also, IDUs who engage in crack smoking can develop oral sores from burns or cuts,⁴³ which may increase HCV transmission risk through oral crack use paraphernalia.

Especially among cocaine-using IDUs, the number of injections per day can be very high, with up to 30 injection episodes during “binge” days; therefore, their risk of blood contact is likely higher than for heroin or amphetamine injectors.^{38,44} The VIDUS study in Vancouver found that frequent cocaine injection was also associated with needle sharing.⁴¹ Cocaine use, injection, and the use of needle-exchange programs were key factors associated with the seroconversion to anti-HCV-positive status of IDUs in a Vancouver cohort.³⁰ Frequent injection, together with the above-described injection risks, increases the probability of blood contact, thereby enhancing HCV transmission risks.

However, knowledge of serostatus may alter injection and drug use risk behaviors. A recent study found that 61% of the sample of 197 out-of-treatment IDUs in Denver, CO, were unaware that they were anti-HCV positive. Participants who were unaware of their anti-HCV-positive status were more likely to share equipment, inject with used needles, and report unsafe injection practices.⁴⁵

Biological Risks A number of possible immunological determinants that increase HCV transmission risk are present in populations of IDUs. IDUs, especially those also involved in cocaine/crack and polydrug use may be significantly affected by decreased immunocompetence.^{42,46–49} Increased stress and blood cortisol levels—related to injection drug use behaviors—have been recognized as variables compromising immunity in IDUs.^{50,51} Decreased immunocompetence may have an impact on the body’s ability to act against exposure to HCV, which is important in light of the high rate of exposure of IDUs to HCV-contaminated blood. However, there are also indications that IDUs may exhibit decreased susceptibility to HCV⁵² because of their repeated exposure to the virus, although the evidence on this is still unclear.^{18,53,54}

Possible relevant interactions between HCV and other infectious virological diseases have been suggested to occur, with many infectious diseases more common among those with HCV infection in comparison to those without HCV infection.⁵⁵ Interactions with HIV have been shown to occur on the immunological level, with HIV-infected individuals exhibiting accelerated adverse outcomes and the possibility of increased risk of HCV infection in the presence of HIV.^{43,56,57} Also, HCV infection is more prevalent in alcoholics,^{58,59} and alcohol dependence is common in illicit drug users⁶⁰; thus, IDUs consuming alcohol are at increased risk. There are thus a number of biological factors, most relating to immunosuppression, that may lead to enhanced HCV infectivity in IDUs.

Physical Health Risks IDUs, especially those with a long-term drug use history, in general tend to display a poorer health status.¹² In a Toronto cohort of untreated illicit opiate users, with a majority of IDUs, 54% of participants reported that they were currently experiencing severe health problems, and 33% reported having been hospitalized in the last 12 months.³² Studies of illicit drug user populations across Canada reported disproportionately high frequencies of medical visits to emergency rooms or physicians; conversely, illicit drug users report a high frequency of medical emergency situations in which required medical help was not

available or accessible.^{32,61,62} Disproportionate levels of compromised physical health of IDUs may be related in part to greater susceptibility of HCV infection and thus the high rate of HCV within populations of IDUs.

Sexual Risks Another risk factor for HCV infection common in IDUs is the disproportionate involvement of this population in sex trade work and high-risk sexual activities. Although risk for HCV through sexual transmission is low, HCV can be transmitted through high-risk sexual activities, such as unprotected sex, and is exacerbated by sexual contact with multiple partners⁴; such individuals are also at increased risk of acquiring sexually transmitted infections.⁶³ A study of patients (N=6,668) of sexually transmitted disease clinics in Edmonton found that engaging in prostitution or trading sex for drugs and not using condoms were significant risk factors for anti-HCV positivity.⁶⁴ IDUs have also been reported to be more likely than noninjecting drug users to engage in sex trading.⁶⁵ One study also found a correlation between receiving money for sex and anti-HCV positivity in a sample of IDUs in Harlem, New York²⁸; similarly, selling sex was reported as an independent risk factor for anti-HCV seroconversion in a sample of young IDUs in San Francisco, California.³⁷ In the Toronto sample of untreated illicit opiate users mentioned here, 31% had engaged in unprotected vaginal or anal intercourse in the past year.³² In a sample of IDUs in Toronto, respondents always used condoms more often with clients (53%) than with casual sexual partners (30%).⁶⁶

Illegal shooting galleries and crack houses often have areas set aside for sexual activities,⁶⁷ which may further exacerbate the risk of sexually transmitted infections and HCV. Ethnographic data have observed how some IDUs will beg with offers of sex for small amounts of drugs.³⁸ This practice enhances the risk of HCV because the individual may engage in unprotected sex, and the drug received in return may be what was left over after the drug “giver” had already done his or her injection. High-risk sexual activities are also documented in crack users, specifically involving multiple partners, trading sex for money or drugs, and inconsistent use of condoms.^{60,68,69}

Social Factors Poor health, lack of social integration, poverty, gender issues, and inadequate access to health services are important risk factors for disease in the general population,⁷⁰ and these risk dynamics are further exacerbated in populations of IDUs.⁷¹ In a cocaine-using sample in Vancouver, those with unstable housing conditions were significantly more likely to use emergency room services,⁶² suggesting a poorer health status for those more economically disadvantaged. Social marginalization—as is, for example, reflected by poverty and poor housing frequent among IDUs in Canada and worldwide^{61,72,73}—is correlated with higher prevalence of HCV risks or infection.²

For example, economic disadvantage has also been suggested as contributing to continued drug use,^{74,75} and there is evidence that economic deprivation leads to sharing behaviors vis-à-vis syringes, other equipment, and drugs.^{76,77} The pooling of money to purchase drugs has been found to correlate with HCV seropositivity.³⁷ A few studies have also suggested that unstable housing or lack of a “home” or safe private space is correlated with injection risk and public injection.^{32,78,79} Many subjects in the study of illicit opiate users in Toronto had injected in outdoor or semipublic areas (including streets, cars, and alleyways).³² Outdoor injection has been shown to be correlated with the reuse of needles not cleaned by bleach,⁸⁰ although the utility of bleach cleaning in the prevention of HCV transmission is still unclear.

Certain sociodemographic variables have also been suggested to influence risk in IDUs, including gender (women more at risk of sharing because of the nature of their social relationships)^{77,81} and racial or ethnic status.^{79,82,83}

TREATMENT IMPLICATIONS

Although the pharmacotherapeutic treatment of HCV in general populations has made great progress in recent years,^{84,85} there are still a number of key dynamics and characteristics of HCV treatment that are specifically relevant for IDUs and need to be considered to ensure feasibility of HCV treatment in this population.

One important consideration is the differential treatment duration and response, which are dependent on the infecting HCV genotype. There are at least six major HCV genotypes and several subtypes, which differ in their geographic distribution.⁸⁶ Genotypes 1, 2, and 3 are the most common in North America.^{86,87} Genotypes 1 and 3 are more prevalent in IDUs,^{35,88–90} although different patterns are observed worldwide.^{22,91} Although HCV genotypes are generally not related to disease severity,^{87–89,92} they do affect treatment duration and response. Genotype 1 requires a 48-week course of pegylated interferon/ribavirin therapy with a 40%–46% probability of sustained viral clearance; in contrast, genotypes 2 and 3 require 24 weeks of therapy, and approximately 76%–82% of treated people respond.^{46,93–95} Therefore, knowledge of genotype is required to guide treatment duration and response.

Potential drug interactions also need to be considered. For example, it has been suggested⁹⁶ that interferon and pegylated interferon (peginterferon) can lead to an increase in serum methadone levels, especially in the presence of alcohol. This is especially important for illicit opiate users who may begin HCV treatment in the context of a methadone program. Also, there is evidence that alcohol use decreases treatment response rates to interferon therapy.⁹⁷

Psychiatric comorbidity status and susceptibility are also key concerns for possible HCV treatment, primarily focusing on the frequent and often severe neuropsychiatric (mostly depression, but also psychosis) side effects of interferon therapy regimes. Psychiatric comorbidity (i.e., depression, anxiety disorders, and psychosis) is disproportionately prevalent in drug user populations.^{98–104} In fact, many illicit drug users have been shown to engage in substance use as a form of self-medication for psychiatric conditions.^{105–107} HCV treatment and its potential psychiatric side effects may thus initiate a vicious cycle exacerbating drug use and its related risks in this population.¹⁰⁸

Although IDUs may disproportionately seek or access certain health care services (particularly emergency services), they also experience barriers to adequate preventive and nonemergency care, including issues of trust and stigma in relation to health care providers, fear of detection of illicit drug use and punitive consequences, and the inability to enter the health care system without a primary physician.^{32,71} In Australia, HCV-related dynamics of discrimination within the health care system have been recognized as a barrier to HCV treatment access for IDUs and other illicit drug users.^{109,110} A study of Seattle, Washington, IDUs found that HCV reporting to public health services for the sample was extremely low, and the authors suggested the reasons for this were related in part to the poor access of IDUs to the health care system.¹¹¹ Thus, a number of treatment issues specific to IDU populations will need to be addressed if HCV treatment is to be provided in an effective manner.

Previous State of Hepatitis C Virus Treatment for Injection Drug Users

Until recently, both Canada and the United States suggested that HCV treatment for illicit drug users was not recommended.¹¹² In the United States, for example, it was advocated¹¹³ that “[HCV] treatment of patients . . . who are actively using illicit drugs should be delayed until these habits are discontinued for at least 6 months” (p. 24). In Canada, a guide to HCV treatment supported by the Canadian Medical Association¹¹⁴ stated that “[c]ontinued use of injected . . . street drugs will permit re-infection with hepatitis C, so there is no point going for therapy until this habit has been stopped” (p. 69). In an urban population of HIV and HCV co-infected patients in Boston, Massachusetts, assessed for suitability for interferon treatment, 70% were deemed ineligible by infectious disease and hepatology staff in a medical clinic, with active drug or alcohol use cited as one of the main reasons.¹¹⁵

Although the exclusion of illicit drug users from HCV treatment has been rationalized for the most part by specific “contraindications” relating to active drug use, psychiatric comorbidity, and concerns with adherence,^{108,1156} the categorical barring of illicit drug users from HCV treatment is being questioned.^{84,116} Rather, it can be argued that stigma and systemic and ideological factors may reflect a population-specific form of discrimination¹¹⁷ that leads to IDUs being denied treatment.^{112,118}

New Hepatitis C Virus Treatment: The Chance for Hepatitis C Virus Treatment for Injection Drug Users?

Over recent years, the new generation of pharmacotherapeutic treatments—specifically peginterferon in combination with ribavirin—has become established as a substantively improved form of therapy for HCV.^{119,120} The treatment regimes have already been described in the section relating to treatment implications for IDUs.

Pegylated interferon by injection can be administered once a week, thus easing compliance and medical visit requirements.⁸⁴ Psychiatric side effects of this therapy have also been reduced in severity.¹²¹ The fact that sustained virological responders clear the virus completely from the body has led to the optimistic conclusion that HCV has become a “curable disease.”¹²² Therefore, treatment should be made widely available and accessible to those infected to reduce individual and social burden related to HCV infection. Interferon-plus-ribavirin therapy for HCV has also been determined to be a cost-effective approach to treating chronic HCV.^{123–125}

A few encouraging HCV treatment studies have been successfully conducted with the special target population of IDUs. The Table provides data regarding the evaluation of HCV treatment in a selection of studies with samples of illicit drug users. Positive results were found in an experimental HCV treatment study of drug users, with a 36% sustained viral response rate when treated with interferon or interferon/ribavirin combination therapy, regardless of success in the substance use detoxification program.^{126,127} An Italian study of newly detoxified heroin users (within 2–4 weeks of detoxification treatment) found an enhanced response to interferon alfa-n2b treatment (8 weeks of treatment) for the user group in comparison to controls without a history of drug addiction, although there were no data on sustained virological response.¹²⁸

An evaluation study of the safety, tolerability, and efficacy of interferon/ribavirin combination therapy in HCV-infected illicit opiate injector patients engaged in methadone maintenance treatment found that the end-of-treatment response rate was similar to that of patients without a history of illicit drug use.¹²⁹ Researchers in Munich conducted a study of treatment with interferon alfa plus ribavirin for

TABLE. Summary of published studies on treatment of chronic hepatitis C in injection drug users

Reference	Treatment setting	Antiviral treatment	Number treated	Sustained virological response (percentage of patients)
126, 127	In-/outpatient detoxification	Interferon or interferon/ribavirin combination	50	36%
128	Inpatient detoxification	Interferon	47	Not determined
131	Outpatient methadone substitution and unspecific	Interferon/ribavirin combination	42	43% in the methadone substitution group 28% in the former addiction group
130	Outpatient methadone maintenance	Interferon/ribavirin combination	50	54%

psychiatric risk groups ($n=81$), including psychiatric patients, methadone treatment clients, patients with former addictions, and a control group.¹³⁰ Virological response of those with drug use histories was comparable to that of the psychiatric and the control groups, although the former addiction group did have significantly higher dropout rates.

A Norwegian study¹³¹ provided 5-year follow-up data on 27 IDUs treated successfully (sustained virological response) for chronic HCV infection with interferon alpha with or without ribavirin, with all but one remaining HCV-RNA (ribonucleic acid) negative at the follow-up point of 5 years after treatment. However, this study required patients to be illicit drug use free for at least 6 months prior to HCV treatment and did not provide follow-up data on the viral nonresponders.

Although the data for these studies are encouraging, the small sample sizes make conclusions on widespread feasibility and effectiveness of HCV treatment for drug users premature. Given that IDUs are currently the major risk population for HCV infection and related disease, the crucial questions are whether these advances in HCV treatment can be generalized into an opportunity for broad-scale HCV treatment for IDUs as well as whether, subsequent to the initiation of treatment, ways can be found to reduce HCV transmission risk in this target population. It indeed seems that the time has come for a targeted and proactive HCV treatment approach for IDUs, and that it is feasible and desirable from a public health perspective. However, the complexity of the problem as well as particular characteristics and needs of the target population of drug users—regarding HCV treatment as well as posttreatment prevention—leave some key challenges for wide-scale operationalization as well as knowledge gaps that require addressing for a fully evidence-based HCV treatment campaign for IDUs.

In the following, we outline and discuss key challenges and issues relating to HCV treatment of IDUs:

Are IDUs Interested in and Motivated for Hepatitis C Virus Treatment? One cannot categorically assume that HCV-infected IDUs are interested in and motivated for HCV treatment even if it were widely available and accessible. First, many IDUs are not aware of their HCV status⁴⁵ or are not interested in knowing. Second, the lives of IDUs are chaotic and described by short-term existential needs and concerns,¹³² including the need to obtain drugs and funds to buy drugs, being at risk of death or disease from multiple causes, being in conflict with the law, and frequently lack of shelter. HCV treatment may be a low priority for IDUs, especially if there is a lack of acute symptoms related to their HCV status, because it can be many years before more tangible and severe disease consequences materialize. Also, to date there has been no systematic ranking of HCV-related health consequences in the assessment of the global burden of disease, as this has been done for HIV.¹³³ It is therefore difficult to gauge the rank order of HCV in relation to other health consequences related to injection drug use. A crucial research effort would be to address this area to further inform the need and motivation for HCV treatment in IDUs.

However, in an ongoing multisite cohort study of untreated users of illicit opiates, the majority of whom are injectors, in sites across Canada ($N=455$ at preliminary analysis), 36.9% listed HCV infection and its related complications when asked for their “primary physical health problem.”²⁹ This figure clearly indicates that HCV infection represents a real and tangible health problem in populations of illicit drug users. On the other hand, there is evidence that a considerable proportion of drug users may not be interested in HCV treatment.

In Rhode Island, a survey of 306 former IDUs currently in a methadone maintenance program were asked about their willingness to receive interferon HCV treatment. After being informed of the risks and benefits of treatment, the number of treatment injections required, probability of successful therapy, treatment side effects, and the need for liver biopsy, only 53% indicated that they would definitely or probably enter treatment.¹³⁴

A Swiss study reported the reasons for nonparticipation in HCV treatment for drug users deemed eligible for treatment.¹¹⁶ Among the 28.3% of patients who refused the HCV treatment offered, the main reasons stated for refusal were side effects, the need to have blood drawn, and the need to come in for regular office visits during treatment. On the basis of the above, more information is required to gauge IDUs' interest and readiness for HCV treatment.

How Would Hepatitis C Virus Treatment Best Be Delivered to IDUs? Treatment for HCV in IDUs should be initiated through an individualized approach,¹¹⁸ as for all HCV infected people,¹¹² and there should be no automatic or implicit exclusion of IDUs from treatment.¹³⁵ Important principles to consider in the operationalization of treatment are the need for effective access and support and a trusting provider environment.^{136,137} These treatment environment qualities may best be accomplished by utilizing community organizations familiar with and adapted for the special profiles and needs of drug user clienteles. In Canada, the relatively broad availability of needle-exchange and methadone treatment programs,^{138,139} especially in the urban centers, could provide for some of the supporting infrastructure.

A related challenge for effective HCV treatment is attaining maximum adherence to the treatment regime because treatment effectiveness is directly correlated with adherence.¹⁴⁰ Although there are widespread assumptions that illicit drug users are not capable of adherence to long-term pharmacotherapeutic treatment regimes, experience regarding treatment of other infectious diseases of drug users (e.g., HIV and tuberculosis) has demonstrated the possibility of comparably "normal" or good compliance rates.^{141,142} For the most marginalized injection drug use patients, the possibility of peginterferon monotherapy (no ribavirin) may be considered. This treatment regime does not require the daily ribavirin component and may be considered especially in patients with genotypes 2 and 3, for which response rates are as high as 40%, although it is still not as effective as pegylated interferon/ribavirin treatment.¹²⁰ Embedding HCV treatment into other comprehensive programs of social, health, addiction, or treatment services that drug users trust, need, and frequent regularly (e.g., methadone treatment or needle-exchange program) may facilitate treatment acceptance and adherence; individualized therapy plans and reward systems (e.g., the possibility of methadone "take-homes") may reinforce desired effects. HCV treatment demonstration projects for illicit drug users in Europe and the United States using a combination of the above strategies have shown positive initial results, with adherence rates of 80% and more.^{126,129}

How Could Treatment Side Effects Be Managed? One of the most problematic side effects of interferon-based treatment for HCV is psychiatric symptoms, primarily depression or anxiety.^{95,143,144} It has been reported that interferon treatment has initiated such psychiatric episodes in patients with no prior psychiatric history, as well as aggravated symptoms in people for whom they previously existed. As discussed, a disproportionately high number of illicit drug users demonstrate psychiatric comorbidities.¹⁴⁵

Self medication dynamics of drug use^{105–107} were discussed in this article in relation to IDUs and psychiatric status. IDUs may experience novel or aggravated depression symptoms as an HCV treatment side effect and attempt to compensate for these depression effects with more of the “remedy” that exposed them to HCV in the first place (i.e., drug use and its anticipated self-medicating effect). This may undermine the ability for treatment efficacy and adherence and also heighten the chances of HCV reinfection because of drug injection and related risks.

The fact that a few experimental HCV treatment studies with psychiatrically comorbid patients have concluded that treatment is possible, safe, and acceptable for such patients when properly monitored^{129,146} and that antiviral treatment does not per se lead to increased risk of psychiatric side effects¹³⁰ is encouraging. However, the challenges and range of potential consequences of psychiatric side effects in IDUs are complex. Currently, interferon-related mild-to-moderate depression can be managed with selective serotonin reuptake inhibitors,¹⁴⁷ although there is no agreement in the field whether preventive medication therapy is advisable or if the use of antidepressants should be limited to those with symptoms.¹⁴⁸ Many psychiatric side effects of interferon therapy are also dose related, so individualized therapy may affect clinical manifestations.¹⁴⁴

A thorough assessment of other nonpsychiatric side effects of HCV treatment is also required, including more investigation into the interactions among methadone, alcohol, and interferon.⁹⁶

How to Prevent Hepatitis C Virus Reinfection of IDUs During or After Treatment?

Possible reinfection with HCV is one of the great challenges potentially undermining the long-term success and value of HCV treatment. In IDU patients, this is a particular challenge because the habits of IDUs related to drug use may persist during and even after successful treatment. It is certainly desirable that IDUs will undergo addiction treatment in parallel to HCV treatment, with abstinence from drug use—bearing the main risks of HCV transmission—the possible outcome. However, given that addiction has been recognized as a chronic disease,¹⁴⁹ it is unlikely that this result will or can be accomplished in all, or even a majority, of IDUs who are ready to undergo HCV treatment. For a comprehensive HCV treatment strategy for IDUs to work and be worthwhile, it therefore must be part of broad secondary HCV prevention strategies targeting IDUs who are at risk for continued drug use and thus possible HCV reinfection.

A small HCV treatment study with IDUs observed rather low HCV reinfection rates by utilizing targeted prevention.¹³¹ Comprehensive HCV reinfection prevention strategies aimed at IDUs must build on known and existing prevention measures (i.e., comprehensive risk education, needle exchange, peer outreach programs).^{150–152} Such programs should also include injection drug use risk interventions that are currently under discussion in Canada, including supervised injection facilities.^{153,154} Increasing knowledge of HCV for users, as delivered by targeted peer and outreach programs, may also serve to reduce risk behaviors.¹⁵⁵

Finally, a further important measure is that the range and diversity of available addiction treatments, including opiate maintenance treatment for opiate-using IDUs, which has been shown to reduce infectious disease risk and transmission.^{156,157}

How to Improve the Social Environment for Effective Hepatitis C Virus Treatment for Injection Drug Users?

The role of social determinants and environment in health has been evidenced,^{70,158,159} and it is widely documented that IDUs are subject

to numerous counterproductive socioenvironmental factors that negatively influence their health status. An HCV treatment strategy for IDUs must take into consideration the broad determinants of health to address clinical therapeutic needs. The lack of stable housing, poverty, and lack of access to proper health and social care all contribute to the systemic marginalization of IDUs and represent a powerful barrier barring IDUs from effective prevention and treatment in the Canadian context.⁷¹ One critical factor is the criminalization of most IDUs, which hinders many from accessing care because of stigma and other systemic obstacles and may lead to contact with an environment recognized as conducive to HCV transmission: correctional facilities.¹⁶⁰

One final factor, with both sociocultural and ethical implications, relates to the social status of drug users and their “deservingness” of receiving expensive medical treatment. In ethical, medical, and general social circles, strong resistance has been expressed against providing drug users with treatment, especially for a disease they were seen as having brought on themselves through their “immoral” drug use behavior.^{161–163} Specifically, the categorical exclusion of illicit drug users from HCV treatment, as it was proclaimed and practiced until recently,^{113,114} seems neither medically tenable nor necessary^{112,116,163}; thus, a process of innovative education and acculturation in professional and societal arenas must begin and be translated into everyday attitudes and practice. An interdisciplinary focus is required to share expertise from numerous areas, including hepatology, addiction medicine, and social services.¹¹²

CONCLUSIONS

The prevalence of HCV among illicit drug users presents a substantial and increasing disease burden of HCV, with significant downstream public health consequences and an ongoing source of HCV transmission. A targeted and proactive approach to address the availability and effectiveness of HCV treatment for IDUs in Canada is urgently needed to determine if this can improve HCV control measures on the population level given the recent feasibility of pharmacological cure. In this article, we have outlined what some of the challenges and needs are for IDUs in the Canadian context.

Experimental HCV treatment studies abroad have demonstrated that HCV treatment of illicit drug users is feasible, that it can produce similar outcomes as with non-drug-using patients, that side effects are controllable in this population, and that secondary prevention or treatment programs may be an appropriate and effective vehicle of delivering HCV treatment to drug users.

Recently, the NIH Consensus Development Conference on the Management of Hepatitis C,¹²² declared in the final statement:

Recent, albeit limited, experience has demonstrated the feasibility and effectiveness of treating chronic HCV in people who use illicit injection drugs. . . . Thus, it is recommended that treatment of active [IDUs] is considered on a case-by-case basis, and that active [injection drug use] in and of itself not be used to exclude such patients from antiviral therapy. (p. 23)

This new consensus statement explicitly underlines the eligibility and need of IDUs for HCV treatment and should be operationalized and evaluated in the Canadian context. The new knowledge coming from treatment studies of IDUs must be further

developed and assessed to determine the utility of treatment as an instrument of reducing the HCV disease burden. However, it is clear that HCV treatment must be part of a comprehensive harm reduction program focusing on HCV itself as well as the wider harms of injection drug use.

Other countries have chosen to lead the way with experimental and targeted HCV treatment initiatives for IDUs. From both a public health and an individual welfare perspective, the time is right to combine scientific knowledge and professional action into a targeted and proactive HCV treatment approach for IDUs in Canada.

ADDENDUM

In the interest of most up-to-date information published in this journal, we would like to refer the reader to two scientific developments that have occurred since the above manuscript was accepted. First, Dr. Robert Remis' recent comprehensive estimation of HCV prevalence and incidence in Canada in 2002¹⁶⁴ essentially confirmed the primary epidemiological contribution of illicit drug use to the HCV burden described in our paper. Second, the new Canadian Consensus Statement on Hepatitis C was published in May 2004.¹⁶⁵ This document represents a step forward compared to the earlier position described above, as it is recognized that "a significant proportion of the current [HCV] infections [occur] in vulnerable populations"; further, it is claimed that "this document, unlike previous documents, does not exclude active injection drug users from therapy," and that "in all cases, the decision to treat has to be individualized" (2004:9ff). However, among other details, the document still lists "ongoing and untreated alcohol or drug abuse" as one of the general contraindications for HCV treatment.

REFERENCES

1. Remis RS, Hogg RS, Krahn MD, Preiksaitis JK, Sherman M. *Estimating the Number of Blood Transfusion Recipients Infected by Hepatitis C in Canada, 1960–1985 and 1990–1992*. Ottawa, Ontario, Canada: Laboratory Centre for Disease Control; 1998.
2. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *New Engl J Med*. 1999;341:556–562.
3. Alter MJ. The epidemiology of acute and chronic hepatitis C. *Clin Liver Dis*. 1997;1:559–568.
4. Zou S, Tepper M, Giulivi A. Current status of hepatitis C in Canada. *Can J Public Health*. 2000;91:S10–S15.
5. Patrick D, Buxton J, Bigham M, Mathias R. Public health and hepatitis C. *Can J Public Health*. 2000;91:S18–S21.
6. World Health Organization. The world health report 1998—life in the 21st century: a vision for all. *Wkly Epidemiol Record*. 1998;73:145–152.
7. Alter MJ, Margolis HS, Krawczynski K, et al. The natural history of community-acquired hepatitis C in the United States. *N Engl J Med*. 1992;327:1899–1905.
8. Seeff LB. Natural history of hepatitis C. *Hepatology*. 1997;26:21S–28S.
9. Zou S, Forrester L, Giulivi A. Hepatitis C update. *Can J Public Health*. 2003;94:127–129.
10. Zou S, Tepe M, ElSaadany S. Prediction of hepatitis C burden in Canada. *Can J Gastroenterol*. 2000;14:575–580.
11. Wong JB, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality and costs in the United States. *Am J Public Health*. 2000;90:1562–1569.
12. Cherubin CE, Sapira JD. The medical complications of drug addiction and the medical assessment of the intravenous drug user: 25 years later. *Ann Intern Med*. 1993;119:1017–1028.

13. Flamm SL, Parker RA, Chopra S. Risk factors associated with chronic hepatitis C virus infection: limited frequency of an unidentified source of transmission. *Am J Gastroenterol*. 1998;93:597–600.
14. Conry-Cantilena C, VanRaden M, Gobble J, et al. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. *N Engl J Med*. 1996;334:1691–1696.
15. Tortu S, Neaigus A, McMahon J, Hagen D. Hepatitis C among noninjecting drug users: a report. *Subst Use Misuse*. 2001;36:523–534.
16. Harsch HH, Pankiewicz J, Bloom AS, et al. Hepatitis C virus infection in cocaine users—a silent epidemic. *Community Mental Health J*. 2000;36:225–233.
17. Strader DB. Understudied populations with hepatitis C. *Hepatology*. 2002;36:S226–S236.
18. Hagan H. Hepatitis C virus transmission dynamics in injection drug users. *Subst Use Misuse*. 1998;35:1197–1212.
19. Kelen GD, Green GB, Purcell RH, et al. Hepatitis B and hepatitis C in emergency department patients. *N Engl J Med*. 1992;326:1399–1404.
20. Crofts N, Hopper JL, Bowden DS, Breschkin AM, Milner R, Locarnini SA. Hepatitis C virus infection among a cohort of Victorian injecting drug users. *Med J Aust*. 1993;59:237–241.
21. Coppola RC, Masia G, di Martino ML, et al. Sexual behaviour and multiple infections in drug abusers. *Eur J Epidemiol*. 1996;12:429–435.
22. Diamantis I, Bassetti S, Erb P, Ladewig D, Gyr K, Battegay M. High prevalence and coinfection rate of hepatitis G and C infections in intravenous drug addicts. *J Hepatol*. 1997;26:794–797.
23. Garfein R, Doherty MC, Monterroso ER, Thomas DL, Nelson K, Vlahov D. Prevalence and incidence of hepatitis C virus infection among young adult injection drug users. *J Acquir Immun Defic Syndr*. 1998;18:S11–S19.
24. Palitzsch KD, Hottentrager B, Schlottman K, et al. Prevalence of antibodies against hepatitis C virus in the adult German population. *Eur J Gastroenterol Hepatol*. 1999;11:1215–1220.
25. Fuglsang T, Fouchard JR, Ege PP. Prevalence of HIV and hepatitis B and C among drug addicts in the city of Copenhagen. *Ugeskr Laeger*. 2000;162:3860–3864.
26. Denis B, Dedobbeleer M, Collet T, et al. High prevalence of hepatitis virus infection in Belgian intravenous drug users and potential role of the “cotton-filter” in transmission: the GEMT study. *Acta Gastroenterol Belg*. 2000;63:147–153.
27. Hagan H, Thiede H, Weiss NS, Hopkins SG, Duchin J, Alexander ER. Sharing of drug preparation equipment as a risk factor for hepatitis C. *Am J Public Health*. 2001;91:42–46.
28. Diaz T, Des Jarlais D, Vlahov D, et al. Factors associated with prevalent hepatitis C: differences among young adult injection drug users in lower and upper Manhattan, New York City. *Am J Public Health*. 2001;91:23–30.
29. Fischer B, Rehm J, Baliunas D, et al. OPICAN Toronto site: Baseline data overview. Paper presented at: IHRT All-Projects Conference; Sept. 28–29, 2002; Toronto, Ontario, Canada.
30. Patrick D, Tyndall M, Cornelisse P, et al. Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection. *CMAJ*. 2001;165:889–895.
31. Lamothe F, Vincelette J, Bruneau J, et al. Prevalence, seroconversion rates and risk factors for hepatitis B core, hepatitis C and HIV antibodies among intravenous drug users (IDU) of the Saint-Luc Cohort (abstract 221). 6th Annual Canadian Conference on HIV/AIDS Research, May 1997. *Can J Infect Dis*. 1997;28A.
32. Fischer B, Medved W, Gliksman L, Rehm J. Illicit opiates in Toronto: a profile of current users. *Addict Res Theory*. 1999;7:377–415.
33. Miller CL, Spittal PM, Laliberte N, Li K, O’Shaughnessy M, Schechter M. Risk factors for HIV and HCV prevalence and incidence among young injection drug users in a Canadian city coping with an epidemic. Paper presented at: 11th Annual Canadian Conference on HIV/AIDS Research; April 25–28, 2002; Winnipeg, Manitoba, Canada.

34. Poulin C, Single E, Fralick P. *Canadian Community Epidemiology Network on Drug Use (CCENDU): Second National Report*. Ottawa, Ontario, Canada: Canadian Centre on Substance Abuse; 1999.
35. Serfaty MA, Lawrie A, Smith B, et al. Risk factors and medical follow-up of drug users tested for hepatitis C—can the risk of transmission be reduced? *Drug Alcohol Rev*. 1997;16:339–347.
36. Meili D, Marcinko J, Bertisch-Moellenhoff B, et al. Possible transmission routes of viral diseases during communal preparation of drugs for i.v. use. *Suchttherapie*. 2002;3:S20–S26.
37. Hahn JA, Page-Shafer K, Lum PJ, et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. *J Infect Dis*. 2002;186:1558–1564.
38. Bourgois P, Bruneau J. Needle exchange, HIV infection, and the politics of science: confronting Canada's cocaine injection epidemic with participant observation. *Med Anthropol*. 2000;18:325–350.
39. Short L, Bell D. Risk of occupational infection with blood-borne pathogens in operating and delivery-room settings. *Am J Infect Control*. 1993;21:343–350.
40. Moss AR, Hahn JA. Invited commentary: needle exchange—no help for hepatitis? *Am J Epidemiol*. 1999;149:214–216.
41. Wood E, Tyndall MW, Spittal PM, et al. Unsafe injection practices in a cohort of injection drug users in Vancouver: could safer injecting rooms help? *CMAJ*. 2001;165:405–410.
42. Thomas DL, Vlahov D, Solomon L, et al. Correlates of hepatitis C virus infections among injection drug users. *Medicine*. 1995;74:212–220.
43. Porter J, Bonilla L, Drucker E. Methods of smoking crack as a potential risk factor for HIV infection: crack smokers' perceptions and behavior. *Contemp Drug Probl*. 1997;24:219–347.
44. Archibald CP, Ofner M, Strathdee SA, et al. Factors associated with frequent needle exchange program attendance in injection drug users in Vancouver, Canada. *J Acquir Immune Defic Syndr*. 1998;17:160–166.
45. Kwiattkowski CF, Corsi KF, Booth RE. The association between knowledge of hepatitis C virus status and risk behaviors in injection drug users. *Addiction*. 2002;97:1289–1294.
46. Davis GL, Esteban-Mur R, Rustgi VK, et al. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. *N Engl J Med*. 1998;339:1493–1499.
47. Diepolder HM, Zachoval R, Hoffmann RM, Junge MC, Gerlach T, Pape GR. The role of hepatitis C virus specific CD4⁺ lymphocytes in acute and chronic hepatitis. *J Mol Med*. 1996;74:583–588.
48. Tubaro E, Santiangeli C, Belogi L, et al. Methadone versus morphine: comparison of their effect on phagocytic functions. *Int J Immunopharmacol*. 1987;9:79–88.
49. Cushman P, Gupta S, Grieco MH. Immunological studies in methadone maintained patients. *Int J Addict*. 1977;12:241–253.
50. Pellegrino T, Bayer BM. In vivo effects of cocaine on immune cell function. *J Neuroimmunol*. 1998;83:139–147.
51. Roy E, Haley N, Leclerc P, Boivin J-F, Vincelette J. Risk factors for hepatitis C virus infection among street youths. *CMAJ*. 2001;165:557–560.
52. Mehta S, Cox A, Hoover D, et al. Protection against persistence of hepatitis C. *Lancet*. 2002;359:1478–1483.
53. Dore G, Freeman A, Kaldor J. Immunity against hepatitis C virus infection. *Lancet*. 2002;360:1019–1020.
54. Post J, Freeman A, Harvey C, French R, Lloyd A. Immunity against hepatitis C virus infection. *Lancet*. 2002;360:1020.
55. El-Serag H, Bhupinderjot A, Richardson P, Rabeneck L. Association between hepatitis C infection and other infectious diseases: a case for targeted screening? *Am J Gastroenterol*. 2003;98:167–174.

56. Thomas DL. Hepatitis C and human immunodeficiency virus infection. *Hepatology*. 2002;36:S201–S209.
57. Sulkowski MS, Mast EE, Seeff LB, Thomas DL. Hepatitis C virus infection as an opportunistic disease in persons infected with human immunodeficiency virus. *Clin Infect Dis*. 2000;30:S77–S84.
58. Vento S, Cainelli F. Does hepatitis C virus cause severe liver disease only in people who drink alcohol? *Lancet Infect Dis*. 2002;2:303–309.
59. Dieperink E, Willenbring M, Ho SB. Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: a review. *Am J Psychiatry*. 2000;157:867–876.
60. Booth RE, Kwiatkowski CF, Chitwood DD. Sex related HIV risk behaviors: differential risks among injection drug users, crack smokers, and injection drug users who smoke crack. *Drug Alcohol Depend*. 2000;58:219–226.
61. Ottaway CA, Erickson PG. Frequent medical visits by cocaine-using subjects in a Canadian community: an invisible problem for health practitioners? *J Subst Abuse Treat*. 1997;14:423–429.
62. Palepu A, Strathdee SA, Hogg RS, et al. The social determinants of emergency department and hospital use by injection drug users in Canada. *J Urban Health*. 1999;76:409–418.
63. Terrault NA. Sexual activity as a risk factor for hepatitis C. *Hepatology*. 2002;36:S99–S105.
64. Romanowski B, Preiksaitis J, Campbell P, Fenton J. Hepatitis C seroprevalence and risk behaviors in patients attending sexually transmitted disease clinics. *Sex Transm Dis*. 2003;30:33–38.
65. Fuller CM, Vlahov D, Ompad DC, Shah N, Arria A, Strathdee SA. High-risk behaviors associated with transition from illicit non-injection to injection drug use among adolescent and young adult drug users: a case-control study. *Drug Alcohol Depend*. 2002;66:189–198.
66. Myers T, Millson M, Rigby J, et al. A comparison of the determinants of safe injecting and condom use among injecting drug users. *Addiction*. 1995;90:217–226.
67. Inciardi JA. The Miami sex-for-crack market. In: Ratner MS, ed. *Crack Pipe as Pimp: an Ethnographic Investigation of Sex-for-Crack Exchanges*. New York: Lexington Books; 1993:36–68.
68. Hwang L-Y, Ross MW, Zack C, Bull L, Rickman K, Holleman M. Prevalence of sexually transmitted infections and associated risk factors among populations of drug abusers. *Clin Infect Dis*. 2000;31:920–926.
69. Haydon E, Fischer B, Strike C, Rehm J, Millson P. *Crack Use and Hepatitis C in Canada: a Review of Research Evidence and Questions*. Ottawa, Ontario, Canada: Health Canada; 2002.
70. Evans R, Barer M, Marmor T. *Why Are Some People Healthy and Others Not?* New York: A. de Gruyter; 1994.
71. Canadian HIV/AIDS Legal Network. *Injection Drug Use and HIV: Legal and Ethical Issues*. Montreal, Quebec, Canada: Canadian HIV/AIDS Legal Network; 1999.
72. Page-Shafer KA, Cahoon-Young B, Klausner JD, et al. Hepatitis C virus infection in young, low-income women: the role of sexually transmitted infection as a potential cofactor for HCV infection. *Am J Public Health*. 2002;92:670–676.
73. Logan TK, Leukefeld C. Sexual and drug use behaviors among female crack users: a multi-site sample. *Drug Alcohol Depend*. 2000;58:237–245.
74. Schroeder JR, Latkin CA, Hoover DR, Curry AD, Knowlton AR, Celestano DD. Illicit drug use in one's social network and in one's neighborhood predicts individual heroin and cocaine use. *Ann Epidemiol*. 2001;11:389–394.
75. Lovell AM. Risking risk: the influence of types of capital and social networks on the injection practices of drug users. *Soc Sci Med*. 2002;55:803–821.
76. Mandell W, Vlahov D, Latkin C, Oziemkowska M, Cohn S. Correlates of needle sharing among injection drug users. *Am J Public Health*. 1994;84:920–924.
77. Sherman S, Latkin C, Gielen A. Social factors related to syringe sharing among injecting partners: a focus on gender. *Subst Use Misuse*. 2001;36:2113–2136.

78. Patrick D, Strathdee SA, Archibald CP, et al. Determinants of HIV seroconversion in injection drug users during a period of rising prevalence in Vancouver. *Int J STD AIDS*. 1997;8:437–445.
79. Harvey E, Strathdee S, Patrick D, et al. A qualitative investigation into an HIV outbreak among injection drug users in Vancouver, British Columbia. *AIDS Care*. 1998;10:313–321.
80. Latkin CA, Mandell W, Vlahov D, Oziemkowska M, Celetano DD. People and places: behavioral settings and personal network characteristics as correlates of needle sharing. *J Acquir Immun Defic Syndr*. 1996;13:273–280.
81. Strathdee S, Patrick D, Archibald CP, et al. Social determinants predict needle-sharing behaviour among injection drug users in Vancouver, Canada. *Addiction*. 1997;92:1339–1347.
82. Estrada AL. Epidemiology of HIV/AIDS, hepatitis B, hepatitis C and tuberculosis among minority injection drug users. *Public Health Rep*. 2002;117:S126–S134.
83. Craib KJP, Spittal PM, Wood E, et al. Risk factors for elevated HIV incidence among Aboriginal injection drug users in Vancouver. *CMAJ*. 2003;68:19–24.
84. Zeuzem S, Feinman SV, Rasenack J, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med*. 2000;343:1666–1672.
85. Fried M, Shiffman M, Reddy K, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002;347:975–982.
86. Nolte FS. Hepatitis C virus genotyping: clinical implications and methods. *Mol Diagn*. 2001;6:265–277.
87. Chaudhary RK, Tepper M, Eisaadany S, Gully PR. Distribution of hepatitis C genotypes in Canada: results from the LCDC sentinel health unit surveillance system. *Can J Infect Dis*. 1999;10:53–56.
88. Kleter B, Brouwer JT, Nevens F, et al. Hepatitis C virus genotypes: epidemiological and clinical associations. *Liver*. 1998;18:32–38.
89. Bourlière M, Barberin JM, Rotily M, et al. Epidemiological changes in hepatitis C virus genotypes in France: evidence in intravenous drug users. *J Viral Hepat*. 2002;9:62–70.
90. Andonov A, Chaudhary RK. Genotyping of Canadian hepatitis C virus isolates by PCR. *J Clin Microbiol*. 1994;32:2031–2034.
91. Abraham HD, Degli-Esposti S, Marino L. Seroprevalence of hepatitis C in a sample of middle class substance abusers. *J Addict Dis*. 1999;18:77–87.
92. Ramalho R, Costa A, Pires A, et al. Correlation of genotypes and route of transmission with histologic activity and disease stage in chronic hepatitis C. *Dig Dis Sci*. 2000;45:182–187.
93. Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet*. 1998;352:1426–1432.
94. Fried MW, Shiffman ML, Reddy RK, et al. Pegylated (40 kDa) interferon alfa-2a (Pegasys) in combination with ribavirin: efficacy and safety results from a phase III, randomised, actively controlled, multi-center study. *Gastroenterology*. 2001;5:55.
95. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001;358:958–965.
96. Neuman MG, Monteiro M, Rehm J. Drug interactions between psychoactive substances and antiretroviral therapy in individuals infected with human immunodeficiency and hepatitis C viruses. *AIDS*. In press.
97. Bhattacharya R, Shuhart M. Hepatitis C and alcohol: interactions, outcomes and implications. *J Clin Gastroenterol*. 2003;36:242–252.
98. Mueser K, Yarnold P, Bellack A. Diagnostic and demographic correlates of substance abuse in schizophrenia and major affective disorder. *Acta Psychiatr Scand*. 1992;85:48–55.
99. Brown R, Monti P, Myers M, et al. Depression among cocaine abusers in treatment: relation to cocaine and alcohol use and treatment outcome. *Am J Psychiatry*. 1998;155:220–225.

100. Flynn P, Craddock S, Luckey J, Hubbard R, Duntzman G. Comorbidity of antisocial personality and mood disorders among psychoactive substance-dependent treatment clients. *J Personal Disord.* 1996;10:56–67.
101. Weiss R, Martinez-Raga J, Hufford C. The significance of a coexisting opioid use disorder in cocaine dependence: an empirical study. *Am J Drug Alcohol Abuse.* 1996;22:173–184.
102. Magura S, Kang S-Y, Nwakeze P, Demsky S. Temporal patterns of heroin and cocaine use among methadone patients. *Subst Use Misuse.* 1998;33:2441–2467.
103. Krausz M, Degkwitz P, Kuhne A, Verthein U. Comorbidity of opiate dependence and mental disorders. *Addict Behav.* 1998;23:767–783.
104. Marlowe D, Husband S, Lamb R, Kirby K, Iguchi M, Platt J. Psychiatric comorbidity in cocaine dependence. Diverging trends, axis II spectrum, and gender differentials. *Am J Addict.* 1995;4:70–81.
105. Khantzian E. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am J Psychiatry.* 1985;142:1264.
106. Murphy S, Khantzian E. Addiction as a “self-medication” disorder: application of ego psychology to the treatment of substance abuse. In: Washton A, ed. *Psychotherapy and Substance Abuse: a Practitioner’s Handbook*. London: Guilford Press; 1995:161–175.
107. Khantzian E. The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. *Harv Rev Psychiatry.* 1997;4:231–224.
108. Gutfreund KS, Bain VG. Chronic viral hepatitis C: management update. *CMAJ.* 2000;162:827–833.
109. Crofts N, Louie R, Loff B. The next plague: stigmatization and discrimination related to hepatitis C virus infection in Australia. *Health Hum Rights.* 1997;2:2.
110. Treloar CJ, Hopwood MN, Loveday SK. Hepatitis C-related discrimination in health-care. *Med J Aust.* 2002;177:233–234.
111. Hagan H, Snyder N, Hough E, et al. Case-reporting of acute hepatitis B and C among injection drug users. *J Urban Health.* 2002;79:579–585.
112. Edlin BR, Seal KH, Lorrwick J, et al. Is it justifiable to withhold treatment for hepatitis C from illicit-drug users? *N Engl J Med.* 2001;345:211–214.
113. National Institutes of Health. Management of hepatitis C. *NIH Consensus Statement Online.* 1997;15:1–41.
114. Heathcote JE, Yim C, Thai Q, Sherker A. *Your Personal Health Series (Canadian Medical Association): Hepatitis C*. Toronto, Ontario, Canada: Key Porter Books; 2001.
115. Fleming CA, Craven DE, Thornton D, Tumilty S, Nunes D. Hepatitis C virus and human immunodeficiency virus coinfection in an urban population: low eligibility for interferon treatment. *Clin Infect Dis.* 2003;36:97–100.
116. Huber M, Schmid P, Vernazza P, Meili D. Reasons for the lack of treatment of hepatitis C infection in drug dependent patients in opiate substitution. *Suchttherapie.* 2002;3:S27–S30.
117. Berkman LF, Kawachi I. A historical framework for social epidemiology. In: Berkman LF, Kawachi I, eds. *Social Epidemiology*. Oxford, UK: Oxford University Press; 2000:3–12.
118. Davis GL, Rodrigue JR. Treatment of chronic hepatitis C in active drug users. *Engl J Med.* 2001;345:215–217.
119. Di Bisceglie AM, Hoofnagle JH. Optimal therapy of hepatitis C. *Hepatology.* 2002;36:S121–S127.
120. Chander G, Sulkowski MS, Jenckes MW, et al. Treatment of chronic hepatitis C: a systematic review. *Hepatology.* 2002;36:S135–S144.
121. Schaefer M. Neuro-psychiatric side effects of interferon-alpha in drug addicts: reasons, frequency and therapy. *Suchttherapie.* 2002;3:S72–S77.
122. National Institutes of Health. *Management of Hepatitis C: Final Statement*. Washington, DC: National Institutes of Health; 2002.
123. Siebert U, Sroczynski G, Rossol S, et al. Cost effectiveness of peginterferon-2b plus ribavirin versus interferon-2b plus ribavirin for initial treatment of chronic hepatitis C. *Gut.* 2003;52:425–432.

124. Salomon J, Weinstein M, Hammitt J, Goldie S. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. *JAMA*. 2003;290:228–237.
125. Sagmeister M, Wong JB, Mullhaupt B, Renner EL. A pragmatic and cost-effective strategy of a combination therapy of interferon alpha-2b and ribavirin for the treatment of chronic hepatitis C. *Eur J Gastroenterol Hepatol*. 2001;13:483–488.
126. Backmund M. Interferon therapy and detoxification treatment. *Suchttherapie*. 2002;3:S67–S71.
127. Backmund M, Meyer K, von Zielonka M, Eichenlaub D. Treatment of hepatitis C infection in injection drug users. *Hepatology*. 2001;34:188–193.
128. Neri S, Bruno CM, Abate G, et al. Controlled clinical trial to assess the response of recent heroin abusers with chronic hepatitis C virus infection to treatment with interferon alpha-n2b. *Clin Ther*. 2002;24:1627–1635.
129. Schaefer M, Schmidt F, Folwaczny C, et al. Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. *Hepatology*. 2003;37:443–451.
130. Sylvestre DL. Treating hepatitis C in methadone maintenance patients: an interim analysis. *Drug Alcohol Depend*. 2002;67:117–123.
131. Dalgard O, Bjoro K, Hellum K, et al. Treatment of chronic hepatitis C in injection drug users: 5 years' follow-up. *Eur Addict Res*. 2002;8:45–49.
132. Bickel W, Vuchinich R. *Reframing Health Behavior Change With Behavioral Economics*. Mahwah, NJ: Erlbaum; 2000.
133. World Health Organization. *The World Health Report 2002: Reducing Risks, Promoting Healthy Life*. Geneva, Switzerland: World Health Organization; 2002.
134. Stein M, Maksad J, Clarke J. Hepatitis C disease among injection drug users: knowledge, perceived risk and willingness to receive treatment. *Drug Alcohol Depend*. 2001;61:211–215.
135. Edlin BR. Prevention and treatment of hepatitis C in injection drug users. *Hepatology*. 2002;36:S210–S219.
136. Strathdee S, van Ameijden EJ, Mesquita F, Wodak A, Rana S, Vlahov D. Can HIV epidemics among injection drug users be prevented? *AIDS*. 1998;12:S71–S79.
137. Broadhead RS, Heckathorn DD, Weakliem DL, et al. Harnessing peer networks as an instrument for AIDS prevention: results from a peer-driven intervention. *Public Health Rep*. 1998;113:42–57.
138. Fischer B, Rehm J, Blitz-Miller T. Injection drug use and preventive measures: a comparison of Canadian and Western European jurisdictions over time. *CMAJ*. 2000;162:1709–1713.
139. Brands J, Brands B, Marsh D. The expansion of methadone prescribing in Ontario, 1996–1997. *Addict Res Theory*. 2000;8:485–496.
140. McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology*. 2002;123:1061–1069.
141. Marco A, Cayla JA, Serra M, et al. Predictors of adherence to tuberculosis treatment in a supervised therapy programme for prisoners before and after release. *Eur Respir J*. 1998;12:967–971.
142. Gourevitch MN, Wasserman W, Panero MS, Selwyn PA. Successful adherence to observed prophylaxis and treatment of tuberculosis among drug users in a methadone program. *J Addict Dis*. 1996;15:93–104.
143. Renault P, Hoofnagle JH, Park Y, et al. Psychiatric complications of long-term interferon alfa therapy. *Arch Intern Med*. 1987;147:1577–1580.
144. Fried MW. Side effects of therapy of hepatitis C and their management. *Hepatology*. 2002;36:S237–S244.
145. Frei A, Rehm J. Die Prävalenz psychischer Komorbidität unter Opiatabhängigen: eine Metaanalyse bisheriger Studien. *Psychiatr Prax*. 2002;29:258–262.

146. Van Thiel DH, Friedlander L, De Maria N, Molloy PJ, Kania RJ, Colantoni A. Treatment of chronic hepatitis C in individuals with pre-existing or confounding neuropsychiatric disease. *Hepatogastroenterology*. 1998;45:328–330.
147. Musselman DL, Lawson DH, Gunnick JF, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med*. 2001;344:961–966.
148. Kraus MR, Schafer A, Scheurlen M, Miller AH, Musselman DL, Nemeroff CB. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med*. 2001;345:375–376.
149. Leshner A. Addiction is a brain disease, and it matters. *Science*. 1997;278:45–47.
150. Hagan H, Desjarlais DC, Freidman SR, Purchase D, Alter M.J. Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. *Am J Public Health*. 1995;85:1531–1537.
151. Trautmann F. Peer support as a method of risk reduction in injection drug-user communities: experiences in Dutch projects and the “European peer support project.” *J Drug Issues*. 1995;25:617–628.
152. Hankins C. Syringe exchange in Canada: good but not enough to stem the HIV tide. *Subst Use Misuse*. 1998;33:1129–1145.
153. Fischer B, Rehm J, Kim G, Robins A. Safer injection facilities (SIFs) for injection drug users (IDUs) in Canada: a review and call for an evidence-focused pilot trial. *Can J Public Health*. 2002;93:336–338.
154. Dolan K, Kimber J, Fry C, Fitzgerald J, McDonald D, Trautmann F. Drug consumption facilities in Europe and the establishment of supervised injecting centres in Australia. *Drug Alcohol Rev*. 2000;19:337–346.
155. Heimer R, Clair S, Grau LE, et al. Hepatitis-related knowledge is low and risks are high among HIV-aware injection drug users in three US cities. *Addiction*. 2002;97:1277–1287.
156. Sorensen JL, Copeland AL. Drug abuse treatment as an HIV prevention strategy. *Drug Alcohol Depend*. 2000;59:17–31.
157. Marsch L. The efficacy of methadone maintenance interventions in reducing opiate use, HIV risk behavior and criminality: a meta-analysis. *Addiction*. 1998;93:515–532.
158. Woodward A, Kawachi, I. Why reduce health inequalities? *J Epidemiol Community Health*. 2000;54:923–929.
159. Link BG, Phelan J. Social conditions as fundamental causes of disease. *J Health Soc Behav*. 1995;35:80–94.
160. EMCDDA European Monitoring Centre for Drugs and Drug Addiction. *Study on Assistance to Drug Users in Prisons*. Lisbon, Portugal: European Monitoring Centre for Drugs and Drug Addiction; 2001.
161. Glannon W. Responsibility, alcoholism, and liver transplantation. *J Med Philos*. 1998;23:31–49.
162. Caplan AL. Ethics of casting the first stone: personal responsibility, rationing and transplants. *Alcohol Clin Exp Res*. 1994;18:219–221.
163. Rehm J, Fischer B, Haydon E, Room R. Abstinence ideology and somatic treatment for addicts—ethical considerations. *Addict Res Theory*. 2003;11:287–293.
164. Remis R. Estimating the incidence and prevalence of hepatitis C in Canada. Presented at the *Second Canadian Conference on Hepatitis C: New Knowledge, New Hope*, Vancouver, BC, March 27–30, 2004.
165. Sherman M, Bain V, Villeneuve J-P, et al. *Management of Viral Hepatitis: A Canadian Consensus Conference*. Toronto; 2004.