**Title: Treatment Uptake and Outcomes Among Current and Former Injection Drug Users
Receiving Directly Observed Therapy Within a Multidisciplinary Group Model for the
Treatment of Hepatitis C Virus Infection**

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Keywords: hepatitis c virus; treatment; injection drug users; pegylated interferon; ribavirin; multi-disciplinary

ABSTRACT

Injection drug use accounts for the majority of incident and prevalent cases of hepatitis C virus (HCV) infection. However, very few injection drug users (IDUs) have received treatment for this condition given issues of medical or psychiatric co-morbidity, ongoing substance abuse and a widely held belief that such individuals will not be able to adhere to the requirements of therapy, including regular medical follow-up. With this in mind, we sought to evaluate HCV treatment uptake and outcomes among current and former IDUs attending a weekly peer support group and receiving directly observed HCV therapy. Utilizing the existing infrastructure for the management of addictive disease, we have developed a model of “one-stop shopping” whereby the treatment of addiction, HCV and other medical conditions are fully integrated, with the collaboration of nurses, counselors, addiction specialists, infectious disease specialists, primary care physicians and researchers. Subjects interested in receiving treatment for HCV infection were referred to a weekly peer-support group and evaluated for treatment. Patients received therapy with pegylated interferon- α 2a or - α 2b, both in combination with ribavirin. All injections were directly observed. Overall, we observed a high uptake of HCV treatment among attendees, with 51% either receiving or about to receive therapy. To date, 18 patients have initiated treatment for HCV infection and 12 have completed therapy. Overall, 8/12 (67%) subjects achieved an end of treatment response (Genotype 1 – 67%, Genotypes 2/3 – 67%), despite

ongoing drug use in 75% of patients during treatment. These data demonstrate that with the appropriate programs in place, a high uptake of HCV treatment can be achieved among IDUs referred to a peer-support group. Moreover, the treatment of HCV in current and former IDUs within a multidisciplinary DOT program can be successfully undertaken, resulting in ETRs similar to those reported in randomized controlled trials.

INTRODUCTION

Hepatitis C virus (HCV) is a significant global health burden, with over 170 million people infected worldwide (Shepard *et al.*, 2005). Injection drug use (IDU) remains the primary mode of HCV acquisition in the developed world (Shepard *et al.*, 2005). However, HCV treatment programs for illicit drug users have not been part of the response to this explosive epidemic. Reports from Australia and Canada demonstrated that in 2003 and 2004, respectively, only 3-4% of these individuals had received treatment for HCV infection (Grebely *et al.*, 2006b; NCHECR., 2003). This low uptake of HCV treatment is associated with barriers including lack of follow-up with appointments, issues of medical or psychiatric co-morbidity and ongoing substance abuse (Falck-Ytter *et al.*, 2002; Fishbein *et al.*, 2004; Fleming *et al.*, 2003; Restrepo *et al.*, 2005).

Response rates of ~55% are observed in patients receiving pegylated interferon and ribavirin, a figure that exceeds 80% in individuals carrying HCV genotype 2 or 3 infection (Fried *et al.*, 2002; Hadziyannis *et al.*, 2004; Manns *et al.*, 2001; McHutchison *et al.*, 1998). In the past, guidelines had excluded illicit drug users from being considered for therapy unless they had abstained from risk behaviors for HCV transmission for at least 6 months. However, data from our centre (Grebely *et al.*, 2006c) and others (Backmund *et al.*, 2001; Dalgard, 2005; Litwin *et al.*, 2005; Matthews *et al.*, 2005; Mauss *et al.*, 2004; Neri *et al.*, 2002; Schaefer *et al.*, 2003; Sylvestre *et al.*, 2005; Taylor, 2005; Van Thiel *et al.*, 2003) suggest that illicit drug users can be successfully treated for HCV infection. Programs with the highest success rates tend to use an existing infrastructure for the treatment of addiction into which HCV therapy can be integrated. The key is to ensure engagement in care before, during and after a decision to initiate treatment

has been made. However, there are very little data investigating the specific components of various programs that are important for successful treatment of HCV infection in illicit drug users.

One potential strategy for improving outcomes is the development and implementation of support groups for patients leading up to treatment for HCV infection. This provides a mechanism for regularly scheduled follow-up, patient education and peer support that may even be continued during the course of HCV therapy. With this in mind, we sought to evaluate the uptake and response to treatment among current and former IDUs infected with HCV enrolled in a weekly support group designed to enhance long-term engagement in medical care.

METHODS

All patients were HCV-infected illicit drug users attending an inner city multidisciplinary health clinic (the Pender Community Health Centre, PCHC) located in Vancouver, Canada. The PCHC has a mandate to provide primary care for residents of this area and offers addiction services including methadone maintenance therapy, needle exchange, and counseling. There are up to seven physicians, four registered nurses, six drug and alcohol counselors and on-site consultation with infectious diseases specialists.

For this study, we sought to evaluate the rate of HCV treatment initiation and outcomes among individuals attending a weekly support group for HCV infection. Starting in March 2005, subjects with detectable HCV RNA and an interest in receiving HCV treatment were referred by clinic physicians and addiction counselors to the group. The model for support was based on the O.A.S.I.S model developed in Oakland, CA (Sylvestre et al., 2005). Attendance to the once-weekly group was not mandatory, but was recorded from the first day that the patient attended the group and monitored at subsequent weekly meetings. Addictions counselors moderated the group, with nurses and research staff supporting its conduct. This group provided an opportunity for treatment candidates to interact directly with those that were receiving or had completed treatment and to gain insight into the evaluation of liver disease and what to expect during treatment. Patients who qualified for HCV treatment on medical grounds would then be seen by clinic physicians for HCV evaluation and to plan for the initiation of therapy.

Funding for HCV treatment in British Columbia is provided through government programs and is either partially or fully reimbursed (based on patient income level). The clinical criteria for government reimbursement are: documented viremia, along with either elevated alanine aminotransferase (ALT) enzyme levels (1.5 times the upper limit of normal on 2 occasions at least 3 months apart) *or* liver biopsy demonstrating at least Knodell stage 2 fibrosis with no evidence of decompensated cirrhosis. Men and women >19 years of age who fulfilled government criteria for subsidized treatment and in whom there was a reasonable expectation of adherence to therapy were eligible to receive it. Patients with any cause of chronic liver disease other than HCV, pregnant or breastfeeding women, those with active suicidal ideation, psychosis or mania or those judged inappropriate for treatment by their physician, based on their medical or psychiatric condition, or their current addiction status (daily injection drug use in the setting of unstable housing) were not offered treatment for HCV infection.

Once a patient was judged to be a candidate for treatment (based on attendance to pre-treatment medical evaluations, social stability and absence of medical or psychiatric co-morbidities), a clinic physician completed a medical history and physical examination. Patients underwent testing for HIV, HCV and hepatitis B virus as well as baseline hematology and biochemistry testing. Nursing staff provided education about treatment and side effects. Patients were required to see an addiction counselor to assess psychiatric status (depression and suicide risk), social stability and illicit drug use, with an emphasis on ongoing risk for HCV transmission. Once therapy was initiated, patients attended the clinic weekly to be evaluated by a nurse and to receive PEG-IFN injections administered by clinic staff (RBV was self-administered). During these visits, the nurse specifically documented adherence, illicit drug use, side effects and

ensured appropriate longitudinal monitoring was conducted. Interferon adherence was assessed by direct observation and ribavirin adherence was self-reported weekly. Addiction counselors provided additional individual support, with particular attention to symptoms of depression.

Subjects initiating therapy were entered into a prospective, observational efficacy trial. Patients received combination therapy with ribavirin (800-1200 mg/day) along with either pegylated interferon- α 2b (PEG-IFN- α 2b, 1.5 μ g/kg once-weekly) or pegylated interferon- α 2a (PEG-IFN- α 2a, 180 μ g once-weekly). Treatment duration was 48 weeks (HCV genotype 1) or 24 weeks (HCV genotypes 2/3). Staff administered all PEG-IFN injections under direct observation and RBV was self-administered. The primary end point for this trial was end of treatment response (ETR), defined as having HCV RNA <50 IU/mL at the end of treatment (COBAS AMPLICOR HCV Test v2.0, Roche Diagnostic Systems, Mississauga, Canada). The Mann-Whitney test was used to assess differences in median attendance between groups of patients, while Fisher's exact test was used to assess differences in proportions. All two-sided p-values <0.05 were considered statistically significant. All experimental procedures were implemented in accordance with the Helsinki Declaration of 1975. The University of British Columbia Clinical Research Ethics Board approved this study.

RESULTS

Uptake of HCV Treatment

Overall, 80 subjects were referred to the group over a period of 80 weeks, with the mean attendance being 12 subjects per week (range 3-20). The disposition of the 80 subjects referred into the program is shown in Figure 1. Among the 8 (10%) in whom it was decided that treatment would not be initiated, 6 did not require treatment, while 2 had contraindications for immediate treatment (1 – diabetes/malnutrition/depression, 1 – severe depression). In total, 23 (29%) were lost to follow-up. Ten percent (8/80) of subjects had completed or initiated treatment for HCV infection prior to attending the group. Twenty-five percent of subjects (20/80) were currently under evaluation for treatment of HCV and 26% (21/80) had initiated or completed treatment for HCV infection. In a comparison of subjects that had initiated or completed treatment for HCV infection (21/80) and those lost to follow up (23/80), those having received treatment for HCV infection had a higher median attendance [22.7 meetings (Interquartile range, IQR = 13-32) vs. 3.4 meetings (IQR=1-5, $P<0.001$)] and were more likely to attend >3 clinic visits (100% vs. 35%, $P<0.001$) than those lost to follow up.

Baseline Characteristics

Of the 21 subjects who initiated treatment for HCV infection, 18 received care at this site and were enrolled into a prospective observational study of HCV therapy. The other three received treatment elsewhere. Subjects received either PEG-IFN- α -2a (n=14) or PEG-IFN- α -2b (n=4) in combination with RBV. The demographics and clinical characteristics of the 18 subjects enrolled in this study to date are shown in Tables 1 and 2. All patients had IDU as a risk factor for HCV infection. The mean attendance to the weekly group prior to initiating therapy was 79%, while

the mean time to treatment initiation after presenting to the group was 9.5 weeks. Of the 18 subjects treated at PCHC, 56% (n=10) had reported illicit drug use in 6 months preceding therapy, while the median time of drug abstinence was 4 months. Seven subjects (39%) were actively using illicit drugs at the time of therapy initiation. A high proportion of treated subjects were infected with HCV genotype 2 (22%) and genotype 3 (56%). Eight subjects (44%) were receiving methadone maintenance therapy.

Patient Disposition

The disposition of the 18 study subjects is shown in Figure 1. Treatment is still ongoing in 6 patients, while 12 have completed or discontinued therapy. Of the 12 that have completed treatment, early discontinuation was required in 8/12 (67%) of subjects, with 5 experiencing treatment-limiting adverse events (4 - depression and 1 - anemia). Two of the four subjects who discontinued due to depression chose not to receive antidepressants prior to or during treatment for HCV. One subject remained viremic after 24 weeks of therapy (HIV co-infected). Two subjects were discontinued from treatment due to non-adherence associated with ongoing illicit drug use.

End of Treatment Responses and Drug Use

In total, 12 patients completed or discontinued treatment. At baseline, 9/12 subjects were receiving prophylactic treatment with antidepressants (7 – citalopram, 1 – venlafaxine, 1 – amitriptyline), while no patient started antidepressants during treatment. The median duration of non-injection and injection drug abstinence among all 12 patients completing therapy was 5 and 8 months, respectively. Nine subjects (75%) used illicit drugs and four subjects (33%) used

injection drugs at least once during treatment (all four injectors used heroin). Of these, 1 used cocaine alone (non-injection), 3 used cocaine (non-injection) and heroin (injection), 2 used heroin alone (1 - non-injection and injection, 1 - injection) and 1 used methamphetamine alone (non-injection). Five of the nine subjects also used marijuana during treatment (with 3 also having used heroin, cocaine or methamphetamine). The mean number of days of drug use during treatment was 2, 3, 11 and 54 per individual for cocaine, heroin, methamphetamine and marijuana respectively. As shown in Figure 2, the proportion of patients responding to HCV therapy in those having completed or discontinued treatment was 8/12 (67%). In total, 2/3 (67%) and 6/9 individuals (67%) infected with HCV genotype 1 and HCV genotypes 2/3 had an ETR.

Adherence and Safety

In all patients having completed or discontinued therapy for HCV infection (n=12), 57.8% of medication doses were administered over a median of 14 (genotypes 2/3) or 28 (genotype 1) weeks. The on-treatment mean directly observed adherence to interferon was 99.1%, while the mean self-reported adherence to ribavirin was 97.7%. Adverse events were mild to moderate in severity and typical of treatment with pegylated interferon and ribavirin. The most commonly reported adverse events were fatigue (100%), nausea (92%), anorexia (83%), headache (67%) and depression (67%). Only 2 patients required dose-reductions in RBV, while no patient required a dose-reduction of PEG-IFN.

DISCUSSION

Historically, the uptake of HCV treatment has been low among IDUs, despite this group being at highest risk for HCV (Shepard et al., 2005). A number of studies have demonstrated that IDUs can be successfully treated for HCV infection (Backmund et al., 2001; Dalgard, 2005; Litwin et al., 2005; Mauss et al., 2004; Neri et al., 2002; Schaefer et al., 2003; Sylvestre et al., 2005; Taylor, 2005; Van Thiel et al., 2003). However, there are little data evaluating programs for successfully engaging these individuals in HCV care and the specific programmatic components that are important for success. One potential strategy for improving patient engagement in care would be increased reliance on peer-support as a tool, coupled with directly observed therapy for the delivery of the medications in those requiring treatment.

Overall, we observed a high uptake of HCV treatment among IDUs attending a weekly HCV peer support group. Among attendees, we were first able to identify a proportion of infected subjects that did not require treatment for HCV infection based on disease severity and develop a plan for continued follow-up, which is enhanced by their participation in the group. Only 29% were lost to follow-up. Individuals lost to follow-up tended to exhibit a lower weekly attendance and were less likely to attend >3 clinic visits when compared to subjects initiating treatment for HCV. This suggests that initial attendance provides a strong indication of future attendance and that individualized approaches need to be developed to better engage some individuals in care. However, for the vast majority of HCV-infected IDUs in our clinic, the group provides an important means of identifying individuals with a demonstrated interest in addressing their HCV infection. We observed a high uptake of HCV treatment among attendees, with 51% either

receiving or about to receive therapy. This figure is impressive considering the numerous barriers associated with treatment in this population, speaking to the success of our model.

Our preliminary results are quite encouraging, given that 67% of subjects receiving directly observed therapy with PEG-IFN and RBV achieved an ETR. This response to treatment is no doubt increased by the fact that there was a selection bias of individuals with HCV genotypes 2/3 (78%), which is higher than the prevalence of these genotypes reported in IDUs in Vancouver (41%) (Grebely *et al.*, 2006a). This being said, our results are comparable to those reported in large, randomized controlled trials of PEG-IFN and RBV for the treatment of HCV infection (Fried *et al.*, 2002; Hadziyannis *et al.*, 2004; Manns *et al.*, 2001) and were achieved despite the fact that 56% of subjects had used illicit drugs in the 6 months preceding therapy and that 75% of patients used illicit drugs at least once during their course of treatment. This is similar to results from a previous study at our centre among 40 current and former drug users. Overall, 55% achieved a sustained virologic response (SVR), despite the fact that many individuals continued to use illicit drugs during treatment (Grebely *et al.*, 2006c).

As we move forward, it will be important to further document SVR rates, as the ultimate measure of treatment efficacy. This will be particularly relevant as data now suggest that shorter durations of HCV treatment (such as those received by a number of our subjects) may be efficacious in subjects infected with HCV genotypes 2/3 (Dalgard *et al.*, 2004; Mangia *et al.*, 2005). With this in mind, there is confidence that a large majority will go on to achieve SVR, especially given that the on-treatment adherence to pegylated-interferon and ribavirin was extremely high in this study (95-100%). It is also important to understand that 75% of subjects required early treatment

discontinuation and only 58% received a full course of treatment according to published therapeutic guidelines. Discontinuations were often related to depression, and we need to develop specific strategies for addressing this question

Given that three-quarters of new cases of HCV infection occur in IDUs, it is clear that any comprehensive approach to control this epidemic must include a systematic strategy to address this group. Our study demonstrates that relatively simple programs can be established to engage IDUs in care. At our center, this is accomplished by incorporating an HCV peer-support group into our established multidisciplinary model addressing addiction and other medical conditions simultaneously and includes directly observed therapy for the delivery of medication. Although the specific components required for a successful approach will vary in other centres, appropriate patient selection within a multi-disciplinary model for the delivery of care to this inner city will be required. Such programs will be a valuable approach in the war against HCV infection in the risk group in which it is most prevalent.

Acknowledgements: We thank the staff of the Pender Community Health Centre, and its clients, who agreed to participate in the study.

Financial support. This research was partially supported by Vancouver Coastal Health (Pender Community Health Centre), The Vancouver Coastal Health Research Institute, The British Columbia Medical Services Foundation, Schering Canada and Hoffmann-La Roche. Training support was provided by the Canadian Institutes of Health Research (J.D.R.) and the National Canadian Research Training Program in Hepatitis C (J.G.).

Potential Conflicts of Interest. BC has received grants for clinical research from Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Agouron, and Abbott. BC has also received grants for educational activities from Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Agouron, and Abbott. BC has served as an advisor or consultant to Boehringer Ingelheim, Bristol-Myers Squibb, and Agouron. SD has served as a consultant for Bristol-Myers Squibb and Pfizer.

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Figure 1. Patient Disposition

Table 1. Baseline characteristics among the 18 subjects in whom treatment for HCV infection was initiated.

Characteristic	N=18
Mean Age – years (SD)	42.8 (6.6)
Male sex – n (%)	17 (94%)
Body weight – kg	
Mean (SD)	80.3 (10.9)
≥75 kg – n (%)	12 (67%)
Mean Estimated Duration of Infection – years (SD)	17.1 (6.6)
Drug Abstinence	
< 6 months – n (%)	10 (56%)
Median Time – months (IQR)	4 (0-60)
On Methadone Maintenance Therapy – n (%)	8 (44%)
Median Methadone Dose – milligrams/day (IQR)	123 (75-143)
Mean Beck Depression Index (SD)	9.8 (1-23)
Pre-treatment with antidepressants – n (%)	14 (78%)
HCV Genotype – n (%)	
1	4 (22%)
2	3 (17%)
3	11 (61%)
Median ALT – U/liter (IQR)	141 (85-256)
Median AST – U/liter (IQR)	91 (61-139)
HIV infection – n (%)	4 (22%)

*SD, standard deviation; IQR, Interquartile range

Table 2. Treatment for hepatitis C virus (HCV) infection among the 18 current and former injection drug users initiating therapy at the Pender Community Health Centre in Vancouver, Canada.

Patient	Age in years/sex	HIV Status	HCV Genotype	Drug Abstinence Prior to Treatment (months)	Major Drug(s) Used	Frequency at Time of Last Use	Treatment for Drug Dependency	Type of PEG-IFN + RBV (planned duration)	Status	Outcome
1	39/M	Negative	3a	8	Heroin/Cocaine	Daily	No	<i>α</i> 2a (24 wks)	Completed	SVR
2	41/M	Negative	2b	0	Heroin	Daily	Methadone	<i>α</i> 2a (24 wks)	Ceased week 15	SVR
3	37/M	Negative	3a	3	Heroin	Monthly	Methadone	<i>α</i> 2a (24 wks)	Completed	SVR
4	36/M	Negative	1a	7	Heroin/Cocaine	Daily	No	<i>α</i> 2a (48 wks)	Ceased week 22	SVR
5	37/M	Positive	1utsf	0	Methamphetamine	Daily	Methadone	<i>α</i> 2a (48 wks)	Ceased week 27	NR
6	46/M	Negative	1utsf	0	Marijuana	Daily	No	<i>α</i> 2a (48 wks)	Completed	ETR
7	46/M	Negative	3a	5	Heroin/Crack	Daily	No	<i>α</i> 2a (24 wks)	Ceased week 14	ETR
8	43/M	Positive	3a	20	Heroin	Weekly	Methadone	<i>α</i> 2b (24 wks)	Ceased week 4	NR
9	40/M	Negative	3utsf	8	Cocaine	Other day	No	<i>α</i> 2b (24 wks)	Completed	ETR
10	48/F	Positive	3a	12	Heroin	Daily	Methadone	<i>α</i> 2b (24 wks)	Ceased week 5	NR
11	42/M	Negative	2b	60	Heroin	Daily	Methadone	<i>α</i> 2b (24 wks)	Ceased week 5	ETR
12	48/M	Negative	1b	0	Cocaine/Crack	Daily	No	<i>α</i> 2a (48 wks)	Ongoing week 22	-
13	38/M	Negative	3a	0	Heroin/Crack	Other day	No	<i>α</i> 2a (24 wks)	Ceased week 3	NR
14	45/M	Negative	3a	0	Cocaine	Daily	No	<i>α</i> 2a (24 wks)	Ongoing week 12	-
15	48/M	Positive	3a	3	Cocaine	Daily	Methadone	<i>α</i> 2a (24 wks)	Ongoing week 15	-
16	52/M	Negative	2utsf	0	Cocaine	Monthly	No	<i>α</i> 2a (24 wks)	Ongoing week 14	-
17	28/M	Negative	3a	12	Heroin	Daily	Methadone	<i>α</i> 2a (24 wks)	Ongoing week 16	-
18	56/M	Negative	3a	6	Heroin	Daily	No	<i>α</i> 2a (24 wks)	Ongoing week 19	-

*utsf, unable to subtype further, ETR, end of treatment response; SVR, sustained virological response.

Figure 2. Virological response to treatment according to genotype in the 12 patients having completed therapy as measured by HCV RNA at the end of treatment; ETR.