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Community-based treatment for chronic hepatitis C in drug users: high rates of compliance with therapy despite ongoing drug use

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SUMMARY

Background
Chronic hepatitis C infection is common in drug users. Treatment of injectors is possible under controlled conditions, but many have not yet been included in treatment programmes as there are concerns about their ability to comply with therapy. It is not known which factors influence compliance.

Aim
To examine the hypothesis that active drug users would comply with anti-viral therapy if treatment was delivered in a convenient manner.

Methods
We established a community-based treatment programme and offered anti-viral therapy to all drug users who wanted it. Few pre-treatment requirements were imposed and, by design, compliance with therapy was reviewed after 50 patients had completed treatment.

Results
Of the 441 patients who were known to be HCV RNA positive and attended the specialist addiction services during the period of this study, eighty three patients considered therapy. Twenty patients did not undergo treatment: 14 declined and 6 had medical conditions that precluded it. In 60 episodes (58 patients) where treatment had been completed, compliance was greater than 80% and homelessness, active illicit drug use and pre-treatment antidepressant therapy were not associated with non-compliance. In 25 of 49 treatment episodes that were assessed 6 months after treatment cessation, a sustained virological response (51%) was seen.

Conclusion
Active drug users using illicit drugs can be successfully treated in community-based clinics.

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INTRODUCTION

Chronic infection with the hepatitis C virus (HCV) is common in those who inject drugs.[1] Without treatment, a proportion of those who are infected will develop end stage liver disease and some will die of liver failure or cancer.[2] Effective therapy for chronic HCV infection involves weekly injections of a pegylated interferon and daily consumption of four to six ribavirin tablets.[3] Such treatment leads to a sustained virological response in over 50% of those who comply with the 24- to 48-week course. Poor compliance leads to reduced response rates[3–6] and, as therapy is associated with many side effects,[7] considerable patient motivation is required to maximize the treatment benefits. Therapy is expensive, although cost-effective in the medium term.[8] In view of the complexity of the therapeutic regime, the side effects and concerns that those who continue to inject may re-infect themselves, many authorities have advised that active injectors should not receive therapy; for example, the 2001 UK guidelines recommend that 'current intravenous drug users should not be treated'.[9] Attitudes to therapy in injectors have evolved[10] and many authorities (including the UK National Institute for Clinical Excellence[11]) have suggested that active drug users should be 'considered' for treatment. Small studies have shown that under controlled conditions, some active injectors can complete anti-viral treatment regimes, for example, drug users undergoing detoxification therapy[12, 13] respond well to anti-viral treatment and directly observed therapy in injectors in British Columbia was successful.[14] In these studies, patients with circumstances that were thought to reduce compliance (such as lack of a fixed abode) were excluded and thus compliance in socially challenged injecting drug users has not been assessed. This has led to diverse guidelines for the management of active injectors with hepatitis C[15] and it remains unclear who is likely to benefit from anti-viral therapy.

To identify factors associated with noncompliance to anti-viral therapy, we established a treatment service in the East London Specialist Addiction Unit where all injectors attending the service who expressed an interest in therapy were treated. By design, we analysed the service when fifty individuals had completed therapy and this report describes this cohort (with an additional eight patients who completed treatment during data collection). We find that 'unstable', homeless active injectors with multiple adverse social factors can be successfully treated.

METHODS AND SERVICE DELIVERY

The addiction services in East London and the City have a central blood borne virus nursing team with nine outreach clinics and links to a GP surgery for the homeless. Clients attend to exchange needles and/or access health care services and opiate replacement treatment. In the clinics, clients are reviewed by a nurse who offers virological testing, vaccination and a range of clinical services. In 2004, all patients who tested positive for HCV (HCV RNA positive by Roche Amplicor assay) were offered an appointment at the local liver unit. In response to poor attendance rates, we established, in 2005, a monthly outreach clinic in the central Specialist Addiction Unit where a consultant hepatologist and a nurse reviewed clients who expressed an interest in anti-viral therapy. Details of clients who did not attend for consideration of anti-viral therapy were obtained from the self-completed patient registration documents and no validation was attempted.

All patients were managed according to local protocol. Patients with overt cirrhosis (AST >1.3 times ALT, platelet count <100 or cirrhosis on ultrasound) were offered therapy. Patients without obvious cirrhosis and a brief history of injecting (<10 years) without alcohol abuse were deemed to have 'early – presumed mild' disease and the advantages and disadvantages of treatment discussed. Those who wished to undergo therapy were treated. In patients where the severity of the liver disease was unclear, a liver biopsy was recommended to exclude cirrhosis. After discussion of the histological findings, the patient decided whether or not to undergo therapy. Patients who declined to undergo the biopsy were treated, if they so wished.

Patients were treated with 40 kD pegylated interferon alpha-2a (180 μg/week) and ribavirin (1000–1200 mg for patients with genotype 1 infection and 800 mg for patients with genotype 2 or 3). Patients with genotype 1 were treated for 48 weeks and therapy was discontinued if the viral load had not decreased by 2 logs after 12 weeks therapy. Patients with genotype 2 or 3 received 24 weeks therapy, but those with cirrhosis were advised to receive 48 weeks therapy, as observations from our unit suggest that this may be advantageous (G.R. Foster and R. Marley, unpublished data). In the last year of the programme, patients who had no detectable virus after 4 weeks' therapy ('super responders') were advised to reduce

their treatment duration by 50%.[16] Compliance with medication was assessed by direct questioning, examination of dossett boxes (provided where nurses had concerns regarding compliance) and review of blood tests (anaemia, leucopaenia and thrombocytopaenia) that indicated treatment compliance.

Patients with underlying psychiatric disorders were reviewed prior to treatment and management decisions were overseen by a psychiatrist (VC). Anti-viral therapy was initiated by a named nurse in the outreach clinics and patients were reviewed as required with a recommendation that patients were seen weekly for the first 4 weeks and then monthly. Blood samples from patients with difficult venous access were taken from large veins either in the groin or in the neck.

The detailed review was approved by the local research ethics committee and statistical analysis was performed using SPSS version 14 (SPSS Inc., Chicago, IL, USA).

RESULTS

During a 2-year period (ending in March 2007), 83 patients with chronic hepatitis C chose to attend the outreach liver clinic for consideration of anti-viral therapy. These patients were a self-selected subset of the 441 patients attending the addiction service during the period of study who were known to be HCV RNA positive. Thus, 18.8% of the population attending the addiction service presented for consideration of anti-viral therapy. Fifty-eight patients (13.2%) had completed therapy at the time of writing. Of the 441 patients known to the service who did not attend anti-viral therapy, 391 provided basic demographic data (age and gender). Patients who attended for consideration of anti-viral therapy were slightly older than those who did not attend, but did provide demographic data – the mean age in those who did not attend was 39.6 years compared to 42.2 years ($P = 0.004$) in those who did attend for consideration of treatment. There were no differences in the proportion of female patients in those who did or did not attend for consideration of therapy (female attenders = 23%, female non-attenders = 21%; P = N.S., chi-square). Patients who considered anti-viral therapy effectively 'self-selected' for treatment by their willingness to attend the specialist clinic for further investigation. The baseline demographics of those who attended for therapy are shown in Table 1 – the mean age was 42.2 years and most were male (77%). Eighty patients provided information about current illicit drug use and use of benzodiazepines, heroin and a combination of heroin and crack cocaine was common. Fifteen patients (18%) admitted to concomitant alcohol abuse (defined as >40 units/week). No patient was co-infected with HIV.

In 10 patients, clinical data indicated cirrhosis and 28 patients had a brief history of exposure to HCV (<10 years). The remaining 45 patients were offered a liver biopsy and 31 completed the procedure. Ten biopsies showed cirrhosis or approaching cirrhosis (Modified Ishak score of 5 or 6). Therefore, of 69 patients assessed 19 (27.5%, mean age 43.5 years) had advanced fibrosis; their mean age did not differ from the 49 patients with mild/moderate disease (42 years). Six of 19 (32%) patients with advanced fibrosis had a history of alcohol excess compared to eight of 49 (16%) patients with alcohol abuse and mild disease (P = N.S., chi-square). The 83 patients who considered therapy were managed according to our algorithm. Figure 1 outlines the patient disposition: six patients had significant psychiatric disorders – poorly controlled psychosis (2) or massive (>100 units/week) alcohol consumption that led to a decision that therapy was hazardous. A further cohort of 14 patients declined therapy – four who underwent liver biopsy had minimal disease (two genotype 1 and two genotype non-1) and a further cohort of 10 patients declined to commence treatment. Table 1 summarizes the demographic features of those patients who did or did not commence treatment. Patients who declined therapy were younger (mean age 38.45 years compared to 43.44 years in those treated) and were less likely to consume benzodiazepines.

Sixty-three patients agreed to undergo therapy and fifty-eight patients completed [two patients were re-treated during the assessment period (one changed from methadone to buprenorphine during therapy and then defaulted from follow-up and was retreated, successfully, following stabilization on his new methadone regime) and one grossly obese patient did not respond to normal doses for 3 months and was therefore retreated, unsuccessfully, with double dose pegylated interferon]. Thus, 60 completed treatment episodes have been assessed, although 24 weeks of follow-up (required to define a sustained virological response) has not yet been completed in 11. As patients who take at least 80% of their medication for 80% of the time have maximal chances of responding,

we assessed adequate compliance by this '80/80' rule.[6] In 12 treatment episodes (20%), compliance was <80%, although four patients stopped after a significant period on therapy (>50%) and did achieve a sustained virological response. Table 2 shows an uncorrected, univariate analysis of factors implicated in poor compliance. Consumption of crack and heroin was significantly associated with reduced compliance with those consuming crack and heroin being five times more likely not to comply ($P = 0.024$). However, intake of other illicit drugs did not influence compliance as did pre-treatment therapy with antidepressants. Age, gender and accommodation status did not modify compliance and those without a fixed residence ($n = 13$, usually living in local hostels) were compliant. A stable partner improved compliance ($P = 0.047$). In a multivariate analysis of the six major risk factors for noncompliance (replacement therapy, crack and heroin use, benzodiazepine use, no fixed abode, duration of drug use and presence of a partner), no pre-treatment factor that reduced compliance could be identified, in particular, use of crack and heroin was not significantly associated with poor compliance.

The virological response to therapy is summarized in Figure 1. Of the 49 completed treatment episodes where follow-up was also complete (including patients who withdrew from therapy before treatment was completed), 25 (51%) achieved a sustained virological response and, as expected, response rates were greater in those with genotype non-1 HCV (15 from 27 – 55%) compared with those with genotype 1 (10 from 22 – 45%). Four of the 12 patients who did not comply with treatment achieved a sustained virological response. Multilogistic regression analysis of factors in Table 1 and response to therapy showed no significant association (data not shown) indicating that none of the adverse psychosocial factors analysed in this study modified the response to therapy.

DISCUSSION

In the developed world, the largest reservoir of chronic HCV infection is in injecting drug users. A number of authorities have argued that active injectors with HCV should be treated (10) and several studies have demonstrated that successful treatment of 'stable' injectors is possible. To examine whether more marginalized groups with HCV could be treated, we established a community-based treatment programme where anyone who expressed an interest in therapy was offered treatment, unless he or she had severe medical

Table 1. Baseline characteristics of the 83 patients attending the outreach liver clinic for consideration of anti-viral therapy

	Total ($n = 83$)	Agreed to undergo therapy ($n = 63$)	No therapy ($n = 20$)
Mean age (Years)	42.2	43.44	38.45*
Male gender	64 (77)	48 (76)	16 (80)
No fixed abode	18 (21.7)	13 (20.6)	5 (25)
Stable partner	32 (38.6)	24 (38.1)	8 (40)
Illicit drug use			
Injecting drugs (heroin or crack)	25 (30.1)	18 (28.5)	7 (35)
Using heroin (injecting or smoking)	19 (22.9)	15 (23.8)	4 (20)
Crack use (injecting or smoking)	7 (8.4)	5 (8.1)	2 (10)
Crack and heroin use	18 (21.7)	14 (22.2)	4 (20)
Benzodiazepine	22 (26.5)	21 (33.9)	1 (5)*
No current illicit drug use	20 (24)	13 (20.6)	7 (35)
Excessive alcohol intake (>40 units/week)	15 (18.1)	10 (15.9)	5 (25)
Opiate replacement therapy			
Methadone	56 (67.5)	42 (66.7)	14 (70)
Buprenorphine	10 (12.0)	9 (14.3)	1 (5)
None	17 (20.5)	12 (19)	5 (25)

Values in parenthesis represent percentages.
* $P = 0.01$.

comorbidities. Our analysis of this approach shows that all groups of injectors comply and respond well to treatment.

The East London Specialist Addiction Unit offers a range of services to drug users. It is difficult to assess accurately the number of individuals accessing the service as many clients attend episodically, sometimes under different names and many leave the region after a short stay. We estimate that approximately 2200 users attend annually. A majority are not active injectors and our database indicated that during the period of this study, 600 clients were HCV antibody positive and 441 were HCV RNA positive. Over the 2-year study period, over 80 injectors with hepatitis C attended the outreach liver clinic and thus some 18% of the regions' injectors who were known to be infected have used the service to date. It is probable that this group represents a 'self-selecting' group of individuals who are likely to be compliant but, nevertheless, our figures indicate that a substantial proportion of injectors are willing and able to accept therapy, if it is offered to them. The patients who attended therapy during the first 2 years of the programme were, on average, older then those who did not attend and it is probable that this self-selecting group was not representative of the injecting community. It is probable that the average age of the injectors who did not attend therapy was lower than that

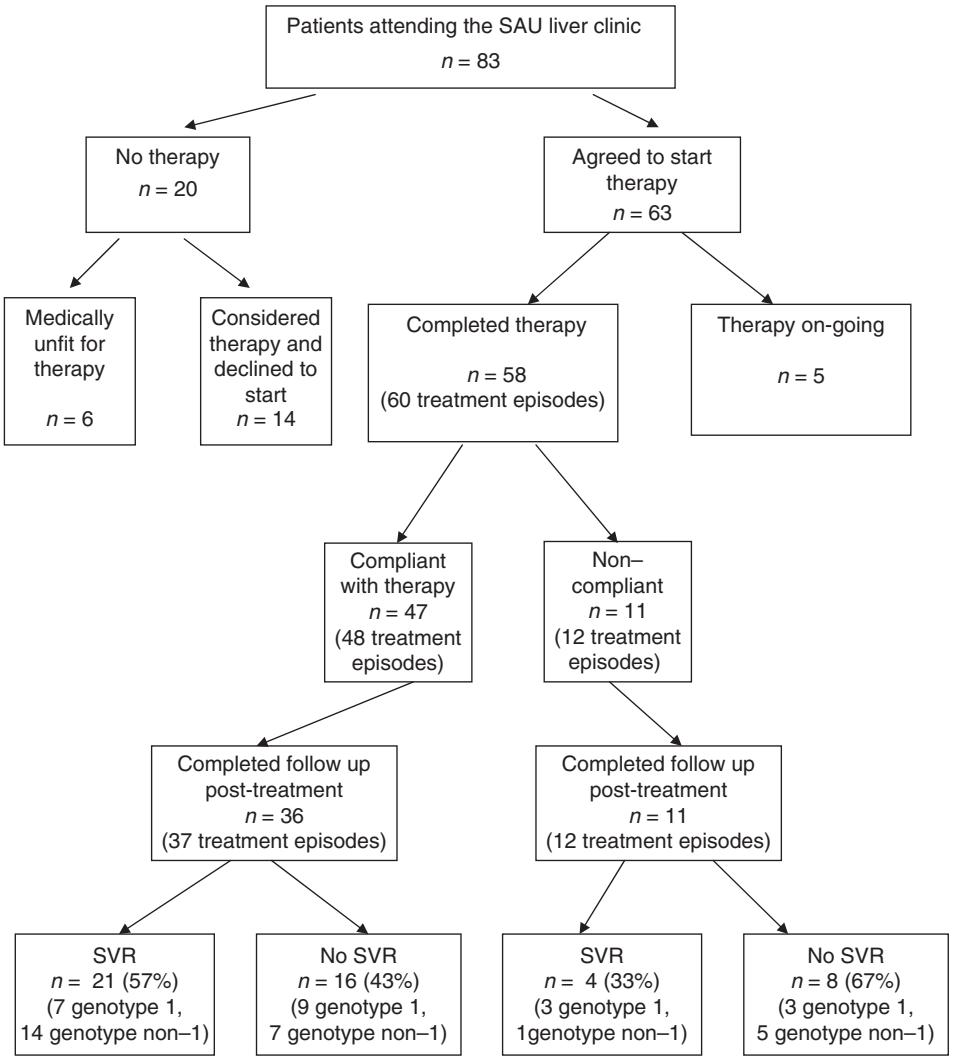

Figure 1. Outcome for patients attending the outreach specialist addiction unit liver clinic.

reported here, as clients who declined to provide a date of birth are more likely to be younger than those who do comply with requests for information. It is important to note that this is an ongoing treatment programme and since the completion of this research, a further cohort of 40 patients have commenced anti-viral treatment, although the treatment outcomes are not yet known. Thus, over a 3-year period, approaching 25% of injectors known to be chronically infected with HCV in 2005 have come for anti-viral therapy. The impact this will have upon the complications of injecting drug use and advanced liver disease is impossible to determine at present.

In this chaotic population of patients who are often reluctant to undergo hospital-based investigations, we adopted a pragmatic approach to pre-treatment

Table 2. Results from the univariate analyses of factors associated with compliance – taking >80% of the prescribed drugs for 80% of the time (60 treatment episodes)

	Noncompliant (n = 12)	Compliant (n = 48)	OR for noncompliance (95% CI)	P-values
Age (years)	42.0	44.21		0.34
Gender				
Male	10	36		
Female	2	12	0.6 (0.11–3.13)	0.71
Residence				
Fixed abode	7	40		
No fixed abode	5	8	3.6 (0.9–14.14)	0.073
Partner				
Partner	2	23		
Single	10	25	4.6 (0.9–23.5)	0.047
Pretherapy antidepressants				
No antidepressants	11	37		
Taking antidepressants	1	11	0.3 (0.03–2.7)	0.43
Length of drug use, n = 49 (years)	13.33	17.1		0.32
Length not injecting, n = 28 (years)	9.5	7.46		0.67
Injecting illicit drugs				
No illicit injecting	7	35		
Illicit injecting*	5	13	1.9 (0.52–7.14)	0.48
Heroin use (injection or smoking)				
Not taking heroin	10	35		
Taking heroin	2	13	0.54 (0.1–2.79)	0.37
Crack and heroin use†				
Not taking crack and heroin	6	40		
Taking crack and heroin	6	8	5 (1.3–19.5)	0.024
Extent of drug use				
Drug use on most days	1	5		
Occasional drug days	9	19	2.37 (0.24–23.36)	0.644
Benzodiazepine use				
Taking benzodiazepines	2	17		
Not taking benzodiazepines	10	31	2.74 (0.54–13.98)	0.31
Replacement therapy				
Not Taking replacement therapy	4	8		
Taking replacement therapy	8	40	0.4 (0.1–1.65)	0.23
Cirrhosis				
No cirrhosis	9	35		
Cirrhosis	3	13	1.11 (0.26–4.8)	1.0

* Fifteen taking heroin, three injecting other drugs.
† Only three patients were taking crack alone.

investigation and we avoided a liver biopsy, if possible. Thus, patients with a short history of illicit injecting were presumed to have mild disease and in some, we identified cirrhosis on clinical grounds. It is probable that these assumptions were correct in the majority, but we accept that some patients may have been misdiagnosed. Our assessment of liver damage indicates that nearly 30% of our patients in their mid forties had cirrhosis. Previous studies from our unit[17] looking at the prevalence of cirrhosis in teetotal immigrants with HCV acquired from medical intervention showed cirrhosis in less than 25% in patients under 50. It is not clear whether the more progressive disease seen in our cohort of injecting drug users is related to prolonged duration of infection, past alcohol abuse or more rapidly progressive disease in those who inject drugs.

We agreed to treat all patients who were willing to undergo therapy. However, some patients had uncontrolled psychoses and therapy was deemed hazardous. We did not offer therapy to alcoholics who were consuming more than 100 units of alcohol a week as previous studies have indicated poor response rates in this group.[18] These patients were provided with support to encourage them to reduce their alcohol consumption and we hope to be able to offer them therapy at a later date. In the remaining patients, therapy was offered and patients with presumed adverse factors, such as lack of a fixed abode, were treated. We defined compliance as consumption of greater than 80% of the drugs for greater than 80% of the time and our compliance rates (just over 80%) are comparable with those in previous studies in nondrug using populations, for example, in the initial clinical trial evaluating pegylated interferon alpha-2a and ribavirin, in which patients with ongoing drug use were excluded, 22% of patients withdrew from treatment.[19] We were unable to identify any pre-treatment psychosocial factor that reduced compliance in our drug using population; we found that patients who were living in hostel accommodation were compliant as were patients actively consuming large amounts of illicit drugs. The number of such patients was relatively small, but the observation that eight of 13 homeless patients completed treatment (seven homeless patients (54%), including two who did not comply, achieved a sustained virological response) makes it difficult to justify excluding such patients from therapy. Clearly, the data from this relatively small series may not be applicable to other areas as services for homeless drug users will differ markedly. However, the high levels of compliance seen in all of the different patient groups should encourage others to consider relaxing their criteria for therapy and evaluating compliance in their own 'difficult-to-treat populations'. During the treatment programme, we noted only one serious adverse event in one crack using patient who became psychotic and required hospitalization. It is unclear whether this was related to illicit drug use (crack) or pegylated interferon, but it does indicate the need for careful surveillance of this patient group.

To deliver anti-viral therapy to this group of patients, we used existing services as far as possible. East London has relatively generous services for clients at risk from blood borne viruses and these include seven outreach clinics staffed by nurse practitioners as well as a general practitioner for homeless patients who has a specialist blood borne virus nurse attached to the practice. Patients were seen by the same nurse who provided needle exchange or other medical services and all the blood borne virus nurses in the programme received additional training in the management of patients receiving anti-viral therapy. The nurses involved in delivering anti-viral therapy were general nurses (rather than psychiatric nurses) and all had received special training in phlebotomy in patients with difficult-to-access veins; blood samples were taken from the neck and groin veins when indicated. Emergency medical back up was provided 24 h a day by one of the two consultant hepatologists who were contacted no more than once a month on average. Senior psychiatric support was available to the nursing team at all times and facilities for emergency psychiatric admission were established in advance of the programme. Thus, a support network was established prior to commencing an anti-viral treatment programme, but the inclusion of anti-viral treatment in the blood borne virus nursing duties did not lead to significant problems with staff overstretch and no new nurses were appointed. However, we recognize that the East London Unit has staffing and other resources that may not be available elsewhere and extending the anti-viral programme to other regions is likely to require additional resources and training.

Treatment of injecting drug users raises concern regarding possible re-infection with HCV necessitating re-treatment. In other studies, treatment of active injectors has not been associated with high rates of re-infection, but it is possible that this will not apply to our, more chaotic, population. To date, we have

detected one patient who became re-infected after a sustained virological response, although the period of follow-up is relatively short and prolonged observation of this cohort will be needed to determine the true re-infection rates. Long-term follow-up of this cohort is in progress to address this important issue.

In a chaotic group of active injectors, we find that effective anti-viral therapy is possible. However, successful therapy requires extensive support and our experience suggests that provision of therapy in a familiar, nonhospital environment is important. High quality nursing support by multi-skilled nurses who are familiar with the patient population and who are able and empowered to obtain blood samples in non-conventional ways appears to be important and easy access to experienced psychiatric support is required. Even with such resources in place, only a minority of active injectors will agree to undergo treatment, but it is to be hoped that as the drug using community recognizes that anti-viral therapy is available and effective, a larger proportion of injectors will avail themselves of the option of treatment. Further studies to determine optimal ways of expanding the numbers of injectors who access treatment services and studies to identify and manage factors that may be associated with future re-infection are required to allow safe, cost-effective services for patients with multiple psychosocial problems to receive the benefits that may be conveyed by successful anti-viral therapy.

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