# Change in injecting behaviour among people treated for hepatitis C virus

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**TITLE**

Change in injecting behaviour among people treated for hepatitis C virus: the role of intimate partnerships.

**SHORT RUNNING TITLE**

Change in injecting behaviour during treatment for hepatitis C.

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**CONFLICT OF INTEREST STATEMENT**

AM, FS, FA and PD declare no conflict of interest. BPS has received honoraria for lectures from Janssen-Cilag, Merck Sharp & Dohme and Gilead Sciences. JFD has received honoraria for lectures and research grants from Janssen-Cilag, Roche, Merck Sharp & Dohme, AbbVie, Bristol-Myers Squibb and Gilead Sciences.

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**ABSTRACT**

Injecting behaviour in people who inject drugs is the main risk factor for hepatitis C virus (HCV) infection. Psychosocial factors such as having a partner who injects drugs and living with other drug users have been associated with increases in injecting risk behaviour. This study aimed to investigate changes in injecting behaviour during treatment for HCV infection whilst exploring the role of psychosocial factors on patients' injecting behaviour. Eradicate-C was a single centred clinical trial (ISRCTN27564683) investigating the effectiveness of HCV treatment within the injecting drug using population between 2012 and 2017. A total of 94 participants completed up to 24 weeks of treatment, with social and behavioural measures taken at different intervals throughout treatment. Data for 84 participants was analysed retrospectively to explore mechanisms of potential behavioural changes which had occurred during treatment.Injecting frequency reduced significantly between baseline (week 1) and every 4-weekly interval until week 26. Not being on Opiate Substitution Therapy (OST) was associated with a statistically significant decrease in injecting frequency, $\chi^2$ (1) = 10.412, p =.001, as was having a partner who also used drugs, in particular when that partner was also on treatment for HCV infection, Z= -2.312, p=.021. Treating a ' hard-to-reach population for HCV infection is not only possible, but also bears health benefits beyond treatment of HCV alone. Enrolling couples on HCV treatment when partners are sero-concordant, has shown enhanced benefits for reduction in injecting behaviour. Implications for practice are discussed.

**Keywords**

Hepatitis C, People who inject drugs, Injecting behaviour, Partner, Opiate substitution therapy.

**Abbreviations**

HCC – Hepatocellular Carcinoma; HCV - Hepatitis C Virus; IFN – Interferon; IEP – Injecting Equipment Provision; LARC – Long-Acting Reversible Contraception; OST - Opiate substitution therapy; PEG-INF – Pegylated Interferon; PWID - People who inject drugs; RBV - Ribavirin; SVR – Sustained Virological Response.

**MAIN TEXT**

**Introduction**

Over 71 million people worldwide are chronically infected with the hepatitis C virus [1-2]. The disease burden is axiomatic, with an estimated HCV-related mortality of 400,000 people a year [1]. The most common transmission route in Western countries remains injecting drug use, with an estimated 60-80% of the HCV-positive population having acquired the virus via injecting risk behaviour [3-5]. A variety of psychosocial factors have been associated with injecting risk behaviour: injecting frequency, poly-drug use, having a sexual partner who also injects, trust and risk perception to name a few [6-8]. Despite the continued injecting risks carried out by people who inject drugs, many studies have

shown that fears of non-adherence and low sustained-virological response (SVR) rates are unjustified, with people who inject drugs (PWID) showing both successful adherence and high SVR rates [3, 9-10].

Psychosocial factors seem to have conflicting effects on injecting risk behaviour and HCV treatment success. Published literature reports an association between HCV treatment success rates and social support [11]. Peers help to increase motivation, feelings of hope and strength to complete treatment, as well as decreasing internalised stigma and shame related to HCV and substance misuse, reducing use of substances itself [12-13]. Yet, historically, close relationships with other PWID, such as romantic partnerships and living with other drug users, are among the factors most strongly linked to continued injecting risk behaviour [6-8]. A possible explanation of these polar effects could be that in a hostile environment where the behaviours of vulnerable adults are influenced negatively by partners, a positive sense of acceptance, belonging and self-worth can stem from these partnerships [14]. Integrated models of behaviour change attempt to explain how couple dynamics can influence risk and health behaviours [15].

HCV treatment itself seems to have a wider effect on PWID than curing hepatitis C alone. It has been associated with a decrease in ancillary injecting equipment sharing after treatment completion [16], suggesting treatment might impact the injecting behavoiur as well as HCV. Midgard and colleagues [17] investigated changes in behaviour during and after treatment, and reported a decrease in recent injecting drug use, alcohol use and an increase in opiate substitution therapy (OST) uptake throughout HCV treatment and at follow-up. However, they found no changes in daily injecting, use of sterile or shared equipment [17]. Only a few studies have investigated the effects of HCV treatment on risk behaviour [16-17] and no literature to date has investigated the role of psychosocial factors such as romantic partnerships and living situation on risk behaviour during and following HCV treatment.

The Eradicate-C study was carried out to investigate the effectiveness of interferon-based HCV treatment on current PWID, characterised by a strenuous lifestyle and erratic engagement with healthcare services. This study aimed to investigate changes in injecting behaviour during treatment, examining the role of psychosocial factors on hypothesised injecting behaviour change.

**Methods**

*Study design*

Eradicate-C was a single centred clinical trial investigating the effectiveness of HCV treatment within the injecting drug using population between 2012 and 2017. Participants were seen on a weekly basis for 26 consecutive weeks for treatment and the additional period of follow-up. The nurses, starting on visit 2 of the study, provided a weekly injection of 180µg pegylated interferon α (PEG-IFNα) and supplied participants with a week's worth take-home daily dose of between 400 – 1400 mg (weight based) of self-administered ribavirin (RBV). Patients presenting with a genotype 1 infection, also received protease inhibitors: telaprevir or simeprevir. The study treatment mirrored the standard of care treatment duration of 24 weeks for genotype 1 infections and of 16 weeks for genotypes 2 and 3 infections. All participants completed behavioural and social measures at different time points during the 26 visits of treatment.

The study was conducted in accordance with the Declaration of Helsinki and the principles of good clinical practice (GCP). The study was co-sponsored by the University of Dundee and NHS Tayside, and was ethically reviewed and approved by the East of Scotland Research Ethics Service REC 2. It was also registered with the National Institute for Health Research (NIHR) on UK Clinical Trials Gateway as ISRCTN27564683.

*Outcomes*

The primary outcome of the Eradicate-C study was to analyse SVR12 in the PWID population, which resulted in an 81.1% genotype 1 and 82.5% genotype 2 & 3 achieving SVR. The total SVR12 rate for all participants was 81.9%.

In this paper, the outcomes of interest were the behavioural and social measures collected during treatment. The primary outcome was injecting frequency throughout treatment (collected at visit 1, 4, 8, 12, 20, 24 and 26). Independent variables analysed were OST, living situation, living with other drug users, having children, having a partner, having a partner who used drugs/alcohol and the EQ5D scores. These measures were taken at visit 1 and visit 26, with the exception of OST, taken every visit from visit 2 to follow up (visits 27 and 28).

*Study participants*

A total of 94 participants completed up to 24 weeks of treatment between January 2013 and December 2016 within the largest Injecting Equipment Provision (IEP) service in Dundee (Scotland, UK). Participants were aged between 18 and 70 years, had an active HCV infection and reported current illicit drug use (defined as those who had injected in the past 4 weeks)which was confirmed through injection sites inspection.This study analysed behavioural and social data from visit 1 and visit 8 of treatment. Not all 94 participants who completed treatment provided data for both visits, reducing the pool of participants to 84 for the present analysis.

*Analysis*

Data was analysed using IBM SPSS Statistics 22. Descriptive analyses were run to obtain characteristics of the sample. If data was missing for one visit (e.g. visit 8) but available for immediately preceding and subsequent weeks (e.g. visits 7 and 9), an average score was used for the required missing visit. If immediately preceding and subsequent visit scores were not available, data was considered missing. Non-parametric testing was selected following data testing for violation of normality, which showed skewed data with kurtosis at all time points. A square root transformation was attempted to normalise distributions and eliminate outliers, but distribution remained skewed. Outliers were included in the analysis as non-parametric use of medians signifies outliers hold less influence over test results. The null hypothesis (no difference in injecting frequency at different time points) was tested with a non-parametric Friedman test, and subsequent post-hoc analyses using Wilcoxon Signed Ranked tests were run to identify where differences lay.

Effect size *r* was calculated with Rosenthal's formula $r = \frac{Z}{\sqrt{N}}$ [18], where Z is the post hoc Wilcoxon Signed Rank Test score and N is the number of observations. The coefficient *r* is more commonly used as a correlation coefficient to measure the strength of a relationship; however, it is a versatile coefficient and it is used, especially within non-parametric testing, as a measure of experimental effect [19].

Once identified that the largest injecting frequency difference was observed between week 1 and week 8 of the study, this difference was used to create a new dependent variable of injecting change, used in the analysis both as a categorical variable, to allow for Crosstab explorations using multiple categorical social factors, and as a continuous variable, to allow investigation of significant differences between the most important categorical social factors using Mann-Whitney U tests.

**Results**

A total of 106 participants consented to treatment. Two never completed baseline measures: 1 participant did not meet inclusion criteria and 1 participant died before starting treatment and completing baseline data. Of the remaining 104 consented, 94 completed treatment, but only 84 had completed behavioural and social data. Ten participants never commenced treatment: 3 spontaneously cleared the infection, 4 were lost to follow-up, 2 were treated on standard pathway after becoming drug-free and 1 was in prison out-with the catchment area. The remaining 10 consented participants who completed treatment had data missing for the visit 8 follow-up and were therefore not included in this sub-study analysis. Characteristics of participants at enrolment are presented in Table 1.

Table 1 shows $\chi^2$ for the 2*2 tables, except for Partner uses drugs, where the smallest expected number is too small to be informative. There are 3 variables which make significance on $\chi^2$: On OST, Has children and Has partner.

Only 32 of the 84 participants presented a complete set of data on injecting frequency at the 8 time points. A Friedman test for differences in weekly injecting frequency among the time points gave a significant result, $\chi^2$ (7) = 36.44, p< .001. The median for week 1 was 4.5, for week 4 was 2, and thereafter for weeks 8 to 26 the median was 1. The range for the 8 time points was always between 0-14 and 0-30. The results and effect sizes of post hoc analyses are shown in Table 2.

Week 8 was the time point at which the largest decrease in injecting was observed. Figure 1 shows the difference in mean injecting frequency between week 1 and week 8 of treatment among the grouping variables analysed above.

Chi-Square tests were run to explore associations between participant characteristics and injecting behaviour change as judged by the new variable Better or Not Better (Table 3). Odds ratio for the association between having a partner who used drugs and 'Better' was uninformative as one of the 2x2 factors equalled 0, causing the calculation to be impossible. The odds of reducing injecting behaviour were over 5 times as high for participants not on OST on week 2 compared to those who were on OST (OR 5.22; 95% CI 1.83-14.90; p=.002).

A Mann-Whitney U test showed that those who had a partner who used drugs and was also on treatment for HCV (N=22) reduced their injecting frequency significantly more than those whose partner was not on treatment (N=20), Z= -2.312, p=.021, medium effect size *r* =0.36. The mean weekly injecting difference was M = 5.65 (95% CI: -0.23 to 11.54) (Figure 1). These results were confirmed by analysing the association between the injecting frequency difference between week 1 and week 8 in couple members. Couples were assigned a couple ID. All couples were heterosexual.

The male-female Pearson's correlation coefficient was $r = .629$, p = .038, which meant that when males reduced their injecting, so did their female partners and vice versa.

**Discussion**

The findings of this paper show a significant reduction in injecting frequency between baseline, i.e. before the start of HCV treatment, and every other time point. The largest reduction was recorded between week 1 (baseline) and week 8, with injecting frequency stabilising thereafter whilst on treatment.

Possible mechanisms of behaviour change were explored using baseline social factors.

*Benefits for non-OST patients*

Firstly, not being on OST on week 2 of treatment (first treatment visit recording this information) was found to be associated with a significant reduction in injecting frequency. It has been widely demonstrated that OST impacts injecting drug use [20-23]. Meta-analysis and pooled analysis of the effect of OST and Needle and Syringe Programmes (NSP) on incidence of HCV infections [22] reported a mean injecting frequency reduction of 20.8 injections per month (95% CI: -27.3 to -14.4), though OST did not reduce lifetime timeframe duration of injecting [23]. So it is possible that the patients who were on treatment for HCV and were already enrolled on OST, had previously reduced their injecting frequency before starting HCV treatment. Previous studies however, have attributed decreases in ancilliary injecting equipment and decrease in recent injecting drug use to enrolment in HCV treatment [16-17]. Enrolment on OST might therefore attenuate the effects of receiving HCV treatment on injecting behaviour.

On the other hand, those who were not on OST on week 2 of Eradicate-C had not experienced the behavioural benefits of OST before their engagement with HCV treatment. It is well recognised that PWID are reluctant to access healthcare services, generally due to a lack of material resources, complicated and lengthy referral pathways, experience of stigma and poor relationship with healthcare providers [24-27]. For these individuals who were not on OST, engagement with HCV nurses might have been the only contact with any healthcare provider. Given the regular and considerate nature of this contact, a therapeutic relationship with the nurses providing the HCV treatment might have functioned as a behaviour change mechanism these patients had not experienced because not enrolled on OST. Therapeutic alliance was not measured in this study, yet previously published literature attests for the importance of this factor on healthcare outcomes relating to this population [28-31]. Meta-analyses have shown positive therapeutic alliance to increase patients' engagement and retention within drug services, as well as motivation, treatment readiness and treatment experience [31]. The results of this study suggest a possible negative correlation between engagement in HCV treatment and injecting behaviour frequency in populations who have mimimum contact with other healthcare services.

*Behaviour change in intimate partnerships*

The observed reduction in weekly injecting frequency was also linked to drug-using status of romantic partners. Those who had a partner who used drugs were more likely to reduce their injecting frequency, a reduction difference of more than 9 injections a week. This finding was surprising, as previous literature associated having a partner who uses drugs, in particular those injecting, with increased frequency of injecting and of sharing of injecting equipment [6-8, 14]. A variety of papers have been published on the power imbalance and social inequalities that drive injecting risk behaviour in heterosexual couples, in particular in women who inject drugs, who often rely on their male partner to acquire, prepare and inject the drugs [32-34]. Disregard of injecting risk occurs as a consequence of emotional closeness, intimacy, trust and commitment [14, 34-35]. Given the high level of sero-concordance in people who inject drugs in intimate partnerships [14], the study team identified patients in dyadic intimate partnerships who had both been enrolled on the Eradicate-C trial. The trial nurses identified 22 participants in couples. The final study findings confirmed that members of couples both treated for HCV on Eradicate-C were significantly more likely to reduce their injecting than other individuals.This effect was explored through models of behaviour change explaining the influence of partners on each other's health-related behaviour. The Interdependence model of couple communal coping and behaviour change [15], explores couple dynamics and their influence on motivation and health behaviour change.

In the general population, the health benefits of being married or in a committed intimate relationship are well documented [14-15]. People in romantic partnerships tend to be healthier, engage with health care services and show a longer lifespan [15]. The role of intimate partnerships within the drug using population, however, has often been linked to increased risk-taking behaviour and generally has been viewed as a bad influence on health [14, 32-35]. Qualitative studies have shown that HCV management within couples could help consolidate a relationship, introducing sentiments such as feeling valued and cared for [14]. PWID generally experience hostile social environments, and intimate partnerships which involve sentiments such as those above, might represent one of the only types of meaningful social support and care that PWID encounter [14]. Social support is regarded as an essential part of HCV treatment, with many care pathways for PWID involving the role of a peer support worker as integral part of the treatment [36], providing empathy and trustworthiness to patients on treatment. However, it is not simply individualistic social support perception that has to be considered to explain the study findings.

Lewis' couples' interdependence theory [15] explains how motivation transformation can occur when partners experience a health event which is not only significant for the self, but has cognitive and emotional significance for the relationship. The attribution of significance of the health event to the dyad rather than the individual is the result of automatic consideration of partnership roles, subjective norms, commitment, quality of the relationship, and trust [15]. HCV infection is a health threat that has both emotional and cognitive implications on the relationship and on each partner. These implications help transform motivation from 'individual-focused' to 'relationship-focused', adding a layer of complex interplay between intrapersonal and interpersonal behaviour change processes. Once motivation has become 'relationship-focused', couples work together through communal coping to achieve better health through shared action to manage the health threat [15, 37]. Communal coping requires shared beliefs that joint effort is advantageous to combat HCV, communication about HCV infection between partners and cooperation between partners to manage HCV and its treatment. Communal coping

impacts health behaviour through the processes of outcome efficacy and couple efficacy [15, 37]. The couple's belief about the effectiveness of the coping/action strategies, i.e. HCV treatment, coupled with the couple's confidence about engaging in joint coping, i.e. reducing injecting frequency will ensure HCV is less likely to recur in the couple, will influence the behavioural outcome. The responsibility of the couples' (and individual) health therefore lies equally on both partners, enabling the couple to become the unit for risk-reducing behaviour change [14-15]. Associations between changes in self-perception and self-care have been identified before [12, 38]. Often these self-perceptions are intended as the 'self' as an 'addict' becoming the 'self' as a 'patient worthy of HCV treatment' [12, 14]. A similar process of psychological alteration might take place within the couple, with the couple's identity changing from 'drug-using partners' to 'HCV-treated partners, who coped with effects of treatment and achieved SVR as a unit', presenting a shared sense of 'self'.

*Reinfection*

One of the main challenges of treating patients with ongoing injecting risk behaviour is the risk of reinfection following successful treatment (defined as 12 weeks post-treatment aviremia). Published literature shows that people who have previously been infected (and been treated) are more likely to become infected with HCV once again compared to people who are HCV-naïve [39-42]. In a meta-analysis of 59 studies, Simmons and colleagues [42] report pooled HCV recurrence rates for low-risk, high-risk and HIV co-infected populations after treatment during IFN-era: respectively 1.85/1000 person years of follow-up (PYFU), 22.32/1000 PYFU and 32.02/1000 PYFU. These recurrence rates led to a summary 5-year risk of 0.95%, 10.67% and 15.02% respectively [42].
Reducing injecting risk behaviour is the first step to reduce the risk of HCV reinfection after successful treatment. Reducing injecting behaviour within romantic partnerships could have particular benefits in preventing reinfection, given the widespread injecting equipment sharing practices among sexual partners. The observed injecting frequency reduction within couples during treatment in this study, would seem to suggest a transitive relation between treating couples in a romantic partnership and a reduced risk of reinfection, with the reduced injecting behaviour as the linking factor. This will be investigated in future reinfection studies.

*Conclusions*

This study shows that treating a hard-to-reach population for HCV infection is not only possible, but also suggests health benefits beyond treatment of HCV alone. A significant reduction in injecting behaviour was observed in people who are not on OST and/or couples on HCV treatment when partners are sero-concordant compared to the rest of the sample A complex interplay of relationship-focused motivation transformation, outcome efficacy, couple efficacy and communal coping might improve patients' injecting risk-avoidance behaviour.

A few limitations are recognised within the study. Firstly, albeit the initial sample size seemed promising, missing data at different time points and the selection of different grouping variables considerably reduced the sample size for some of the analyses (N=42). However, the majority of clinical trials experience missing data [43] and the analyses were performed taking this into consideration. Two social variables did show a significant difference between those retained in the study and those lost, suggesting those who were lost to follow-up were less likely to have romantic or family social connections. This observation gives even more importance to this paper's findings of being on HCV treatment with a romantic partner, as it would suggest important social connections can influence engagement with research and healthcare professionals. Secondly, the effect of the results might not be as large for DAA treatment. IFN-based treatment was notoriously harsh and both therapeutic alliance in non-OST patients and communal coping within the couples might have developed strongly as a consequence of this. With the advent of DAA treatment, relationship-focused motivation and communal coping might become less necessary and prominent. Fewer side effects, significantly shorter treatment times and ease of treatment (oral treatment) will render the development of communal coping somewhat unnecessary, therefore reducing the likelihood of couples influencing each others' health-enhancing behaviour change. Shorter treatment times and ease of treatment might also affect the quality of the therapeutic relationship established between hard-to-reach patients and healthcare provider. Once again, this might impact on the hereby observed injecting behaviour change. However, the notion of HCV treatment alone, rather than the hardship endured or the length of treatment time, might be enough to kick-start the motivational transformation within an intimate partnership and effects on communal coping and risk-behaviour reduction could still be observed in the DAA treatment era. Further research on similar populations being treated with IFN-free DAA is needed in order to shed light on the generalisability of these results.

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**TABLES**

**Table 1: Characteristics of participants at enrolment on Eradicate-C study (study population and those lost to follow-up or with missing behavioural data).**

| Characteristic | Study population (N=84) | Lost to Follow-up or Missing Data (N=20) | □□ | Smallest expected |
|---|---|---|---|---|
| Female Sex (%) | 26 (31) | 2 (10) | 3.60 | 5.4 |
| Age, median (IQR) | 34 (23-45) | 33 (25.25-40.75) | | |
| Legal situation: none (%) | 49 (58.3) | 11 (55) | 0.07 | 8.5 |
| *Living situation* | | | | |
| Homeless (%) | 16 (19) | 6 (30) | 1.16 | 4.2 |
| Living in own or rented accommodation (%) | 61 (72.6) | 13 (65) | 0.46 | 5.8 |
| Living alone (%) | 38 (45.2) | 12 (60) | 1.41 | 9.6 |
| Living with partner (%) | 25 (29.8) | 4 (20) | 0.77 | 5.6 |
| Living with parents (%) | 12 (14.3) | 1 (5) | 1.27 | 2.5 |
| Living with other drug users (%) | 30 (35.7) | 5 (25) | 0.83 | 6.7 |
| *Romantic relationships* | | | | |
| Has partner (%) | 42 (50) | 5 (25) | 4.08* Fisher $p$=0.049 | 9.0 |
| Partner uses drugs (% of Has partner) | 34 (81) | 4 (80) | Fisher $p$=1 | Too small |
| Has children (%) | 50 (59.5) | 7 (35) | 3.92* Fisher $p$=0.08 | 9.0 |
| *Healthcare-related measures* | | | | |
| EQ5D Health state score, median (IQR) | 50 (20-80) | 45 (20-70) | | |
| On OST (%) | 60 (71.4) | 4 (20) | 4.06* Fisher $p$=0.07 | 4.3 |
| Methadone dose, median (IQR) | 70 (45-95) | 75 (61-89) | | |
| Weekly injecting frequency, Mean (STD) | 9.39 (8.87) | 11.35 (11.37) | | |

**Table 2: Post Hoc comparisons for weekly injecting frequency between week 1 of treatment and all subsequent repeated measurement every 4 weeks (N=32).**

| | Z | p * | *r* † |
|---|---|---|---|
| **Weeks 1-4** | -3.534 | < .001* | -.63 |
| **Weeks 1-8** | -5.459 | < .001* | -.97 |
| **Weeks 1-12** | -5.265 | < .001* | -.93 |
| **Weeks 1-16** | -4.759 | < .001* | -.84 |
| **Weeks 1-20** | -3.768 | < .001* | -.67 |
| **Weeks 1-24** | -3.225 | .001* | -.57 |
| **Weeks 1-26** | -4.495 | < .001* | -.80 |

* **Wilcoxon Signed Rank tests** Significant at p < .007 with Bonferroni correction
† Effect size *r*: Small = .1, Medium = .3, Large= .5

**Table 3: Chi Square Tests for association between injecting behaviour change variable (better/not better†) and psychosocial factors.**

| Characteristic (N) | $\chi^2$ (df) | p * | Fisher's Exact Test * |
|---|---|---|---|
| Legal situation (82) | 4.254 (4) | .373 | na |
| Living situation (82) | 1.361 (3) | .715 | na |
| Accommodation (82) | .04 (2) | .98 | na |
| Living with other drug users (79) | 2.007 (1) | .157 | .21 |
| *Romantic relationships* | | | |
| Has partner (42) | .023 (1) | .880 | 1 |
| Partner uses drugs* (42) | 4.43 (1) | .035* | .043* |
| Has children (82) | .067 (1) | .795 | .813 |
| *Healthcare-related measures* | | | |
| EQ5D Mobility (80) | .05 (1) | .823 | 1 |
| EQ5D Self-care (80) | 1.088 (1) | .297 | .368 |
| EQ5D Activity (79) | .621 (2) | .733 | na |
| EQ5D Pain (80) | .905 (2) | .636 | na |
| EQ5D Anxiety (80) | 1.159 (2) | .56 | na |
| On OST week 2* (82) | 10.412 (1) | .001* | .003* |

* Significant at p < .05
na: not available

† The difference between week 1 and week 8 injecting frequency was computed and categorised as 'Better' for a difference of ≥ 7or 'Not Better' otherwise

**FIGURE LEGENDS**

**Figure 1: Injecting frequency change by grouping**: * Significant at p < .05