Optimal targeting of Hepatitis C virus treatment among injecting drug users to those not enrolled in methadone maintenance programs

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Running head: HCV treatment and MMT

Abstract

Background: This work used mathematical modelling to explore effective policy for hepatitis C virus (HCV) treatment in Australia in the context of methadone maintenance treatment (MMT).

Method: We consider two models to depict HCV in the population of injecting drug users (IDU) within Australia. The first model considers the IDU population as a whole. The second model includes separate components for those that are or are not enrolled in MMT. The impact of different levels of HCV treatment and its allocation dependent on MMT status were then determined in terms of the steady state levels of each of these models.

Results: Although increasing levels of HCV treatment decrease chronic infection prevalence, initially numbers of acutely infected can rise. This is caused by the high rate of reinfection. We find that no matter the extent of HCV treatment, HCV prevalence cannot be eliminated without limiting risk behaviour. Assuming equal adherence to HCV therapy between MMT and non-MMT, over 84% of HCV treatment should be allocated to those not in MMT. Only if adherence to HCV therapy in non MMT patients falls below 44% of that in MMT then treatment should be preferentially directed to those in MMT.

Conclusions: Contrary to generally held beliefs regarding HCV treatment the majority of therapy should be allocated to those that are still actively injecting. This is due to rates of reinfection and to the high turnover of individuals in MMT. Higher adherence to HCV therapy in MMT would need to be achieved before this changed.

Keywords: Hepatitis C; treatment; modelling

1. Introduction

Hepatitis C virus (HCV) is a significant cause of morbidity and mortality with an estimated 170 million people chronically infected globally (National Centre in HIV Epidemiology and Clinical Research, 2003). Injecting drug use (IDU) is a major risk factor for HCV infection, and the majority of injecting drug users in virtually all nations are HCV positive (Lelutiu-Weinberger et al., 2009; National Centre in HIV Epidemiology and Clinical Research, 2007). Between 70% and 90% of acute HCV cases progress to chronic infection (Guidotti and Chisari, 2006). For those who receive treatment with pegylated interferon and ribavirin, approximately 50% will remain undetectable for HCV RNA 6 months post therapy (Novick and Kreek, 2008). However, HCV treatment is unpleasant and not necessarily well tolerated (Novick and Kreek, 2008). Moreover continued injecting behaviour places the user at risk of reinfection even if they successfully complete treatment (Aitken et al., 2008b).

In these conditions, it is understandable that health practitioners may be reluctant to treat injecting drug users for HCV given concerns over poor compliance and the perceived risk of re-infection (Hopwood and Treloar, 2007; Sylvestre, 2005). Both of these factors (compliance and risk of reinfection) can be significantly mitigated by methadone maintenance treatment (MMT) (Backmund et al., 2005). Compliance with HCV treatment can be enhanced through the daily MMT contact with treatment personnel, in addition to enhancing the initial referral into HCV treatment. Risk of reinfection can be reduced if the methadone treatment successfully reduces or eliminates injecting and other risk behaviour. It is therefore of interest to explore the dynamics of HCV infection, treatment and reinfection in the context of a drug treatment program such as MMT.

This aim of this work was to use mathematical modelling to explore and draw some conclusions about effective policy for HCV treatment in the context of MMT and the likelihood of reinfection.

The extent to which all injecting drug users should receive treatment for Hepatitis C even if they continue to inject or engage in high risk behaviour is of policy interest because it will suggest how resources for HCV treatment could be distributed (between those in MMT and those outside MMT). It is also of ethical interest (Edlin et al., 2001). Importantly, the high rates of movement into and out of MMT (Bell and Burrell, 2006; Bell et al., 2006; Chalmers et al., 2009) may mean that the putative advantages incurred by the MMT population in being treated for HCV may largely disappear.

2. Methods

2.1 The Single Group Model

We consider two mathematical models to depict HCV in the population of IDU. The first model considers the IDU population without separation into those that are or are not enrolled in MMT. The model is depicted in Figure 1 where IDUs are separated into: the susceptible group S, individuals that are injecting but not infected; the acutely infected group A, individuals that have contracted HCV but have yet to pass to the chronic stage of the disease; the chronically infected group, C; the HCV treatment group T; and individuals who have recovered from HCV either spontaneously or through HCV treatment R. Given the short period of acute infection, and that this frequently goes undetected, only chronically infected individuals were assumed to enrol in HCV treatment.

The governing equations for the first model are given in [1]

$$\dot{S}(t) = s - \beta \frac{A+C}{N} S + \lambda R - \mu S,$$

$$\dot{A}(t) = \beta \frac{A+C}{N} S - rA - cA - \mu A,$$

$$\dot{C}(t) = cA - \frac{u}{N} C + (1-g)\eta_F T - \mu C, \qquad [1]$$

$$\dot{T}(t) = \frac{u}{N} C - g\eta_g T - (1-g)\eta_F T - \mu T,$$

$$\dot{R}(t) = rA + g\eta_g T - \lambda R - \mu R,$$

where *N* is the total of the IDU population

$$N = S + A + C + R + T.$$

The terms in the first equation, which describe the rate of change in numbers of uninfected susceptible IDU, represent respectively: the influx of new users at rate s per year, the uninfected users contracting HCV due to sharing with acutely and chronically infected individuals BS where $B = \beta(A + C)/N$, users that have lost immunity at rate λ after previously clearing the disease, and those IDUs in the susceptible group that exit the system due to cessation of risk behaviour or mortality at the rate μ, per year (this same exit rate also applies to all other groups).

The force of infection B is the rate at which susceptible individuals become infected with HCV through exposure to infected users. The force of infection includes the probability that an uninfected individual will become infected when sharing with HCV-infected individuals over the course of a year β. Its value is given by $\beta = 1 - (1 - p)^n$. The parameter n is the number of days per year an IDU injects and shares, and *p* denotes the probability of getting infected each day of injecting and sharing, if sharing is with an HCV infected individual. The infection rate β is multiplied by the proportion of infectious individuals in the total population reflecting the probability of having contact with an infected individual.

Other terms of note are the terms rA and cA, which represent those users infected with the disease that either spontaneously recover at the rate r per year or pass to the chronic stage at the rate c per year and the terms $g\eta_g T$ and $(1-g)\eta_f T$, which represent those users that have entered treatment and succeed in clearing the disease with probability g or have failed treatment with probability $1-g$. In both cases, these users leave HCV treatment at the respective rates η_g and η_f per year.

We consider the rate at which HCV infected IDUs enter treatment to be dependent on the total population given by the treatment function

$$C(u) = u\frac{C}{N}, \qquad [2]$$

(with u being the number of IDUs treated for HCV per year) instead of a treatment function with constant rate of detection and treatment, u^*,

$$C(u) = u^* C.$$

The population dependent case [2] takes into account that there is a limited number of individuals in the total population and the relative effort of first finding IDUs before testing and subsequent HCV treatment (if positive). The two expressions give equivalent results for the steady-state results where $u^* = u/N$.

2.2 The Two Group Model with MMT

The second model separates the IDU population depending on whether individuals are enrolled in MMT. We duplicate the structure of the Single Group model for individuals in MMT (subscript M), and those not in MMT (subscript N). Users are assumed to be able to move between each group at rates a_N, the rate at which users move into MMT and a_M the rate at which users leave

MMT. The dynamics of the Two Group model are altered by two factors: 1) the rate of enrolment in MMT and 2) the relative likelihood of infection due to injecting risk behaviour (β_N/β_M).

The force of infection for users not in MMT is given by,

$$B_N = \beta_N \frac{\beta_N(A_N + C_N) + \beta_M(A_M + C_M)}{\beta_N N_N + \beta_M N_M}, \qquad [3]$$

and for those in MMT treatment,

$$B_M = \beta_M \frac{\beta_N(A_N + C_N) + \beta_M(A_M + C_M)}{\beta_N N_N + \beta_M N_M}, \qquad [4]$$

where N_N and N_M are the total populations of users in each group. The forces of infection for both populations are in essence given by their respective chances of becoming infected through their different injecting/sharing rates, β_N and β_M.The corresponding equations for the Two Group model are

$$\begin{aligned}
\dot{S}_N(t) &= s - B_N S_N + \lambda_N R_N - (\mu_N + a_N)S_N + a_M S_M \\
\dot{A}_N(t) &= B_N S_N - (r_N + c_N + \mu_N + a_N)A_N + a_M A_M \\
\dot{C}_N(t) &= c_N A_N + (1 - g_N)\eta_{f_N} T_N - (C_N(u_N) + \mu_N + a_N)C_N + a_M C_M \\
\dot{T}_N(t) &= C_N(u_N)C_N - \left(g_N\eta_{g_N} + (1 - g_N)\eta_{f_N} + \mu_N + a_N\right)T_N + a_M T_M \\
\dot{R}_N(t) &= r_N A_N + g_N\eta_{g_N} T_N - (\lambda_N + \mu_N + a_N)R_N + a_M R_M \\
\dot{S}_M(t) &= -B_M S_M + \lambda_M R_M - (\mu_M + a_M)S_M + a_N S_N \\
\dot{A}_M(t) &= B_M S_M - (r_M + c_M + \mu_M + a_M)A_M + a_N A_N \\
\dot{C}_M(t) &= c_M A_M + (1 - g_M)\eta_{f_M} T_M - (C_M(u_M) + \mu_M + a_M)C_M + a_N C_N \\
\dot{T}_M(t) &= C_M(u_M)C_M - \left(g_M\eta_{g_M} + (1 - g_M)\eta_{f_M} + \mu_M + a_M\right)T_M + a_N T_N \\
\dot{R}_M(t) &= r_M A_M + g_M\eta_{g_M} T_M - (\lambda_M + \mu_M + a_M)R_M + a_N R_N
\end{aligned} \qquad [5]$$

where we have used the same notation as in the Single Group model [1] but now with indices N and M to denote the different groups. We assume new IDU enter the susceptible group not in MMT S_N.

2.3 Parameter Estimation

We estimated parameters for the models based on IDU and HCV observations in Australia. These estimates are summarised in Table 1. The estimated number of new IDUs per year s, is 4500 (Chalmers et al., 2009). The spontaneous recovery rate, r, and the progression rate to chronic infection c, can be estimated from observations that 25% of all HCV infected individuals clear infection within the first 6 months with the remainder progressing to chronic infection (Micallef et al., 2006; Razali et al., 2007). So we assume an average time in the acute state A, to be 6 months for all individuals. A distinction must be made between those acutely and chronically infected IDUs to take into account the approximately 25% of those infected that clear the virus without treatment (Guidotti and Chisari, 2006). The annual rate of spontaneous recovery is then estimated as the inverse of the time in acute infection (in years) times the probability an individual clears infection (25%) which gives $r = 0.5$ per year. The chronic progression rate c, is similarly estimated from the inverse of the time in acute infection times the probability an individual fails to clear infection 75%. This leads to the parameter estimate $c = 1.5$(year^{-1}).

In Australia, the annual HCV treatment rate is around 1% (Matthews, 2005). The length of HCV treatment is 24 weeks for Genotypes 2 and 3 and 48 weeks for Genotype 1 (Novick and Kreek, 2008; Ostapowicz et al., 1999). Hence we assume an average length of treatment of 36 weeks. We assume that if HCV treatment is successful the patient will stay for the entire course, and that those not successful adhere only half as well, so treatment is for an average period of 18 weeks (Ostapowicz et al., 1999). This leads to the rate η_f of those failing HCV treatment of

52/18 per year and the rate for η_g is 52/36 per year. The probability of success of HCV treatment g is approximately 50% (Novick and Kreek, 2008).

HCV prevalence among IDUs in Australia is approximately 60% (National Centre in HIV Epidemiology and Clinical Research, 2007, 2008). We take an estimate of incidence to be 20% per year (Matthews, 2005; Micallef et al., 2006). This is likely to be an overestimate, but is somewhat accommodated by our under-estimate of reinfection rate (see below). The number of new infections per year is therefore given by

$$\beta \frac{A+C}{N} S = \beta \times 0.6 \times S = 0.2S$$

so that $\beta = \frac{0.2}{0.6} = 1/3$ per year. There is debate about the rate of reinfection in those that have previously cleared infection with estimates ranging from 2% to 47% per year (Aitken et al., 2008a; Backmund et al., 2004; Grebely et al., 2006). We assume a reinfection rate, $\lambda\beta(A+C)/N$, of 5% per year thus $\lambda = 1/4$ but acknowledge that new research suggests it is higher than this.

The exit rate μ, was determined from fitting the steady state prevalence, $(A+C)/N$ of 60%. Assuming that current endemic steady state corresponds to the situation of 1% of the population of IDUs being treated for HCV (u/N=0.01) we estimate the exit rate to be roughly 0.083 per year.

For the Two Group model, we assume that most of the parameters are the same as those for the Single Group model, with the exception being the infection rate β. We do not assume zero injecting whilst in MMT. We use data from Australian clinical trials on the number of days injecting out of MMT and within MMT: those within MMT on average inject approximately 8 fold less than those not enrolled in a program (Mattick et al., 2001; Moore et al., 2007; Teesson et

al., 2006). For values of β that are not too large, $\beta = 1 - (1-p)^n \approx pn$. So an 8-fold higher sharing rate for those not in MMT would then provide a ratio of infection rates over the course of a year of approximately $\frac{\beta_N}{\beta_M} \approx \frac{pn_N}{pn_M} = \frac{n_N}{n_M} = 8.36$.

By assuming 60% HCV population prevalence we obtain $\beta_N = 0.503$ and $\beta_M = 0.06$ compared to $\beta = 1/3 \approx 0.33$ for the Single Group model. On average an individual stays in MMT for 8 months, and stays out of treatment for an average of 12 months before re-entering (Chalmers et al., 2009), so $a_M = 3/2$ and $a_N = 1$.

2.4 Sensitivity Analyses

Results described below are robust to parameter choices (Table 1). Sensitivity analyses revealed that the parameters that had the largest impact on steady state HCV prevalence were the rate of infection pn, and the exit rate μ, where changing these by $\pm 10\%$ resulted in a 4-6% change in the predicted prevalence. There was a smaller 3% change associated with the clearance probability p_c. Perturbations of all other parameters by $\pm 10\%$, resulted in changes in steady state HCV prevalence of less that 1%. The sensitivity analysis for the Two Group model also determined that the infection rate of the non-methadone treatment group, β_N, and the exit rate (when varied equally between the groups), μ, had the largest effect on the predicted steady state prevalence (4-6%).

3. Results

3.1 Single Group Model

Initially we consider the IDU population as a whole, without separation into whether individuals are enrolled in MMT or not. In this instance we investigate, on average, the impact on eventual HCV prevalence of increasing levels of HCV treatment. The eventual prevalence is determined from the steady state value of the mathematical model, and we denote outcomes in terms of

these steady state values. Of particular interest is the extent to which reinfection, for those that clear the infection either spontaneously or after successful HCV treatment, will negate any decreases in expected levels of HCV prevalence with expanded HCV treatment. The risk of HCV reinfection for active drug users has been one of the reasons promulgated for not providing HCV treatment to these individuals (Aitken et al., 2008b; Sylvestre, 2005).

At current HCV treatment levels (1% of IDU, (Matthews, 2005; National Centre in HIV Epidemiology and Clinical Research, 2008) the model reproduces the expected 60% HCV prevalence. As increasing numbers of IDU are enrolled in HCV treatment, the percentage of chronically infected IDU decreases, with the fastest decrease in prevalence occurring for the earliest increases in treatment (see Figure 2). On the other hand the percentage of IDU with acute infection actually increases with small increases in treatment (Figure 2), before eventually decreasing as well. The fastest decrease in acute infection occurs at the highest treatment levels. Both chronic and acute HCV prevalence are estimated to eventually vanish at a treatment level of $\overline{u_1}$ =56.5%.

Although this critical treatment level eventually eliminates infection, it is slow to do so taking 3.3 years for chronically infected numbers to decrease by half and 11.1 years for acute numbers to halve. Implementing this critical treatment level of $\overline{u_1}$ =56.5% from current levels where HCV prevalence is 60%, and the majority of these in the chronic stage, would mean that initially 56.5% of 60% so 33.9% of IDUs would be enrolled in HCV treatment. However as HCV treatment decreases prevalence, this treatment burden also decreases so that after 3 years when chronically infected numbers have halved, then the percentage enrolled in treatment at that time will also halve to 17%.

The ability to eliminate HCV prevalence with suitably high levels of HCV treatment is calculated on parameter levels that duplicate the situation within Australia. It is dependent on rates of

needle sharing, contained within the infection term β, and this must be less than the rates at which acutely infected individuals leave this compartment,

$$\beta \leq r + \mu + c$$

Since $\beta \approx pn$, if sharing n is higher than this then no amount of testing and treatment will eradicate HCV infection.

3.2 The Two Group model: the impact of MMT

The previous analysis investigated the impact of increasing levels of HCV treatment on prevalence, without regard for changes in injecting/sharing when IDU are enrolled in MMT. The proportion of IDU enrolled in MMT can be substantial, with approximately 40,000 individuals currently enrolled in MMT in Australia (Australian Institute of Health and Welfare (AIHW), 2007). In this second model we divide the IDU population into two groups, those in MMT and who therefore inject/share approximately 8-fold less than those not in MMT. We now investigate two aspects of HCV treatment: how does treating U IDU each year impact on eventual HCV prevalence, and how is this best apportioned between individuals in MMT u_M, and those not in MMT u_N, $(u_N + u_M = U)$?

Under the model parameter values the total population of IDU consists of 54,217 individuals, of which 20,990 are in MMT at any one time. If total treatment U amounts to 50% of all IDU then the minimum steady state HCV prevalence of 4.20% is reached if 84% (42%/50%) of HCV treatment is allocated to IDUs not enrolled in MMT while only 16% (8%/50%) is allocated to those in MMT. This is displayed in Figure 3 for those not in MMT: if 50% of the total population are treated, minimum steady state prevalence (vertical axis) is achieved when 42% of those not in MMT are treated (Figure 3). In that situation 22,845 non-MMT individuals will be tested and

the resulting 782 chronically HCV-infected individuals will be treated, whereas 4,263 MMT individuals will be tested and 164 chronically infected individuals entered onto HCV therapy.

This optimal allocation shifts between groups as levels of HCV treatment increase from their current 1% (Figure 4). At current treatment levels all therapy should be targeted to those not in MMT, but with increasing levels of HCV treatment a portion of this shifts to those enrolled in MMT (Figure 4). For the critical treatment level that theoretically eliminates HCV, $\bar{u}_2 = 60\%$ the optimal allocation is approximately 15% to those in MMT and the vast majority 85% to those not in MMT.

In the previous calculations the only difference assumed between the two groups is that those in MMT are less likely to inject and share, and are therefore less likely to become HCV-infected. However achievement of a sustained virological response has been associated with less frequent drug use (Sylvestre, 2005). There is some debate about whether MMT increases compliance with HCV treatment (Ebner et al., 2009; Novick and Kreek, 2008; Treloar and Fraser, in press). Therefore, if we assume that those not in MMT are less adherent to HCV-treatment resulting in lower probability of success for this group ($g_N < g_M$), then the optimal allocation point shifts to favour those in MMT. For the case of 50% treatment of all IDU, if those in the non-MMT group are only 48% as adherent to HCV therapy as those in MMT then allocation of HCV testing becomes equally distributed between groups. However even at this point there will be more individuals treated, rather than just tested, for HCV given the higher HCV prevalence in the non-MMT group. Of the model value of 33,227 individuals not in MMT, 13,550 will be tested and the 2,090 of these who have chronic HCV will be treated. On the other hand only 1,919 MMT individuals will have chronic HCV and be treated.

Numbers entered into HCV therapy in each group will be the same (2,067 individuals) if adherence to HCV therapy in the non MMT group is only 44.3% of that in the MMT group. If adherence to HCV therapy in the non MMT group falls below 44.3% of that in the MMT group then the number tested and treated should be preferentially directed to those in MMT.

4. Discussion and Conclusions

Although increasing HCV treatment can lead to a relatively large decrease in chronically HCV-infected IDU, HCV reinfection significantly impacts on the success of HCV treatment. The numbers acutely infected decay at a slow rate, as those that have previously been chronically infected re-enter the susceptible pool and become infected again. Contrary to expectations this results in higher levels of acute infection for small increases in treatment level.

We have assumed that unlike human immunodeficiency virus (HIV) (Yerly et al., 2001), where viral loads are highest, acute HCV infection is not more infectious than chronic stage disease. Although viral loads are generally highest at acute HCV infection (Herring et al., 2005; Thimme et al., 2001), they generally do not experience a 100-fold decrease to chronic infection as seen in HIV (Murray et al., 1998). However if acute HCV infection is more infectious than chronic stage disease then it will exacerbate the rise in numbers acutely infected IDU when treatment increases, and will further slow the time taken to reduce HCV prevalence.

Those acutely infected were included separately in the models since they can experience spontaneous clearance of HCV infection (Micallef et al., 2006). However those in the acute infection state did not enter HCV therapy in the model. . In Australia in 2006 diagnoses of acute HCV infection accounted for only 431 (3%) of a total of 12,526 HCV diagnoses in that year (National Centre in HIV Epidemiology and Clinical Research, 2007). The difficulty in identifying

acute HCV infection is a global problem with acute HCV infection in the United States in 2007 representing 849 (5%) out of an estimated 17,000 new HCV infections (Centers for Disease Control and Prevention, 2009). However HCV treatment during acute infection can lead to higher rates of sustained virological response (Santantonio et al., 2008). Given that acute HCV infections are more likely to occur in individuals not enrolled in MMT, including the acute group in HCV treatment would further shift the preference towards the non-MMT group, although the change would not be substantial, given the difficulty in identifying this group.

When HCV treatment is sufficiently high, approximately 60%, these models predict that HCV can be eliminated. Regardless of whether this is realistically feasible, our calculations underline the importance of programs that minimise the sharing of infected needles. If sharing is not effectively constrained, then no level of HCV treatment will be able to eliminate the epidemic, even in this simple theoretical setting. It emphasises the role that Needle Syringe Programs have had in containing HIV levels in Australian IDU, and in keeping HCV prevalence, although still high, at levels lower than other communities that have not invested as heavily in prevention (Murray et al., 2003). It also stresses that any push to expand HCV treatment must not be at the expense of preventative measures.

It is difficult to accurately determine the rate of cycling in and out of MMT. While we use recent published estimates, these are averages across diverse populations and indeed, little is known about the rates of entry and exit and lengths of stay in MMT in Australia, because most research measures the proportion remaining in treatment at certain time points (3, 6 and 12 months). These do not easily convert to estimated duration in or out of MMT. We use population parameters of IDU, which are not necessarily heroin only (ie people inject amphetamines and are at risk of HCV infection through any injecting behaviour, not just opioids), and a treatment that is only for heroin (MMT).

Notwithstanding all these limitations, many of which are normal in the course of mathematical modelling (eg (Razali et al., 2007), this work represents the beginning of opportunities to explore, through mathematical modelling, ways in which policy on HCV treatment can be improved. Including more aspects of practical HCV treatment in a population over the long term, such as the spread of drug resistant virus and the impact of new treatment options such as HCV protease inhibitors, will be important components for the future. Although our model is simple, both in terms of the drug treatment (represented by MMT) and in terms of reinfection rate, it reveals some important potential policy implications: that we should be focusing our efforts on treating those with HCV in the community who continue to inject is perhaps at least a counter-intuitive finding. Improved compliance with HCV therapy for those in MMT would need to be high to counteract our finding. Outcome studies are required to derive effect sizes on adherence and therapy success rates. Future models could then use these, providing greater precision in determining the optimal HCV therapy allocation. Changes to these important parameters (adherence, methadone turnover rates, HCV therapy outcomes) may lead to alternate conclusions from those derived here and may confer greater policy relevance to treating those within MMT over those in the community.

The preferential targeting of HCV treatment to those not in MMT is partially a result of the continual recycling of IDUs in and out of MMT. Calculations with longer duration in MMT shift the optimal HCV treatment allocation more to those in MMT. So any measures that can lead to more sustained MMT will have a double effect: it will reduce the likelihood than an individual will continue to inject, and it will offer greater effectiveness of any HCV treatment. Especially if adherence is greater for those in MMT, retention of individuals in MMT can provide a multiplier effect on HCV treatment. Our results of the high proportion of HCV treatment targeted to

individuals who continue to inject may reflect the poor retention and cycling behaviour of patients within MMT rather than any inherent benefit of targeting active IDUs.

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Table 1 Baseline Parameter Sources

Parameter	Definition	Value
s	Number of users starting injecting (per year)	4500
r	Spontaneous recovery rate (per year)	0.5
c	Rate of progression to chronic state *C* (per year)	1.5
p_c	Probability of clearing acute infection	25%
d_{Ac}	Duration of Acute infection (years)	1/2
dT_s	Duration of HCV treatment if succeeding (weeks)	36
dT_f	Duration of HCV treatment if failing (weeks)	18
η_f	Rate of leaving HCV treatment when failing (per year)	52/18
η_g	Rate of leaving HCV treatment when succeeding (per year)	52/36
g	Probability of success of HCV treatment	50%
β	Rate of infection due to sharing (per year per contact with an infected individual)	1/3
λ	Rate of individuals leaving the *R* state (per year)	1/4
u^*	Percentage of individuals on HCV treatment (per year)	1%
u	Number of individuals entering HCV treatment (per year)	539.362
μ	Exit rate per year	0.083
β_N	Rate of infection of IDUs (not in MMT) due to sharing (per year per contact with an infected individual)	0.503
β_M	Rate of infection of IDUs (in MMT) due to sharing (per year per contact with an infected individual)	0.060
u_N	Number of HCV infected IDUs entering treatment not in MMT (users per year)	332.270

u_M	Number of HCV infected IDUs entering treatment in MMT (per year)	209.899
${u_N}^*$	Number of HCV infected IDUs entering treatment not in MMT (per year)	1%
${u_M}^*$	Number of HCV infected IDUs entering treatment in MMT (per year)	1%
dT_m	Duration in MMT (months)	8
a_M	Rate of leaving MMT (per year)	3/2
dT_n	Duration out of MMT (months)	12
a_N	Rate of entering methadone treatment (per year)	1

Figure Legends

Figure 1: Single Group Model.

Figure 2 The effect of the treatment rate (percentage of the total population per year), $\boldsymbol{u}$, on the percentage of acutely infected, $\boldsymbol{A}$, (left) and chronically infected, $\boldsymbol{C}$, (right) users in the endemic steady state.

Figure 3 The estimated HCV prevalence in the endemic steady state is lowest (4.2%) when 42% of those not in MMT receive HCV treatment ($\boldsymbol{u_N}$/N) if we treat 50% of the total population.

Figure 4 The effect of varying the percentage of the total population treated per year on the optimal treatment allocation between non-methadone (solid line) and methadone (dashed line) participants.