EPIDEMIOLOGICAL CONSEQUENCES OF NON-COMPLIANCE TO HCV THERAPY AMONG IDUS

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ABSTRACT

Treatment for infections with hepatitis C viruses has recently developed markedly, and range from nonspecific interferon-based treatments to specific antiviral treatments, such as those that inhibit hepatitis virus coded protein production or activity. Despite advancements in the management of HCV, the epidemic prevalence continues to rise among injection drug misusers who, are responsible for approximately 90% of new HCV cases, because of their poor compliance with treatment requirements and conditions. A simple mathematical model is developed to explore the impact of treatment defaulting on the transimission dynamics of HCV among injection drug misusers. Numerical simulations are provided to support analytical findings.

Key words: *HCV therapy, IDUS, non-compliance, reproductive number, sensitivity analysis.*

1. INTRODUCTION

Injection drug users (IDUs) account for a disproportionately large burden of hepatitis C infection. Ninety percent of new infections worldwide (approximately 90% in Australia, approximately 72% in Canada, and approximately 54% in the United States) are contracted through injection drug use [1], and the majority of chronic infections, particularly in developed countries, are attributed to injection drug misuse [1, 2]. Despite advancements in the management of chronic hepatitis C [3, 4, 5] and suggestions that treatment of recently acquired hepatitis C can lead to sustained virological response (SVR) rates of up to 98% [6, 7, 8], there continues to be a low rate of treatment completion coupled with low treatment uptake among current IDUs. For instance: studies conducted in IDU populations in developed countries suggest that very few IDUs infected with hepatitis C have received antiviral therapy [1, 9]. The Australian annual survey at needle and syringe programs (2001-2007) reported that 90% of persons who know that they are infected with hepatitis C virus have never received treatment, and only 0.9%-2.4% were receiving treatment at the time of the survey [1]. In a cohort of 597 American IDUs, only 26 participants received treatment, and the rate of treatment in this cohort remained relatively stable at $<1\%$ per year [1, 10]

Adhering to a treatment schedule and successfully completing it are crucial to the control of any disease [11, 12]. Poor adherence to self-administration of treatment of a chronic disease is a common behavioral problem [1, 13, 14] including hepatitis C infection [1]. The World Health Organization defines a defaulter as a patient who does not complete the stipulated course of treatment [12]. However, in common parlance, a defaulter is someone who does not complete the stipulated course of treatment. Other terms used synonymously are absentees, discontinuation, non-compliance, non-adherence etc, each having slightly connotation.

Mathematical models have become invaluable management tools for epidemiologists, both shedding light on the mechanisms underlying the observed dynamics as well as making quantitative predictions on the effectiveness of different control measures. The literature and development of mathematical epidemiology is well documented and can be found in [15, 16, 17]. In this paper a simple deterministic mathematical model is used to explore the epidemiological consequences of non-compliance to HCV therapy among injection drug misusers. The structure of the paper is as follows. In Section 2, we formulate the model. In Section 3, we derive analytical results. In Section 4, we present numerical simulations. We conclude with a discussion in Section 5.

2. MODEL FORMULATION

Based on epidemiological status, the population is divided into five classes according to individual's disease status: susceptibles (S), Latently infected (L), infectious individuals (I), defaulters (D) and recoveries (R). The total population (N) at time t is given by, $N = S + L + I + D + R$. New recruits join the susceptible class at a constant rate Λ (assumed susceptible), p denotes a proportion of individuals who have been vaccinated. Susceptible individuals acquire HCV infection at rate $\lambda = \beta(I + D)/N$, where β is the probability of getting infected whenever a susceptible individual uses a contaminated needle, syringe or any other tools that might be used to

share intravenous drugs, γ is the incubation period. HCV infectives are treated at a constant rate ϕ. On treatment a proportion f will fail to complete (defaulters) treatment, and the complementary proportion $(1-f)$ will complete treatment. Natural mortality rate μ is assumed to be constant in all classes. The model takes the form:

$$\begin{aligned} S' &= (1-p)\Lambda - (\mu+\lambda)S, \\ L' &= \lambda S - (\gamma+\mu)L, \\ I' &= \gamma L - (\phi+\mu)I, \\ D' &= f\phi I - \mu D, \\ R' &= (1-f)\phi C - \mu R. \end{aligned} \tag{1}$$

The model flow diagram is depicted in Figure 1.

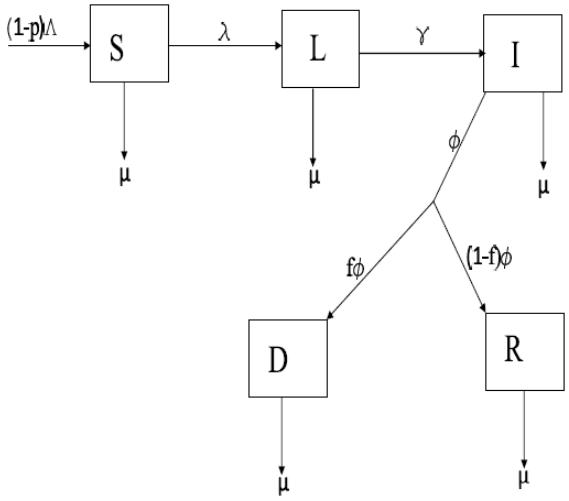

Figure 1: Model flow diagram.

For system (1), the first octant in the state space is positively invariant and attracting; that is, solutions that start where all the variables are non-negative remain there. Thus, system (1) will be analyzed in a suitable region $\Phi \subset \mathbb{R}^5_+$. The region

$$\Phi = \left\{ (S,L,I,D,R) \in \mathbb{R}^5_+ : N \le \frac{(1-p)\Lambda}{\mu} \right\}, \tag{2}$$

is positively invariant and attracting. Existence, uniqueness and continuation results for system (1) holds in this region.

3. ANALYTICAL RESULTS

3.1 The disease-free equilibrium

Model system (1) has an evident Disease-Free Equilibrium (DFE) given by

$$V^0 = \left(S^0, L^0, I^0, D^0, R^0\right) = \left(\frac{(1-p)\Lambda}{\mu}, 0,0,0,0 \right). \tag{3}$$

The linear stability of V^0 is obtained using the next-generation matrix [18] for system (1). Using the notation in [18], the nonnegative matrix F (representing the new infection terms) and the nonsingular matrix V (representing the remaining transfer terms) are given by

$$F = \begin{bmatrix} 0 & \beta & \beta \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

and

$$V = \begin{bmatrix} \gamma+\mu & 0 & 0 \\ -\gamma & \phi+\mu & 0 \\ \mu & -f\phi & 0 \end{bmatrix}.$$

Thus, the reproductive number for system (1) denoted by R_c is given by

$$R_c = \frac{\beta\gamma(f\phi+\mu)}{\mu(\phi+\mu)(\gamma+\mu)}, \tag{4}$$

R_c is a threshold for disease invasion or eradication, under suitable conditions, such as the absence of a backward bifurcation (c.f [19] for more discussion). Using Theorem 2 in [18], the following result is established.

Lemma 1 *The disease-free equilibrium* V^0 *of system (1) is locally-asymptotically stable (LAS) if* $R_c \leq 1$ *and unstable if* $R_c > 1$.

3.1.1 Global stability of DFE

Lemma 2 *The disease-free equilibrium point* V^0*, is globally asymptotically stable if* $R_c \leq 1$ *and unstable if* $R_c > 1$.

Proof. The proof is based on using a Comparison Theorem [20, 21]. Note that the equations of the infected components in system (1) can be written as

$$\begin{bmatrix} L' \\ I' \\ D' \end{bmatrix} = [F-V]\begin{bmatrix} L \\ I \\ D \end{bmatrix} - \beta[1-\frac{S}{N}]\begin{bmatrix} 0 & 1 & 1 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}\begin{bmatrix} L \\ I \\ D \end{bmatrix}$$

where F, and V, are as defined earlier. Since $S \leq N$, (for all $t \geq 0$) in Φ it follows that

$$\begin{bmatrix} L' \\ I' \\ D' \end{bmatrix} \leq [F-V]\begin{bmatrix} L \\ I \\ D \end{bmatrix} \tag{5}$$

Using the fact that the eigenvalues of the matrix $F-V$ all have negative real parts, it follows that the linearized differential inequality system (5) is stable whenever $R_c \leq 1$. Consequently, (L, I, D) $\rightarrow$ (0,0,0) as $t \rightarrow \infty$. Thus, by Comparison Theorem [20] (L, I, D) $\rightarrow$(0,0,0) as $t \rightarrow \infty$ and evaluating system (1) at, L = I = D = 0 gives, $S \rightarrow S^0$ for $R_c < 1$. Hence, the DFE (V^0) is GAS for $R_c \leq 1$.

3.2 Endemic equilibrium

Model system (1) has an Endemic Equilibrium (EE) given by

$$V^* = (S^*, L^*, I^*, D^*, R^*)$$

where

$$\begin{aligned} S^* &= \frac{(1-p)\Lambda}{R_c}, \quad L^* = \frac{(R_c-1)(1-p)\Lambda}{R_c}, \quad I^* = \frac{\gamma(R_c-1)(1-p)\Lambda}{(\phi+\mu)R_c}, \\ D^* &= \frac{f\phi(R_c-1)(1-p)\Lambda}{(\phi+\mu)R_c}, \quad R^* = \frac{\phi(1-f)(R_c-1)(1-p)\Lambda}{(\phi+\mu)R_c}. \end{aligned} \tag{6}$$

Thus, system (1) has an endemic equilibrium V^* which makes biological sense only whenever $R_c > 1$. This leads to Lemma 3. 3 below.

Lemma 3 *There endemic equilibrium* V^* *exists whenever* $R_c > 1$.

The following theorem will be useful.

Theorem 1 *(See [22].) Consider the following general system of ordinary differential equations with a parameter* ϕ

, $$\frac{dx}{dt} = f(x,\phi),\ f:\mathrm{R}^n \times \mathrm{R} \to \mathrm{R}^n and\ \ f \in \mathrm{C}^2(\mathrm{R}^n \times \mathrm{R}). \tag{7}$$

Without loss of generality, it is assumed that 0 is an equilibrium for system (7) for all values of the parameter ϕ; that is, $f(0,\phi) = 0$ for all ϕ. Assume

A1: $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ is the linearisation of system (7) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;

A2: Matrix A has a right eigenvector w and a left eigenvector v corresponding to the zero eigeinvalue.

Let f_k be the k th component of f and

$$\begin{aligned} a &= \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ b &= \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \end{aligned} \tag{8}$$

The local dynamics of (7) around 0 are governed by a and b in the following manner:

i. $a > 0, b > 0$, When $\phi < 0$ with $|\phi| = 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi = 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium;

ii. $a < 0, b < 0$. When $\phi < 0$ with $|\phi| = 1$, 0 is unstable; when $0 < \phi = 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium;

iii. $a > 0, b < 0$. When $\phi < 0$ with $|\phi| = 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi = 1$, 0 is stable, and a positive unstable equilibrium appears;

iv. $a < 0, b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly, a negative equilibrium becomes positive and locally asymptotically stable.

In order to apply the Center Manifold Theory, we make the following change of variables. Set $S = x_1$, $L = x_2$, $I = x_3$, $D = x_4$, $R = x_5$ so that $N = \sum_{n=1}^{5} x_n$ and $\lambda = \beta(x_3 + x_4)/\sum_{n=1}^{5} x_n$. Further, by using vector notation $\vec{x} = (x_1, x_2, x_3, x_4, x_5)^T$, model system (1) can be written in the form $\frac{d\vec{x}}{dt} = F(\vec{x})$, with $F = (f_1, f_2, f_3, f_4, f_5)^T$. That is:

$$\begin{aligned} x_1' = f_1 &= (1-p)\Lambda - (\mu+\lambda)x_1, \\ x_2' = f_2 &= \lambda x_1 - (\gamma+\mu)x_2, \\ x_3' = f_3 &= \gamma x_2 - (\phi+\mu)x_3, \\ x_4' = f_4 &= f\phi x_3 - \mu x_4, \\ x_4' = f_4 &= (1-f)\phi x_3 - \mu x_5. \end{aligned} \tag{9}$$

The method entails evaluating the Jacobian of system (9) at V^0, is given by

$$J(V^0) = \begin{bmatrix} -\mu & 0 & -\beta & -\beta & 0 \\ 0 & -(\gamma+\mu) & \beta & \beta & 0 \\ 0 & \gamma & -(\mu+\phi) & 0 & 0 \\ 0 & 0 & f\phi & -\mu & 0 \\ 0 & 0 & (1-f)\phi & 0 & -\mu \end{bmatrix}, \tag{10}$$

from which it can be shown that

$$R_c = \frac{\beta\gamma(f\phi+\mu)}{\mu(\phi+\mu)(\gamma+\mu)} \tag{11}$$

Suppose β is chosen as a bifurcation parameter. Solving (11) for $R_c = 1$, one gets

$$\beta = \beta^* = \frac{\mu(\phi+\mu)(\gamma+\mu)}{\gamma(f\phi+\mu)} \tag{12}$$

It can be shown that the Jacobian $J(E^0)$ of system (9) at $\beta = \beta^*$ has a right eigenvector (corresponding to the zero eigenvalue) given by $\vec{w} = (w_1, w_2, w_3, w_4, w_5)^T$, where

$$\begin{aligned} w_1 &= -(\mu+\phi)(\mu+\gamma)w_3R_c, \quad w_2 = (\mu+\phi)w_3R_c, \quad w_3 > 0, \\ w_4 &= \frac{f\phi}{\mu}w_3, \quad w_5 = \frac{(1-f)\phi}{\mu}w_3. \end{aligned} \tag{13}$$

Further, the Jacobian $J(V^0)$ has a left eigenvector (associated with the zero eigenvalue) given by $\mathbf{v} = (v_1, v_2, v_3, v_4, v_5)^T$, where

$$v_1 = v_5 = 0, \quad v_2 = \frac{\gamma v_3}{\gamma+\mu}, \quad v_3 > 0, \quad v_4 = \frac{(\mu+\phi)R_c}{(\mu+f\phi)}v_3. \tag{14}$$

The associated non-zero partial derivatives of F at the DFE are given by

$$\begin{aligned} &\frac{\partial^2 f_2}{\partial x_2\partial x_3} = \frac{\partial^2 f_2}{\partial x_2\partial x_5} = \frac{\partial^2 f_2}{\partial x_3\partial x_4} = \frac{\partial^2 f_2}{\partial x_3\partial x_5} = \frac{\partial^2 f_2}{\partial x_4\partial x_5} - \frac{\mu\beta^*}{(1-p)\Lambda}, \\ &\frac{\partial^2 f_2}{\partial x_3^2} = \frac{\partial^2 f_2}{\partial x_5^2} = -\frac{2\mu\beta^*}{(1-p)\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_3\partial\beta^*} = \frac{\partial^2 f_2}{\partial x_4\partial\beta^*} = 1. \end{aligned} \tag{15}$$

From (15), it follows that

$$a = -\frac{2\beta^*(\phi+\mu)(\mu^2R_c + (1-f)(2+\mu R_c)\phi)}{\mu(1-p)(\gamma+\mu)\Lambda}w_3^2v_3 < 0,$$

and (16)

$$b = \frac{(\phi+\mu)R_c}{\beta^*}w_3v_3 > 0.$$

Since $a < 0$ and $b > 0$ hence, the following result is established according to Theorem 1 item (iv) above.

Lemma 4 *The endemic equilibrium* V^* *is locally asymptotically stable for* $R_c > 1$, *but close to* 1.

4. SIMULATION STUDY OF POPULATION-LEVEL EFFECTS

In order to illustrate the results of the foregoing analysis, we have simulated model system (1) using the baseline parameters values summarized in Table 1.

Parameter	Symbol	Sample Value	Range	Source
Recruitment rate	Λ	200 yr^{-1}	N/A	Assumed
Transmissibility	β	0.05	0.025-0.05	[23]
Incubation period	γ	7.3 yr^{-1}	2.433-24.333	[24]
Treatment rate	ϕ	0.02 yr^{-1}	0.01-0.02	[25]
Natural mortality rate	μ	0.0142yr^{-1}	0.01-0.02	[25]
Proportion of defaulters	f	0.533	0.0-1.0	[26]
Proportion of vaccinated individuals	p	0.5	0.0-1.0	[27]

Table 1: Model parameters and their interpretations.

4.1 Sensitivity analysis

In many epidemiological models, the magnitude of the reproductive number is associated with the level of infection. The same is true in model (1). Sensitivity analysis assesses the amount and type of change inherent in the model as captured by the terms that define the reproductive number (R_c). If R_c is very sensitive to a particular parameter, then a perturbation of the conditions that connect the dynamics to such a parameter may prove to be useful in identifying policies or intervention strategies that reduce epidemic prevalence. From equation (4), we observe that in the absence of defaulters, the reproductive number is given by

$$R_{c(f=0)} = R_v = \frac{\beta\gamma}{(\phi+\mu)(\gamma+\mu)}. \tag{17}$$

Thus, R_c can be presented as

$$\begin{aligned} R_c &= \left[1+\frac{f\phi}{\mu}\right]\frac{\beta\gamma}{(\phi+\mu)(\gamma+\mu)} \\ &= \left[1+\frac{f\phi}{\mu}\right]R_v \\ &= \Theta R_v. \end{aligned} \tag{18}$$

Since $\Theta > 1$, it follows that $R_v < R_c$ whenever $f \neq 0$. Thus, an increase on the proportion of defaulters have a negative impact on controlling HCV among injection drug misusers in the presence of HCV vaccination.

Partial rank correlation coefficients (PRCC) were calculated to estimate the of correlation between values of R_c and the nine model parameters across 10^3 random draws from the empirical distribution of R_c and its associated parameters. A large PRCC is indicative of high sensitivity to parameter estimates (PRCCs > 0 will increase R_c when they are increased), while a small PRCC is reflects low sensitivity (PRCCs < 0 will decrease R_c when they are increased) [28]. Figure 2 (a) demonstrates the association between R_c and the parameter β, γ, ϕ, μ when $f = 0,$ clearly we observe that only an increase in either β or γ will result in an increase in R_c (but it is worth noting that γ is most sensitive to R_c compare to β in this case). Furthermore from Figure 2 (a) we observe that an increase in ϕ (treatment rate), or μ (natural mortality rate) will lead to a decrease in R_c, thus an increase in treatment will have a positive impact on controlling HCV.

(b)

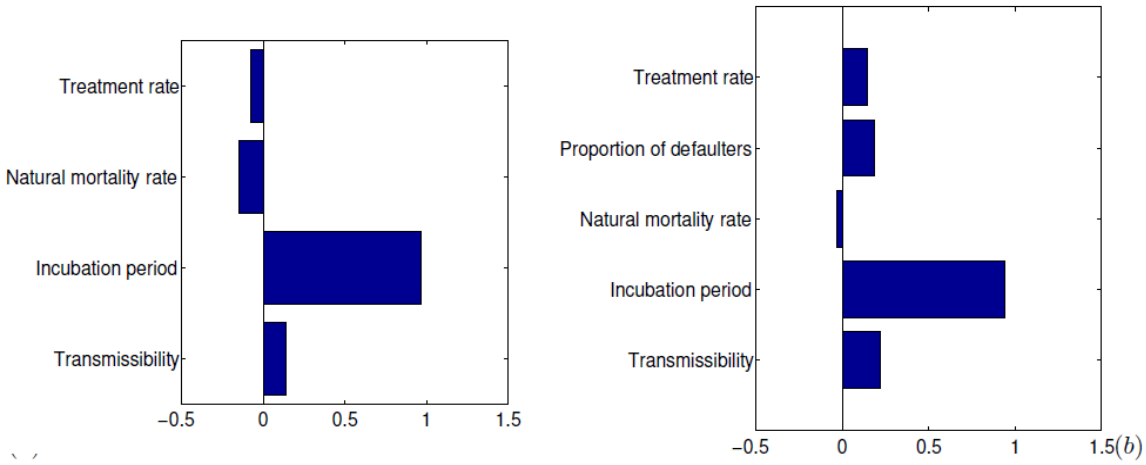

Figure 2: Sensitivity of R_c to all parameters using partial rank correlation coefficients.

Figure 2(b) highlights that only an increase in μ (natural mortality), will lead to a decrease on the magnitude of R_c. Comparing Figure 2(a) and 2(b) we observe that, on (b) an increase in ϕ (treatment rate) increase the magnitude of R_c, clearly this is influenced by the presence of IDUS who discontinue treatment, as we have noted earlier on (a) that an increase in treatment rate will have a positive impact on controlling HCV. Overally, the PRCCs above demonstrates that treatment defaulting has a negative impact on controlling HCV among IDUS.

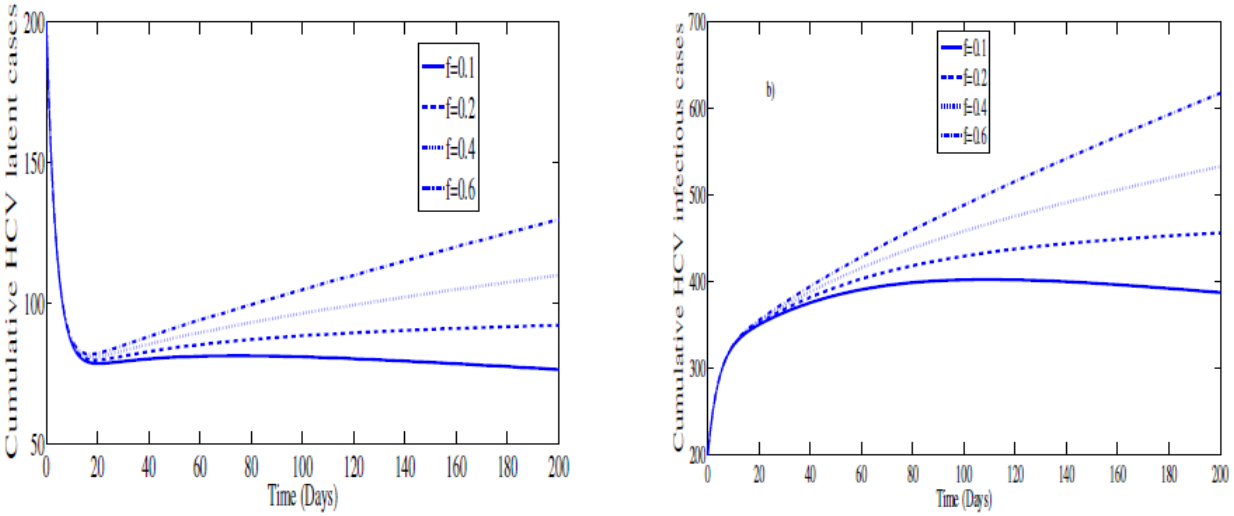

Figure 3: The impact on-compliance to HCV therapy (modeled by parameter (f)) on the transmission dynamics of HCV among injection drug misusers is demonstrated over a period of 200 days. The rest of the parameters are fixed on their baseline values from Table 1, and the following assumed initial conditions are used; $S = 300$, $L = 20$, $I = 20$, $D = 10$ and $R = 10$.

Figure 3 illustrates the impact of treatment compliance on transmission dynamics of HCV among injection drug misusers. The results support the analytical results on equation (18), i.e defaulting will result in an increase in HCV cumulative cases. Apart from demonstrating that treatment discontinue has a negative impact on HCV control among injection drug misusers, we noted that the impact of treatment defaulting will be noted after a period of 20 days, in both HCV latent and infectious cases.

5. DISCUSSION

Chronic hepatitis C is the most common infectious disease among injection drug users (IDUs), because of the allegedly poor compliance of IDUs with treatment requirements and conditions, hepatologists recommend treatment only if former IDUs have spent 6 to 12 months drug free. In this paper a simple deterministic mathematical model is developed to explore the epidemiological consequences to HCV therapy among IDUS. Comprehensively analysis of the model has shown that, the model has a globally-asymptotically stable disease-free equilibrium whenever the associated reproductive ratio is than unity. Using centre manifold theory, it has been established that the model has a

locally-asymptotically stable endemic equilibrium whenever the associated reproductive number is greater than unity. Although, prior studies have demonstrated that vaccination and HCV treatment have a potential to control HCV among injection drug misusers, both analytical and numerical results from this study suggests that non-compliance to HCV therapy has a marked negative impact on controlling HCV among injection drug misusers. This is probably, the reason why HCV prevalence continues to rise among IDUS despite a marked advancement on HCV treatment and vaccination.

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