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# Vertical Transmission of Hepatitis-C Virus (HCV) with Optimal Control on Treatment Expenses

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Author NHS has designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors BMY and NJS have managed the analyses of the study. Author NJS has managed the literature searches. All authors read and approved the final manuscript.*

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## Abstract

The hepatitis C virus infects the liver which does not display an early symptom. As such an infected individual recognize these infections only at the later stage. Around the globe, many individuals suffer from HCV. In this study, we developed a transmission of HCV with five components viz. susceptible, acute infected, chronically infected, hospitalized and recovered individuals. The basic reproduction number was calculated using next-generation matrix. The stability of the model was found at equilibrium points. The disease-free equilibrium is locally asymptotically stable if $R_0 < 1$ otherwise unstable. The control in terms of the treatment cost by government and expenses incurred by patients has been optimized. The model was supported by strong numerical data. It is observed to optimize the maximum amount for treatment cost paid by the Government and minimum amount of treatment paid by the infected individuals; it will help us in decreasing the burden of Hepatitis C in the population. Furthermore, critical factors in terms of model parameters were reported and discussed.

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# 1 Introduction

Hepatitis C virus (HCV) infection is an important worldwide public health problem [1]. Little was known about Hepatitis C until 1975 when the application of the diagnostic test for hepatitis A and B revealed that many cases were neither hepatitis A nor hepatitis B. The causative agent was identified in 1989 as hepatitis C [2]. Out of the total population infected with Hepatitis C virus, approximately 75%–85% will develop Chronic Hepatitis, which may progress to liver fibrosis, cirrhosis, hepatocellular carcinoma, and death [3]. Researchers have calculated that 130–170 million people are infected with HCV (global prevalence: 2%–3%) [4]. The prevalence rates are highest (≥2.5%) in West Africa, Eastern Europe and Central Asia. More than 80% of the global HCV burden is in low and middle-income countries [2]. Approximately 80 million people are estimated to have chronic hepatitis C virus (HCV) infection, with the predominant HCV genotypes being 1 (46%) and 3 (22%) [5] and amongst them, an estimated 700,000 die untreated every year. Despite great successes in virology and diagnostics, several difficulties have prevented an improvement in HCV infection control and elimination. New HCV infections still occur, especially in poor socio-economic regions, where HCV can be endemic, and long-term sequel cause growing economic and health burdens [6].

Hepatitis C is a small, blood-borne virus that remains infectious in dried blood for weeks. The virus spreads via the following ways:

1. Injection with shared, unsterilized equipment, especially when access to harm reduction services is limited or non-existent, tattooing with reused needles, ink and inkwells, unscreened donor blood, blood products and organs
2. Medical and dental procedures in settings with inadequate infection control (including the amount for treatment from government or from infectious)
3. From mother to infant; and from unprotected sex, primarily among HIV-positive men who have sex with men (MSM) [5].

The incubation period of hepatitis C averages 50 days. Following exposure to the virus, infection becomes chronic in 60–80% of cases, while the remaining 20–40% of people who are infected spontaneously clear the virus [2]. People who inject drugs (PWID) are the group with the highest HCV prevalence, an estimated 67%. After exposure to HCV, a strong host immune response is launched which consists of B cells, T cells and phagocytic cells. However, in a majority of patients, the response fails to eradicate the virus, leading to chronic infection [1].

Until 2015, cure rate of Hepatitis C with available treatment (interferon and ribavirin) was about 50% and resulted in numerous side effects from the medicine. In April 2015, WHO included the number of the new DAAs (Direct Acting Antivirals) in the WHO Model List of Essential Medicines [7]. The World Health Assembly adopted the first "*Global Health Sector Strategy on Viral Hepatitis, 2016-2021*". The strategy has a vision of eliminating viral hepatitis as a public health problem and this is encapsulated in the global targets of reducing new viral hepatitis infections by 90% and reducing deaths due to viral hepatitis by 65% by 2030 [8]. In July 2016, WHO issued updated HCV treatment guidelines that include recommendations on preferred DAA-based regimens in May 2016 [9].

Despite the range and severity of the epidemic caused by HCV, the global response to reduce the burden of this disease has been very limited. Ramirez et al. 2014 have studied Mathematical Modeling of Immune Responses to Hepatitis C Virus Infection and optimal strategies for different scenarios. Echevarria et al 2015 studied *Mathematical Modeling of Hepatitis C Prevalence Reduction with Antiviral Treatment Scale-Up in Persons Who Inject Drugs in Metropolitan Chicago* and found that treatment scale-up could dramatically reduce the prevalence rate in Chicago in person who injects drug [1].

In this paper, we formulate a nonlinear Mathematical Model for Hepatitis C Virus with vertical transmission and effective control on the treatment cost. The stability of the model at equilibrium points was discussed in

section 4, the local stability and global stability at HCV free equilibrium point and HCV exist equilibrium point were calculated in section 4.1 and section 4.2 respectively. The optimal control of treatment expense can be achieved by maximizing the amount of treatment paid by Government and minimizing the amount of treatment paid by infected individuals. This optimal control is calculated in section 5. Finally, the study concludes with numerical simulation.

# 2 Notations and Parameters

In this section, we discuss the notations and its parametric values.

**Table 1. Notation and parametric values**

| Notation | | Parametric values |
|---|---|---|
| B | Natural recruitment rate | 1.2 |
| $\mu$ | Natural death rate | 0.01 |
| $\mu_d$ | Disease induced death rate | 0.3 |
| $\lambda$ | Force of infection | |
| $\alpha$ | The rate of acute individuals become chronic | 0.05 |
| $\eta$ | The rate of acute individuals gets hospitalized | 0.4 |
| $\delta$ | The rate of chronic individuals gets hospitalized | 0.8 |
| $\varepsilon$ | The rate of recovered individuals can go to the susceptible class | 0.4 |
| $\nu$ | Vertical transmission rate from pregnant mother to infant. | 0.02 |
| $\gamma$ | The recovery rate if hospitalized individuals | 0.7 |
| N | Total population | 100 |
| $u_1$ | The rate of maximum amount of treatment from Government | [0,1] |
| $u_2$ | The rate of minimum treatment cost paid by infected individuals | [0,1] |

From these assumptions and parametric values, we formulate the mathematical model for HCV.

# 3 Mathematical Model

In this model, the total population is categorized into five compartments: Susceptible(S), Infected ( I) which may be (A) Acute or (C) Chronic, Hospitalized ( H) and Recovered (R). The susceptible is the individual who is uninfected but is able to be infected if exposed. In our model, these are the unborn babies of the Hepatitis C infected mother. The infected are the individual with the disease and can transmit the infection to other susceptible individuals. Hospitalized are the individuals who are infected acutely or chronically and hospitalized. Recovered comprises of individuals who have been recovered from the infection after hospitalization and proper treatment but can be re-infected if exposed again.

## 3.1 Some assumptions underlying the model

a) Susceptible individuals are the unborn babies of Hepatitis C positive mother
b) Babies if get infected can have Acute Hepatitis or Chronic Hepatitis
c) Patents who has acute or chronic hepatitis will get hospitalized may get treatment and recover, may die from acute infection or may die from chronic infection.
d) Patients who recovered may die from natural causes or become susceptible individuals.
e) Age, Sex and Race do not affect the probability of being infected
f) All birth to Hepatitis C positive mother enters susceptible class.

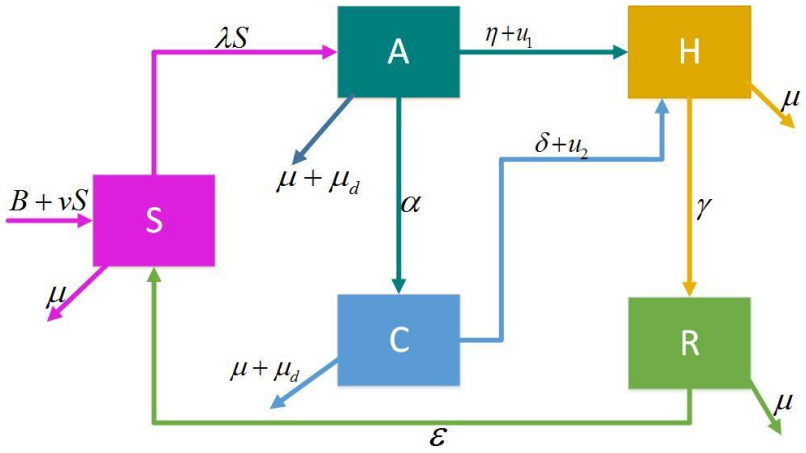



**Fig. 1. Compartmental model**

Considering all these assumptions together with the corresponding notations, the above model as seen in Fig. 1, can be represented mathematically by the following system of differential equations:

$$\frac{dS}{dt} = B + vS + \varepsilon R - \lambda S - \mu S \tag{1a}$$

$$\frac{dA}{dt} = \lambda S - \alpha A - (\eta + u_1) A - (\mu + \mu_d) A \tag{1b}$$

$$\frac{dC}{dt} = \alpha A - (\delta + u_2 + \mu + \mu_d) C \tag{1c}$$

$$\frac{dH}{dt} = (\eta + u_1) A + (\delta + u_2) C - (\gamma + \mu_d) H \tag{1d}$$

$$\frac{dR}{dt} = \gamma H - \varepsilon R - \mu R \tag{1e}$$

Adding all these equations, we have

$$\frac{d}{dt}(S + A + C + H + R) = B + vS - \mu S - (\mu + \mu_d) A - (\mu + \mu_d) C - dH - \mu R < B - \mu(S + A + C + H + R)$$
$$< B - \mu(S + A + C + H + R)$$

which gives $\limsup_{t \to \infty} (S + A + C + H + R < B - \mu(S + A + C + H + R)$

Therefore, the feasible region for (1) is

$$\wedge = \left\{ \left( S, A, C, H, R) / S + A + C + H + R \le \frac{B}{\mu} \right) \right\}$$

where $S > 0, A \ge 0, C \ge 0, H \ge 0, R \ge 0$

Now the basic reproduction number $R_0$ will be found by using the next generation matrix. All the above differential equations have an HCV free equilibrium $X_0 = \left( \frac{B}{\mu}, 0.0.0.0 \right)$

Let $X^{'} = \left( S, A, C, H, R \right)^{'}$ where dash denotes derivative. So that $X^{'} = \frac{dx}{dt} = \Im(x) - \nu(x)$

where $\Im(x)$ denotes the rate of new people who get infected and represents the rate of transfer of HCV, which gives as

$$\Im(x) = \begin{pmatrix} \lambda S \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

and

$$\nu(x) = \begin{bmatrix} \alpha A + \left( \eta + u_1 \right) A + \left( \mu + \mu_d \right) A \\ -\alpha A + \left( \delta + u_2 \right) C + \left( \mu + \mu_d \right) C \\ -\left( \eta + u_1 \right) A - \left( \delta + u_2 \right) C + \gamma H + \mu_d H \\ -\gamma H + \varepsilon R + \mu R \\ -B - \nu S - \varepsilon R + \lambda S + \mu S \end{bmatrix}$$

$$F = \left[ \frac{\partial \Im_i}{\partial x_j} \right], i = 1,2,3,4 \text{ and } j = A, C, H, R, S$$

$$\lambda = \frac{\beta \left( \beta_1 A + \beta_2 C \right)}{N}$$

F and $\nu$ are 2 x 2 matrices defined as

$$F = \begin{bmatrix} \frac{\beta \beta_1 S}{N} & \frac{\beta \beta_2 S}{N} \\ 0 & 0 \end{bmatrix}$$

$$v = \begin{bmatrix} \alpha + \eta + u_1 + \mu_d & 0 \\ -\alpha & \delta + u_2 + \mu + \mu_d \end{bmatrix}$$

$$Fv^{-1} = \frac{1}{A_1 A_2} \begin{bmatrix} \frac{\beta\beta_1 BA_2}{\mu N} + \frac{\beta\beta_1 S\alpha}{\mu N} & \frac{\beta\beta_2 BA_1}{\mu N} \\ 0 & 0 \end{bmatrix}$$

Therefore, basic reproduction number

$$R_0 = \frac{B\beta\left(A_2\beta_1 + \alpha\beta_2\right)}{A_1 A_2 \mu N}$$

With $A_1 = \alpha + \eta + u_1 + \mu + \mu_d$ and $A_2 = \delta + u_2 + \mu + \mu_d$

# 4 Stability of the Model

## 4.1 Local stability of HCV free equilibrium

The HCV free equilibrium is stable if all the eigenvalues of the Jacobian Matrix of the system ((1a)-1(e)) have negative real parts. For this, Jacobian of the system (1) at $X_0 = \left(\frac{B}{\mu}, 0, 0, 0, 0\right)$ takes the form

$$J = \begin{bmatrix} v - \mu & \frac{-\beta\beta_1 S}{N} & \frac{-\beta\beta_2 S}{N} & 0 & \varepsilon \\ 0 & -A_1 + \frac{\beta\beta_1 S}{N} & \frac{\beta\beta_2 S}{N} & 0 & 0 \\ 0 & \alpha & -A_2 & 0 & 0 \\ 0 & \eta + u_1 & \delta + u_2 & -\gamma - \mu_d & 0 \\ 0 & 0 & 0 & \gamma & -\mu - \varepsilon \end{bmatrix}$$

Here

$$J = \begin{bmatrix} -A_1 + \frac{\beta\beta_1 S}{N} & \frac{\beta\beta_2 S}{N} \\ \alpha & -A_2 \end{bmatrix}$$

$$\lambda^2 - \left(-A_1 + A_2 + \frac{\beta\beta_1 B}{\mu N}\right)\lambda - \left(A_1 A_2 - \frac{A_2\beta\beta_1 B}{\mu N} - \frac{\alpha\beta\beta_2 B}{\mu N}\right) = 0$$

Where

$$a_1 = A_1 + A_2 - \frac{\beta\beta_1 B}{\mu N}$$

$$a_2 = -\left( A_1 A_2 - \frac{A_2 \beta\beta_1 B}{\mu N} - \frac{\alpha\beta\beta_2 B}{\mu N} \right)$$

$$= -\left( 1 - \frac{B\beta}{A_1 A_2 \mu N}\left[ A_2\beta_1 + \alpha\beta_2 \right] \right)$$

$$= -\left(1 - R_0\right)$$

This implies that the disease-free equilibrium is locally asymptotically stable if $R_0 < 1$ otherwise unstable.

## 4.2 Endemic point (HCV-exist equation)

Let the endemic equilibrium point be $X^* = \left(S^*, A^*, C^*, H^*, R^*\right)$

With

$$S^* = \frac{1}{\alpha\lambda} A_1 A_2 C$$

$$A^* = \frac{1}{\alpha} A_2 C$$

$$H^* = \frac{C}{\alpha\left(\gamma + u_d\right)}\left[\left(\eta + u_1\right) A_2 + \left(\delta + u_2\right)\alpha\right]$$

$$R^* = \frac{C\nu}{\alpha\left(\mu + \varepsilon\right)\left(\nu + u_d\right)}\left[\left(\eta + u_1\right) A_2 + \left(\delta + u_2\right)\alpha\right]$$

$$X^* = \left(S^*, A^*, C^*, H^*, R^*\right)$$

For this, the Jacobian of the system (1(a)-1(e)) at $X^* = \left(S^*, A^*, C^*, H^*, R^*\right)$ takes the form:

$$J = \begin{bmatrix} -\mu + \nu - \left( \dfrac{\beta\beta_1 C^* + \beta\beta_1 A^*}{N} \right) & -\dfrac{\beta\beta_1 S^*}{N} & -\dfrac{\beta\beta_2 S^*}{N} & 0 & \varepsilon \\ \left( \dfrac{\beta\beta_1 C^* - \beta\beta_1 A^*}{N} \right) & -A_1 + \dfrac{\beta\beta_1 S^*}{N} & 0 & 0 & 0 \\ 0 & -\alpha & -A_2 & 0 & 0 \\ 0 & \eta + u_1 & \delta + u_2 & -\gamma + \mu_d & 0 \\ 0 & 0 & 0 & \gamma & -\mu - \varepsilon \end{bmatrix}$$

$$J=\begin{bmatrix} -\mu+\nu-\left(\dfrac{\beta\beta_1C^*+\beta\beta_1A^*}{N}\right) & -\dfrac{\beta\beta_1S^*}{N} & -\dfrac{\beta\beta_2S^*}{N} \\ \left(\dfrac{\beta\beta_1C^*-\beta\beta_1A^*}{N}\right) & -A_1+\dfrac{\beta\beta_1S^*}{N} & 0 \\ 0 & -\alpha & -A_2 \end{bmatrix}$$

$$\lambda_f=\frac{\beta\beta_1A+\beta\beta_2C}{N}$$

$$\lambda^3+a_1\lambda^2+a_2\lambda+a_3=0$$

$$a_1=\frac{1}{N}\left[S\beta\beta_1+\left(A_1+A_2\right)N+\left(\lambda+\mu+\nu\right)N\right]=\frac{1}{N}\left(A_1+A_2-\frac{S\beta\beta_1}{N}\right)+\left(\lambda+\mu+\nu\right)N$$

$$a_2=\frac{\lambda}{N}\left[-A_2S\beta\beta_1-\alpha\beta\beta_2S-S\beta\beta_1\mu-S\beta\beta_1\nu+A_1A_2N+A_1N\lambda+A_1N\mu+A_1N\nu+A_1NA+A_1N\mu+A_1N\nu\right]$$

$$=\frac{\lambda}{N}\left(R_0-1\right)+\left(A_1+A_2\right)N+\left(\mu+\nu\right)\left(A_1+A_2-\frac{S\beta\beta_1}{N}\right)$$

$$a_3=\frac{1}{N}\left(-A_2S\beta\beta_1\mu-A_2S\beta\beta_1\nu-\alpha S\left(\beta\beta_2\mu-\beta\beta_2\nu\right)+A_1A_2N\left(\lambda+\mu+\nu\right)\right)$$

$$=\frac{S\beta\left(\mu+\nu\right)}{N\left(\lambda+\mu+\nu\right)}$$

This implies $R_0<1$ the endemic equilibrium point $X^*=\left(S^*,A^*,C^*,H^*,R^*\right)$ is locally asymptotically stable.

# 5 Optimal Control

For HCV, an optimal control model is formulated, to derive optimal control on treatment cost for prevention of vertical transmission Hepatitis C, to derive optimal rate of maximum amount of treatment from Government and to derive optimal rate of minimum treatment cost paid by Infected individuals, to minimize the number of infected individuals for model described by equations (1a) to (1f) in the time interval [0, $\tau$ ] with the feasible region as given by $\wedge$.

Considering the cost functions as

$$J\left(u_1,u_2\right)=\int_0^\tau\left(W_1A^2+W_2C^2+W_3H^2+W_4u_1^2-W_5u_2^2\right)dt$$

where, $X=\left(A,C,H\right)$ $u=\left(u_1,u_2\right)$ and $W=\left(W_1,W_2,W_3,W_4,W_5\right)$ are weights to regularise the optimal control.

Using Lagrangian techniques for a problem along with Hamiltonian, the adjoint variable is needed to construct for the optimal control problem given by (1a) to (1f).

Introducing the Lagrangian to derive the optimality conditions,

$$L(x,u,\lambda) = L(A,C,H,u_1,u_2)$$

$$= W_1A^2 + W_2C^2 + W_3H^2 + W_4u_1^2 - W_5u_2^2$$

To determine the minimal value of the Lagrangian, defining the Hamiltonian H for the control problem as

$$H(x,u,\lambda) = L(x,u) + \lambda_1(\dot{A}) + \lambda_2(\dot{C}) + \lambda_3(\dot{H})$$

$$= W_1A^2 + W_2C^2 + W_3H^2 + W_4u_1^2 - W_5u_2^2$$

$$+\lambda_1\left[\lambda S - (\eta + u_1)A - (\mu + \mu_d)A - \alpha A\right]$$

$$+\lambda_2\left[\alpha A - (\delta + u_2)C - (\mu + \mu_d)C\right]$$

$$+\lambda_3\left[(\eta + u_1)A + (\delta + \mu_2)C - (\gamma + \mu_d)H\right]$$

To get optimality Pontrayagian's maximum (minimum) principle, the model is defined as follows.

If $(u_1^*, u_2^*)$ is optimal solution of an optimal control problem then there exists a non-trivial vector function $\lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t))$

Satisfying following equations

$$\dot{\lambda}_1 = -\left[2W_1A + \lambda_1\left(\frac{\beta\beta_1 S}{N}\right) - \alpha(\lambda_1 - \lambda_2) - (\eta + u_1)(\lambda_1 - \lambda_2) - (\mu + \mu_d)\right]$$

$$\dot{\lambda}_2 = -\left[2W_2C + \lambda_1\left(\frac{\beta\beta_2 S}{N}\right) - \alpha(\mu + \mu_d)\lambda_1 - (\delta + u_2)(\lambda_2 - \lambda_3)\right]$$

$$\dot{\lambda}_3 = -\left[2W_3H - (\gamma + \mu_d)\lambda_3\right]$$

$$\frac{\partial H_m}{\partial u_1} = -\left[2W_4u_1 - A(\lambda_1 - \lambda_3)\right] = 0$$

$$\frac{\partial H_m}{\partial u_2} = -\left[-2W_5u_2 - C(\lambda_2 - \lambda_5)\right] = 0$$

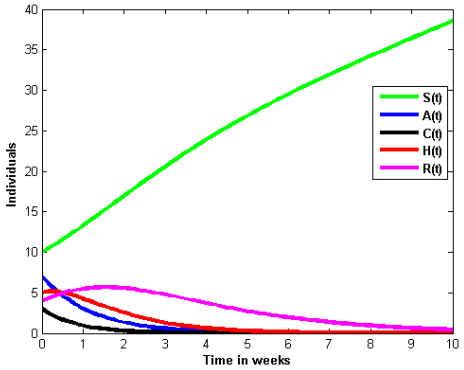
Satisfying optimality conditions for optimal control and the property of control space u give:

$$u_1^* = \frac{1}{2W_4}\left[A(\lambda_1 - \lambda_5)\right]$$

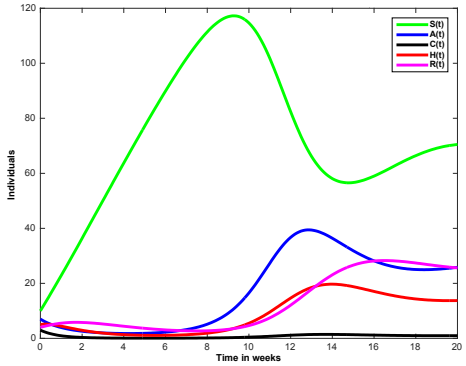
$$u_2^* = \frac{1}{2W_5}\left[C(\lambda_2 - \lambda_3)\right]$$

## 6 Numerical Simulation

For parametric values given in Table 1, basic reproduction number $R_0 < 1$.



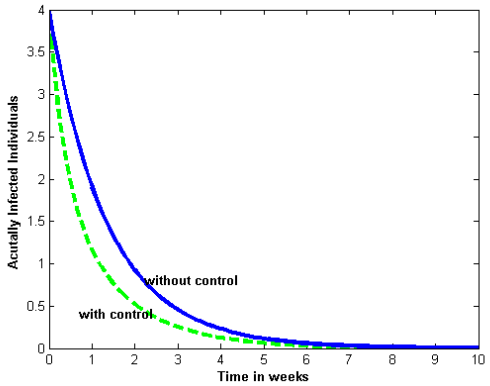

**Global stability of Human Population for $R_0 < 1$**




**Global stability of Human Population for $R_0 > 1$**

**Fig. 2.**

Fig. 2 shows that there is a proportionate increase in susceptible population with time in weeks, but if $R_0 > 1$ , then there is steep rise in susceptible population during the early weeks, reaching peak at about 10 weeks then gradual declined and becomes plateau in about 14 weeks.



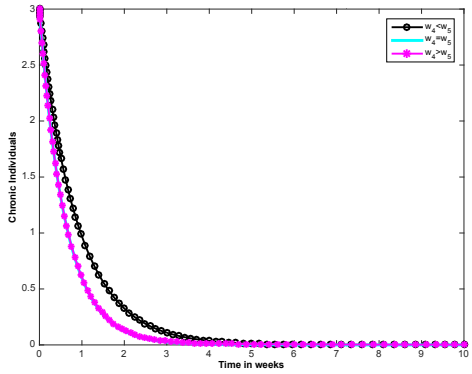




**Fig. 3. Prevalence of HCV with/without control**

Fig. 3 shows the natural course of Hepatitis C in population with and without effective control or treatment. With effective treatment, numbers of individual with acute infection reduces significantly and gets better sooner compared to individuals who did not receive treatment of Hepatitis C. When $W_4$ less than $W_5$, number of individuals who are chronically infected decreases over a period of time and gets stable around 4 to 5 weeks. When is $W_4$ greater than $W_5$, then numbers of individuals who are chronically infected decreases and gets stable earlier at around 3 weeks. When $W_4$ equals $W_5$, it has a stabilizing effect and numbers of individuals who are chronically infected decreases and becomes stable very early.

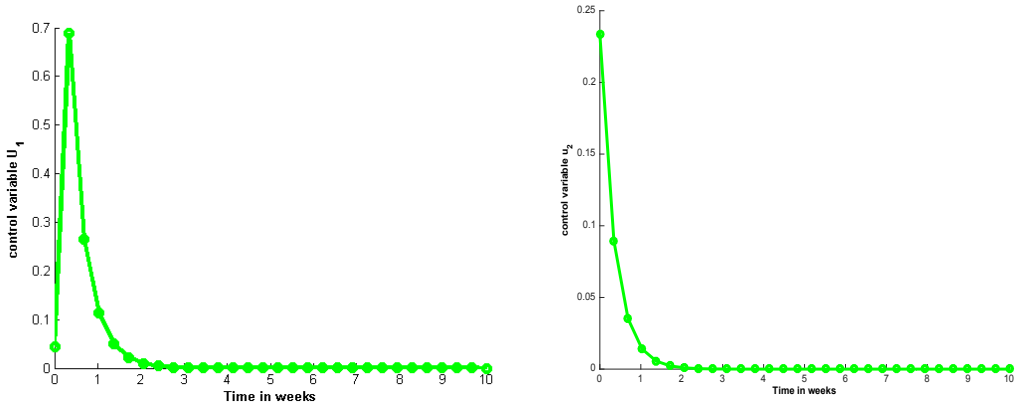



**Fig. 4. Effect of treatment in terms controls**

The figure shows that the rate of maximum amount of treatment from government $u_1$ is peaked in first four days, and declines steeply thereafter to be negligible by end of two weeks. While rate of minimum treatment cost paid by infected individuals $u_2$ is at the peak at the very beginning but declines steeply in next few days to be negligible by the end of the first week.

# 7 Conclusion

In this paper, we formulated a nonlinear Mathematical Model for Hepatitis C Virus with vertical transmission and effective control on the treatment cost. The population is divided into five compartments; susceptible, infected (acute and chronic), hospitalized and recovered. The stability of the model at equilibria was discussed, the local stability and global stability at HCV free equilibrium point and HCV exist equilibrium point were calculated. Numerical simulation shows that if we can optimize the maximum amount for treatment cost paid by the Government and minimum amount of treatment paid by the infected individuals; it will help us in decreasing the burden of Hepatitis C in the population. We recommend future research on co-infection of HCV with HIV or other conditions and their effect on cost. Furthermore, it will be interesting to see effects of different treatment regimens and their duration on total cost and ultimate outcome. Lastly, we also suggest future research to see effects of different age, sex and race on HCV infection and ultimate outcome and cost.

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# Competing Interests

Authors have declared that no competing interests exist.

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