

# Modeling the Dynamics of Hepatitis C Virus and Immune System during Acute Infection

Seleman Ismail<sup>1\*</sup>, Livingstone Luboobi<sup>1,2</sup>, Yaw Nkansah-Gyekye<sup>1</sup>

<sup>1</sup>School of Computational and Communication Science and Engineering, Nelson Mandela  
African Institution of Science and Technology, P.O. Box 447, Arusha, Tanzania

<sup>2</sup>Department of Mathematics, Makerere University, P.O.Box 7062, Kampala, Uganda

\*E-mail of the corresponding author: ismails@nm-aist.ac.tz

## Abstract

In this paper, a mathematical model on the interaction between hepatitis c virus (HCV) and immune system has been developed and analyzed. We have upgraded the model developed by Avendano *et al.*(2002) by including death of hepatocytes due to infection and spontaneous clearance of viruses by a noncytolytic process during acute stage of infection. The next generation matrix operator method has been applied to derive the basic reproductive number  $R_0$ . Also, the stability analysis of the model equilibria has been performed using Meltzer stability theory, Routh-Hurwitz criteria and Lyapunov direct method. The results indicate that the disease free equilibrium point (DFE) is locally asymptotically stable if  $R_0 < 1$  and unstable if  $R_0 > 1$  and the endemic equilibrium point (EE) is both locally and globally asymptotically stable if  $R_0 > 1$  and unstable if  $R_0 < 1$ . We calculated the sensitivity indices of the dynamic threshold  $R_0$  relating to each parameter in the model, where we found that the decrease in the infection rate and the virus production rate have the effect of lessening the infection, which suggests that the disease can be controlled when therapeutic intervention is targeted on these sites. We recommend that antiviral drug therapy should be used to block virus production and so eradicate or reduce the intensity of the disease *in vivo*.

**Keywords:** Hepatitis C virus, Immune system, Basic reproductive number, Disease-free equilibrium point, Endemic equilibrium point.

## 1. Introduction

### 1.1 Hepatitis C Virus Infections

Hepatitis C virus (HCV) has been one of the known types of viruses ever since it was recognized in 1989 (Choo *et al.*,1989; Purcell, 1997). The HCV infection has been one of the main global causes of liver-related diseases and hepatocellular carcinoma (Hoofnagle, 2002; Perz *et al.*, 2006), and one source of deaths to hundreds of thousands of individuals each year from liver failure including liver cancer (Ashfaq *et al.*, 2011). Also, it has been one of the most crucial challenges because of possibly increasing threats it imposes on the global health in terms of the number of people who become infected, the burden it imposes on them and their families and healthcare providers of the countries they live in. It is documented that approximately 130 to 170 million people are infected with HCV worldwide(Lavanchy, 2009).

The channels of transmission of the HCV infection(HCVI) are: blood; blood products; tissue and organs; unsafe medical practices; healthcare provision practices, which are precisely identified as needle stick injuries (Xia *et al.*, 2008); intravenous drug use (Tohme and Holmberg, 2010); sexual transmission (Jafari *et al.*, 2010); body piercings (Lam *et al.*, 2010) and vertical transmission (Owusu-Ofori *et al.*, 2005). In developing countries(DCs), the transmission results from exposure to infected blood and blood products in healthcare provisions centers (HCPCs) while in many developed countries it results from injection drug use(IDU).Also, it is well documented that, in many DCs, the transmission of HCVI is commonly through IDU and unsafe injection practices (Williams *et al.*, 2011), that results from screening and measures for HCV. IDU can be an outstanding risk source for the transmission in developing countries as well (Aceijas and Rhodes, 2007; Nelson *et al.*, 2011). For example, the research findings by Nelson *et al.*(2011) show that China has the highest number of HCV infections due to drug use worldwide. However, the most common channels of transmission in DCs are associated with HCPCs (Hauri *et al.*, 2004; Prati, 2006) and unsafe injections in HCPCs are a principal source of HCV transmission worldwide, which leads to 2 million new HCV infections annually(Hauri *et al.*, 2004).

At early stages of HCV infection, the progress takes a latent period of about 2 weeks to 6 months. Within this period approximately 70% of the infected individuals never experience any symptoms (Busch and Shafer, 2005),

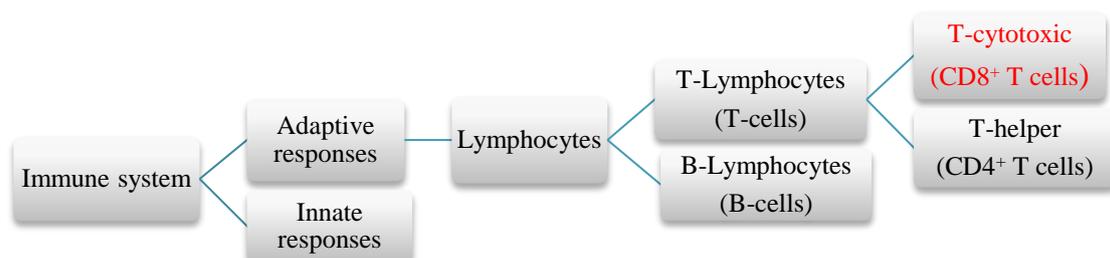
which makes its diagnosis very difficult, i.e. only few cases are diagnosed for medical attention or tested for evidence of HCV infection (Blackard *et al.*, 2008). Also, within this period, approximately 20% to 30% of the infected people spontaneously clear the virus (Rehermann and Nascimbeni, 2005). On the other hand, infected individuals who are symptomatic might show the following physical states: fever, fatigue, decreased appetite, dark urine, joint pain, jaundice; and gastrointestinal complications, which include vomiting, abdominal pain, clay-coloured feces, joint pain and nausea. Literatures from clinical trials reveal that almost 25% of all patients with HCV infection present with jaundice; approximately 10% to 20% of cases progress to the following gastrointestinal symptoms: nausea, vomiting, and abdominal pain (Prevention, 1998)

Hepatitis C virus causes acute hepatitis C infection (AHCI) and chronic hepatitis C infection (CHCI). The AHCI refers to the first 6-month period of infection following acquisition of the virus while CHCI refers to a period beyond the AHCI period. It has been found that approximately 20% to 50% of individuals with HCV infection spontaneously clear the virus within the AHCI period (Kamal, 2008) when there is no treatment. However, in literature about 85% of infected people progress to CHCI, i.e. around 150 million HCV infected people progress to chronic state. The risk of cirrhotic CHCI evolution is around 15% to 30% in 20 years' time and at least 350 deaths each year due to hepatitis C related liver problems mostly caused by liver cirrhosis and hepatocellular carcinoma (Perz *et al.*, 2006). Currently, there is no vaccine for the HCV disease whereas hepatitis A and B virus infections have. However, research in this area is ongoing.

### 1.2 Immune Responses to Invading Pathogens

We may refer the immune system (IS) to as an organic structure in an organism composed of cells and molecules to provide protection against foreign pathogens which are bacteria, viruses and fungi. In this study, however, our discussion focuses on the human immune responses (HIR) against these pathogens. Investigation of the HIR indicates that there two foremost classes of immune responses operating against intruding pathogens (Delves and Roitt, 2000), which are the innate immune responses (IIRs) and the adaptive immune responses (AIRs). The IIRs are also referred to as nonspecific responses while the AIRs refer to specific responses. They function as the first barrier to protect the body against infection. That is, in the presence of pathogens, the IIRs are the first barrier to pathogenic operations in protection of the body against the infection. In this case, macrophages and natural killer cells are examples of cells that respond in a nonspecific fight against these pathogenic actions. In other words, these typical responses are the reactions of the body against an intruder, regardless of the type of pathogen they are combating. Fever, coughing, and sneezing are some examples of IIRs. Conversely, the AIRs result due to the ability of cells and molecules of the IS to recognize the physical structure of a pathogen (Wodarz, 2005). These cells and molecules are able to detect protein composition of the intruding pathogens. As soon as these cells are activated by a signal given by a pathogen, they proliferate ready for the combat.

The lymphocytes, which lay under the AIRs class, are the white blood cells (WBCs) originating from the bone marrow. It is known that a microlitre of human blood contains approximately 2500 WBCs, and which totally amount to  $10^{12}$  WBCs in a mature person (Nowak and May, 2000). The lymphocytes can be classified into two main subdivisions namely B-lymphocytes (BLs) and T-lymphocytes (TLs) abbreviated as B cells and T-cells respectively. The BLs are surrounded with antibodies on their surface membrane which function as receptors to detect the presence of pathogens, where for any pathogen entering the body there is always a specific antibody that can identify it (Nowak and May, 2000). The TLs further branch into: T- helper lymphocytes (THLs) and cytotoxic T-lymphocytes (CTLs), also known as  $CD4^+$  T cells and  $CD8^+$  T cells respectively. The THLs have the role of not only activating the BLs (B-cells) to secrete antibodies and macrophages but also exterminate ingested microbes and activate cytotoxic T-cells to kill infected target cells while the CTLs ( $CD8^+$  cells) can identify and destroy infected or damaged cells. A schematic representation of the types of the IS are summarized in Figure 1.



**Figure 1:** Taxonomy of the immune system (Ramirez, 2014).

### 1.3 Hepatitis C Virus Infection and the Immune Response

The study intends to understand the interactions between hepatitis C virus and immune system. This begins with the fact that when HCV enters the human body hepatocytes are infected, which later become generators of new viruses. Then the  $CD4^+$  T cells activate the B-cells to secrete antibodies and macrophages to eradicate ingested microbes; they also help to activate the  $CD8^+$  T cells to eradicate infected hepatocytes. In the development of this proposed model we simply used the  $CD8^+$  T cells as a representative part in the construction of a nonlinear differential equation to describe the IS role in combating the virus.

In this paper, we modify and extend the model that was developed by Avendano *et al.* (2002) which integrates four compartments: susceptible hepatocytes, infected hepatocytes, hepatitis c virus and  $CD8^+$  T cells. This model assumed that individuals in the classes die naturally at different constant per capita rates. It also assumed that the supply of  $CD8^+$  T cells is proportional to the product of the viral load and the relative number of the  $CD8^+$  T cells in the presence of HCV. Our model includes spontaneous cure by a noncytolytic process and disease-induced death of infected hepatocytes. The model shows that the susceptible and infected hepatocytes compartments are the hepatic population, dying naturally at equal per capita rates.

## 2. Model Formulation

We develop and analyze a mathematical model to study the interaction between hepatitis C virus and immune system. The model incorporates four compartments: susceptible hepatocytes  $S(t)$ , infected hepatocytes (IHs)  $I(t)$ , hepatitis C virus  $V(t)$  and  $CD8^+$  T cells  $T(t)$ , where the hepatic population at time  $t$  is given by  $N(t) = S(t) + I(t)$ . The susceptible hepatocytes  $S(t)$  are constantly recruited at the rate  $\Lambda$  and die naturally at the rate  $\mu_1$ . They become infected at the rate proportional the product  $SV$  with a constant of proportionality  $\alpha_1$ . The infected hepatocytes  $I(t)$  die naturally at a constant rate  $\mu_1$  and at a constant rate  $\delta$  because of infection. They spontaneously recover at a constant rate  $\alpha_2$  and generate virions  $V(t)$  at a constant rate  $\beta$ . The virions die naturally at a constant rate  $\mu_2$ . In the presence of HCV, the  $CD8^+$  T cells  $T(t)$  are activated and supplied at a constant rate  $\lambda$ . The  $CD8^+$  T cells kill infected hepatocytes at the rate proportional to the product  $IT$ , with a constant of proportionality  $\gamma$  and die naturally at a constant rate of  $\mu_3$ .

To achieve our goal, the following assumptions were made:

We assume that susceptible hepatocytes are produced at a constant rate and are equally likely infected by the viruses; the susceptible and infected hepatocytes have equal constant natural death rates; the viruses and the  $CD8^+$  T cells have different constant natural mortality rates. We also assume that the  $CD8^+$  T cells kill some IHs at a constant rate; the remaining IHs recovers at a constant rate while others generate virions at a constant rate; the  $CD8^+$  T cells are generated at a constant rate and the patient can either clear the virus spontaneously or not during AHCI.

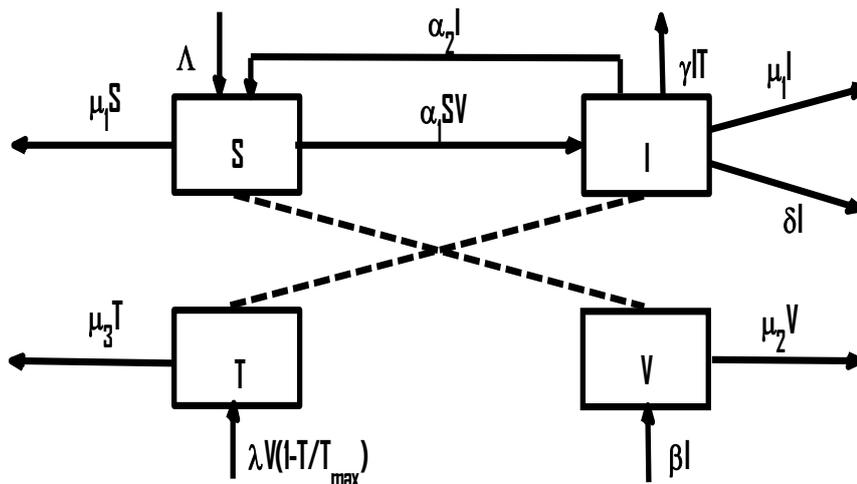
The parameters used in the model are listed and briefly described in Table 1.

**Table 1:** Parameters and their descriptions

Parameter	Description
$\alpha_1$	Per capita rate of infection
$\alpha_2$	Per capita rate of spontaneous cure of infected hepatocytes by a noncytolytic process
$\beta$	Per capita production rate of viruses are within infected hepatocytes
$\gamma$	Rate at which the $CD8^+$ T cells kill infected hepatocytes
$\Lambda$	Per capita production rate production rate of susceptible hepatocytes
$\lambda$	Per capita growth rate of the $CD8^+$ T cells in the presence of HCV
$\mu_1$	Per capita natural death rate susceptible and infected hepatocytes
$\mu_2$	Per capita natural death rate of virions
$\mu_3$	Per capita natural death rate of $CD8^+$ T cells
$\delta$	Disease-induced death rate of infected hepatocytes
$T_{max}$	Maximum $CD8^+$ T cells population level

It is very important to note that we mostly use the symbols  $S$ ,  $I$ ,  $V$  and  $T$  to denote  $S(t)$ ,  $I(t)$ ,  $V(t)$  and  $T(t)$  respectively for brevity of calculations and expressions.

If we consider the above notations and assumptions, we construct a compartmental diagram to demonstrate the HCV dynamics as in Figure 2.



**Figure 2:** Compartmental diagram for the hepatitis C virus model with immune system response.

Based on the assumptions made and relationships existing between the state variables as shown in Figure 2, we construct a system of four non-linear ordinary differential equations describing the dynamics of hepatitis c virus with immune system response.

$$\frac{dS}{dt} = \Lambda + \alpha_2 - \alpha_1 SV - \mu_1 S \quad (1a)$$

$$\frac{dI}{dt} = \alpha_1 SV - \gamma T - \mu_1 I - \delta I - \alpha_2 I \quad (1b)$$

$$\frac{dV}{dt} = \beta I - \mu_2 V \quad (1c)$$

$$\frac{dT}{dt} = \lambda V \left(1 - \frac{T}{T_{\max}}\right) - \mu_3 T \quad (1d)$$

with initial conditions  $S(0) > 0, I(0) \geq 0, V(0) \geq 0, T(0) \geq 0,$

### 2.1 Basic Properties of the Model

In this section, we analyze the properties of the model as the initial stage of understanding the dynamical structures of the model. We begin the analysis by determining the invariant region for each population involved in the model system (1) and then prove that the solutions of the system are positive entities  $\forall t \geq 0.$

#### 2.1.1 Invariant Region

Since the system (1) is modeling of susceptible hepatocytes, infected hepatocytes, virions and the CD8<sup>+</sup> T cells, we assumed that the state variables and parameters are non-negative. As stated earlier, the hepatic population incorporates two compartments  $S(t)$  and  $I(t)$ , which are combined to form  $N(t) = S(t) + I(t)$ , whereby  $N(t)$  stands for the hepatic population at time  $t.$  Moreover, the virions and the CD8<sup>+</sup> T cells are considered as different populations. Then we determined the invariant region for the whole system (1) by dealing with each population in the model. We achieve this through the following theorem:

**Theorem 1:** All forward solutions of the system in  $R_+^4$  are feasible  $\forall t \geq 0$  if they enter the invariant region  $\Gamma = \Omega_L \times \Omega_V \times \Omega_T,$  where

$$\Omega_L = (S, I) \in R_+^2 : S + I \leq N$$

$$\Omega_V = V \in R_+^1$$

$$\Omega_T = T \in R_+^1$$

and  $\Gamma$  is the invariant region of the whole system

**Proof:**

We prove the theorem by initially determining the invariant region for each population, where the solutions are feasible  $\forall t \geq 0$ .

### Hepatic population

We have to determine the invariant region  $\Omega_L$  of the sub-system (Hepatocytes) containing the feasible solutions  $\forall t \geq 0$ . Let  $\Omega_L = \{(S, I) \in R_+^2 : S + I \leq N\}$  be any solution set with non-negative initial conditions.

We know that the hepatic population  $N$  is given by

$$N = S + I$$

Then we find that

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} = \Lambda + N\mu_1 - \delta I - \gamma IT \quad (2)$$

From (2), we obtain

$$\frac{dN}{dt} \leq \Lambda - N\mu_1$$

This implies that

$$N(t) \leq \frac{\Lambda}{\mu_1} + (N_0 - \frac{\Lambda}{\mu_1}) \exp(-\mu_1 t) \quad (3)$$

where  $N_0$  is the initial size of the hepatic population.

From (3), we deduce that

$$N(t) \leq \max\{N_0, \frac{\Lambda}{\mu_1}\} \quad (4)$$

Thus, the feasible solutions of the sub-system are positively invariant in the region

$$\Omega_L = \{N(t) : N(t) \leq \max\{N_0, \frac{\Lambda}{\mu_1}\}\}$$

### Hepatitis c viral population

We have to determine the invariant region  $\Omega_V$  of the sub-system (HCV) containing feasible solutions  $\forall t \geq 0$ .

Let  $\Omega_V = V \in R_+^1$  be any solution with non-negative initial conditions.

From (1c) and (4) we obtain:

$$\frac{dV}{dt} \leq \frac{\beta\Lambda}{\mu_1} - \mu_2 V \quad (5)$$

This implies that

$$V(t) \leq \frac{\beta\Lambda}{\mu_1\mu_2} + (V_0 - \frac{\beta\Lambda}{\mu_1\mu_2}) \exp(-\mu_2 t) \quad (6)$$

where  $V_0$  is the initial size of the hepatitis c viral population.

From (6), we deduce that

$$V(t) \leq \max\left\{V_0, \frac{\beta\Lambda}{\mu_1\mu_2}\right\} \quad (7)$$

Thus, the feasible solutions for the viral population in the system (1) are positively invariant in the region:

$$\Omega_V = \left\{V(t) : V(t) \leq \max\left\{V_0, \frac{\beta\Lambda}{\mu_1\mu_2}\right\}\right\}$$

### CD8<sup>+</sup> T cells population

We have to determine the invariant region  $\Omega_T$  of the sub-system (CD8<sup>+</sup> T cells) containing feasible solutions  $\forall t \geq 0$ . Let  $\Omega_T = V \in R^1$  be any solution with non-negative initial condition.

From (1d) and (7), we obtain

$$\frac{dT}{dt} \leq \frac{\lambda\beta\Lambda}{\mu_1\mu_2} \left(1 - \frac{T}{T_{\max}}\right) - \mu_3 T \quad (8)$$

This implies that

$$T(t) \leq \frac{\lambda\beta\Lambda T_{\max}}{\lambda\beta\Lambda + \mu_1\mu_2\mu_3 T_{\max}} + \left(T_0 - \frac{\lambda\beta\Lambda T_{\max}}{\lambda\beta\Lambda + \mu_1\mu_2\mu_3 T_{\max}}\right) \exp\left[-\left(\frac{\lambda\beta\Lambda}{\mu_1\mu_2 T_{\max}} + \mu_3\right)t\right] \quad (9)$$

where  $T_0$  is the initial size of the CD8<sup>+</sup> T cells population.

From (9), we deduce that

$$T(t) \leq \max\left\{T_0, \frac{\lambda\beta\Lambda}{\lambda\beta\Lambda + \mu_1\mu_2\mu_3 T_{\max}}\right\} \quad (10)$$

Thus, the feasible solutions of the subsystem are positively invariant in the region

$$\Omega_T = \left\{T(t) : T(t) \leq \max\left\{T_0, \frac{\lambda\beta\Lambda}{\lambda\beta\Lambda + \mu_1\mu_2\mu_3 T_{\max}}\right\}\right\}$$

Thus,  $\Gamma = \Omega_L \cup \Omega_V \cup \Omega_T \in R_+^2 \times R_+^1 \times R_+^1$  such that

$$\Omega_L = \{(S, I) \in R_+^2 : N(t) \leq \max(N_0, \Lambda/\mu_1)\}$$

$$\Omega_V = \left\{V(t) : V(t) \leq \max\left\{V_0, \frac{\beta\Lambda}{\mu_1\mu_2}\right\}\right\}$$

$$\Omega_T = \left\{T(t) : T(t) \leq \max\left\{T_0, \frac{\lambda\beta\Lambda}{\lambda\beta\Lambda + \mu_1\mu_2\mu_3 T_{\max}}\right\}\right\}$$

We conclude that the model system (1) is positively invariant in the region  $\Gamma$ . Thus, the model is epidemiologically and mathematically realistic.

### 2.1.2 Positivity of Solutions

Since the system (1) refers to modeling of populations, where all state variables and parameters are assumed to be non-negative  $\forall t \geq 0$ , we have to test for positivity of the state variables using the equations of the model. We achieve this through the following theorem:

**Theorem 2:** *If the initial values of a given system are  $\{S(0), I(0), V(0), T(0) \in R_+^4\} \geq 0$  then the solution set  $\{(S(t), I(t), V(t), T(t))\}$  consists of positive entities  $\forall t \geq 0$*

**Proof:** We test for positivity of each state variable.

From (1c), we have

$$\frac{dV}{dt} \geq -cV \tag{11}$$

This implies that

$$V(t) \geq V_0 \exp(-ct) \tag{12}$$

where  $V_0$  is the initial size of the viral population.

From (12), we have:

At  $t = 0$ ,  $V(0) = V_0 \geq 0$ . If  $t > 0$ ,  $\exp[-\mu_1 t] > 0$  as  $\mu_1 > 0$ . So, we have:  $V(t) \geq \exp(-\mu_1 t) \geq 0$ ,  $\forall t \geq 0$

From (1a), we have:

$$\frac{dS}{dt} \geq -(\alpha_1 V + \mu_1)S \Rightarrow \frac{dS}{S} \geq -(\alpha_1 V + \mu_1)$$

That is,  $S \geq S_0 \exp[-(\alpha_1 V + \mu_1)t]$  (13)

where  $S_0$  is the initial size of the susceptible hepatocytes sub-population.

At  $t = 0$ ,  $S(0) = S_0 \geq 0$ . If  $t > 0$ ,  $\exp[-(\alpha_1 V(t) + \mu_1)t] > 0$  as  $\alpha_1 V(t) + \mu_1 > 0$ . So, we have:  $S(t) \geq \exp[-(\alpha_1 V(t) + \mu_1)t] \geq 0$ ,  $\forall t \geq 0$ .

From (1d), we have:

$$\frac{dT}{T} \geq -\left(\frac{\lambda V + \mu_3 T_{\max}}{T_{\max}}\right)dt \tag{14}$$

Then, we obtain:

$$T(t) \geq T_0 \exp\left[-\left(\frac{\lambda V + \mu_3 T_{\max}}{T_{\max}}\right)t\right] \tag{15}$$

where  $T_0$  is the initial size of the CD8<sup>+</sup> T cells population.

At  $t = 0$ ,  $T(0) = T_0 \geq 0$ . If  $t > 0$ ,  $\exp\left[-\left(\frac{\lambda V + \mu_3 T_{\max}}{T_{\max}}\right)t\right] > 0$  as  $\frac{\lambda V + \mu_3 T_{\max}}{T_{\max}} > 0$ . So, we have:

$$T(t) \geq \exp\left[-\left(\frac{\lambda V + \mu_3 T_{\max}}{T_{\max}}\right)t\right] \geq 0, \forall t \geq 0.$$

From (1b), we have:

$$\frac{dI}{dt} \geq -(\gamma T + \mu_1 + \alpha_2)I$$

That is,

$$I(t) \geq I_0 \exp[-(\gamma T + \mu_1 + \alpha_2)t] \tag{16}$$

where  $I_0$  is the initial size of the infected hepatocytes sub-population.

At  $t = 0$ ,  $I(0) = I_0 \geq 0$ . If  $t > 0$ ,  $\exp[-(\gamma T(t) + \mu_1 + \alpha_2)t] > 0$  as  $\gamma T(t) + \mu_1 + \alpha_2 > 0$ . So, we have:

$$S(t) \geq \exp[-(\gamma T(t) + \mu_1 + \alpha_2)t] \geq 0, \forall t \geq 0.$$

Since the solution set  $\{S(t), I(t), V(t), T(t)\}$  consists of positive entities  $\forall t \geq 0$ , we conclude that the model system (1) is epidemiologically and mathematically realistic (Hethcote, 2000).

### 3. Existence of Disease Free Equilibrium Point (DFE)

In the absence of HCV, there are no infected hepatocytes and so the  $CD8^+$  T cells of the immune system are not generated to combat the infected hepatocytes. Then we calculate the values of  $S$ ,  $I$  and  $T$  if  $V = 0$ . Using the notations by Chong *et al.* (2015), we can compute the disease free equilibrium point  $U_0 = (S^*, I^*, V^*, T^*)$  if

$$dS/dt = 0, dI/dt = 0, dV/dt = 0 \text{ and } dT/dt = 0 \tag{17a}$$

That is

$$\Lambda + \alpha_2 I - \alpha_1 S V - \mu_1 S = 0, \alpha_1 S V - \gamma T - \mu_1 I - \delta I - \alpha_2 I = 0, \beta I - \mu_2 V = 0 \text{ and}$$

$$\lambda V \left(1 - \frac{T}{T_{\max}}\right) - \mu_3 T = 0,$$

where

$$S^* = \frac{\Lambda + \alpha_2 I^*}{\alpha_1 V^* + \mu_1}, \quad I^* = \frac{\mu_2 V^*}{\beta} \quad \text{and} \quad T^* = \frac{\lambda T_{\max} V^*}{\lambda V^* + \mu_3 T_{\max}} \tag{17b}$$

In the absence of HCV, we find that

$$I^* = \mu_2(0)/\beta = 0 \quad T^* = (\lambda T_{\max}(0))/(\lambda(0) + \mu_3 T_{\max}) = 0$$

Using  $I^* = 0$  and  $V^* = 0$ , we find that  $S^* = (\Lambda + \alpha_2(0))/(\alpha_1(0) + \mu_1) = \Lambda/\mu_1$

Thus, we have:

$$\therefore U_0 = (S^*, I^*, V^*, T^*) = (\Lambda/\mu_1, 0, 0, 0) \tag{18}$$

### 3.1 The Basic Reproductive Number

**Definition 1:** The basic reproduction number  $R_0$  is defined as the average number of secondary infections produced when a single infected individual is introduced into a host population where all individuals are susceptible in the period of infection (Dietz, 1975; Diekmann *et al.*, 1990; Van den Driessche and Watmough, 2002). Also, it is known as the basic reproduction ratio or basic reproductive rate (Hethcote, 2000).

Relevant to our study, this dynamical threshold can be defined as the average number of infections instigated by an infectious hepatocyte in a hepatic population (the liver) during the period of infection. The basic reproductive number is a very important threshold since it can be used as a reference to determine whether the disease (HCV infection) persists in the hepatic population or goes to extinction (Diekmann *et al.*, 1990; Van den Driessche and Watmough, 2002). We see that if  $R_0 < 1$  the infection dies out and it spreads if  $R_0 > 1$ .

We compute the basic reproductive number by using the technique developed by Diekmann *et al.* (1990) and improved by Van den Driessche and Watmough (2002) as follows:

If we assume  $F$  as a non-negative  $m \times m$  matrix and  $Y$  as a non-singular  $M$  – matrix such that

$$F = \left[ \frac{\partial F_i(U_0)}{\partial x_j} \right] \text{ and } Y = \left[ \frac{\partial Y_i(U_0)}{\partial x_j} \right] \text{ with } 1 \leq i, j \leq m$$

where  $F_i$  is the occurrence of new infections in compartment  $i$ ,  $Y_i = Y_i^- - Y_i^+$  in which  $Y_i^+$  is the rate of transfer of entities into compartment  $i$  by all other means while  $Y_i^-$  is the rate of transfer of entities out of compartment  $i$ , and  $U_0^*$  is the disease free equilibrium state (point), it follows that the basic reproductive number is the spectral radius(dominant eigenvalue) of  $FY^{-1}$  which is denoted by  $R_0 = \rho(FY^{-1})$

If we rearrange the equations of the system (1) in such a way that the infectious classes occur first, we obtain a system of equations represented by

$$x'_i = f_i(x) = F_i(x) - Y_i(x), i = 1, 2, \dots, n$$

At this juncture, we assume that each function  $f_i$  is continuous and at least twice differentiable in the region  $\Gamma$ . We then derive  $F_i$  and  $V_i$  as

$$F_i = \begin{bmatrix} \alpha_1 SV \\ \beta I \end{bmatrix} \text{ and } Y_i = \begin{bmatrix} (\lambda T + \mu_1 + \delta + \alpha_2)I \\ \mu_2 V \end{bmatrix}$$

Then, we have:

$$F = \frac{\partial F_i(U_0)}{\partial X_j} = \begin{bmatrix} \frac{\partial f_1}{\partial I} & \frac{\partial f_1}{\partial V} \\ \frac{\partial f_2}{\partial I} & \frac{\partial f_2}{\partial V} \end{bmatrix} = \begin{bmatrix} 0 & \alpha_1 S^* \\ \beta & 0 \end{bmatrix}$$

$$Y = \frac{\partial Y_i(U_0)}{\partial X_j} = \begin{bmatrix} \frac{\partial y_1}{\partial I} & \frac{\partial y_1}{\partial V} \\ \frac{\partial y_2}{\partial I} & \frac{\partial y_2}{\partial V} \end{bmatrix} = \begin{bmatrix} \lambda T^* + \mu_1 + \delta + \alpha_2 & 0 \\ 0 & \mu_2 \end{bmatrix}$$

where

$$f_1 = \alpha_1 SV \quad f_2 = \beta I \quad y_1 = (\lambda T + \mu_1 + \delta + \alpha_2)I \quad y_2 = \mu_2 V$$

At the disease free equilibrium state  $U_0^*$ , i.e. using the result (13), we find that

$$F = \begin{bmatrix} 0 & \frac{\alpha_1 \Lambda}{\mu_1} \\ \beta & 0 \end{bmatrix} \text{ and } Y = \begin{bmatrix} \mu_1 + \delta + \alpha_2 & 0 \\ 0 & \mu_2 \end{bmatrix}$$

Then the inverse matrix  $Y^{-1}$  and the product  $FY^{-1}$  were computed to obtain:

$$Y^{-1} = \begin{bmatrix} \frac{1}{\mu_1 + \delta + \alpha_2} & 0 \\ 0 & \frac{1}{\mu_2} \end{bmatrix} \text{ and } FY^{-1} = \begin{bmatrix} 0 & \frac{\alpha_1 \Lambda}{\mu_1 \mu_2} \\ \frac{\beta}{\mu_1 + \delta + \alpha_2} & 0 \end{bmatrix}$$

Since Van den Driessche and Watmough (2002) define  $R_0$  as the spectral radius( $\rho$ ) of  $FY^{-1}$ , then we have:

$$R_0 = \rho(FY^{-1}) = \max(\lambda_1, \lambda_2),$$

This means we initially determine the eigenvalues,  $\lambda$ , of  $FY^{-1}$  from

$$|FY^{-1} - \lambda I| = 0$$

That is,

$$\begin{vmatrix} -\lambda & \frac{\alpha_1 \Lambda}{\mu_1 \mu_2} \\ \frac{\beta}{\mu_1 + \delta + \alpha_2} & -\lambda \end{vmatrix} = 0$$

$$\Rightarrow \lambda^2 - \frac{\alpha_1 \beta \Lambda}{\mu_1 \mu_2 (\mu_1 + \delta + \alpha_2)} = 0$$

The eigenvalues of  $FY^{-1}$  are

$$\lambda_1 = \sqrt{\frac{\alpha_1 \beta \Lambda}{\mu_1 \mu_2 (\mu_1 + \delta + \alpha_2)}} \text{ and } \lambda_2 = -\sqrt{\frac{\alpha_1 \beta \Lambda}{\mu_1 \mu_2 (\mu_1 + \delta + \alpha_2)}}$$

Thus, the basic reproductive number  $R_0 = \max(\lambda_1, \lambda_2) = \sqrt{\frac{\alpha_1 \beta \Lambda}{\mu_1^2 \mu_2 + \mu_1 \mu_2 \delta + \mu_1 \mu_2 \alpha_2}}$

#### 4. Existence of Endemic Equilibrium Point (EE)

We obtain the endemic equilibrium point  $E^* = (S^*, I^*, V^*, T^*)$  if  $V \neq 0$ , which is derived as follows:

Substituting  $I^* = \mu_2 V^* / \beta$  into  $(\Lambda + \alpha_2 I^*) / (\alpha_1 V^* + \mu_1)$  converts (12b) into (14), where the expressions

for  $S^*, I^*$  and  $T^*$  all appear in terms of the state variable  $V^*$ .

$$S^* = \frac{\Lambda \beta + \alpha_2 \mu_2 V^*}{\alpha_1 \beta V^* + \beta \mu_1} \quad I^* = \frac{\mu_2 V^*}{\beta} \quad T^* = \frac{\lambda T_{\max} V^*}{\lambda V^* + \mu_3 T_{\max}} \quad (19)$$

Substituting  $S^*, I^*$  and  $T^*$  from (19) into equation  $\alpha_1 S V - \gamma I T - \mu_1 I - \delta I - \alpha_2 I = 0$  in (17a), we obtain a quadratic equation in terms of  $V^*$

$$P(V^*) = a_2 (V^*)^2 + a_1 (V^*) + a_0$$

where the coefficients are given by

$$a_2 = \alpha_1 \alpha_2 \beta \lambda \mu_3 - \alpha_1 \beta \mu_2 \lambda (\mu_1 + \delta + \alpha_2);$$

$$a_1 = \alpha_1 \beta^2 \lambda \Lambda + \alpha_1 \alpha_2 \mu_3^2 T_{\max} - \alpha_1 \beta \lambda \gamma \mu_2 T_{\max} - \mu_2 (\mu_1 + \delta + \alpha_2) (\alpha_1 \beta \mu_3 T_{\max} + \lambda \mu_1 \beta);$$

$$a_0 = \alpha_1 \beta^2 \mu_3 \Lambda T_{\max} - \beta \mu_1 \mu_2 \lambda \gamma T_{\max} - \mu_1 \mu_2 \mu_3 \beta (\mu_1 + \delta + \alpha_2) T_{\max}$$

**Theorem 4:** The HCV model system (1) has:

- i) A unique endemic equilibrium point if  $a_0 < 0$ , which implies  $R_0 > 1$
- ii) A unique endemic equilibrium point if  $a_1 < 0$  and  $a_0 = 0$  or  $a_1^2 - 4a_2 a_0 = 0$

iii) Two endemic equilibrium points if  $a_0 > 0, a_1 < 0$  and  $a_1^2 - 4a_2a_0 > 0$

iv) No solution otherwise.

### 5. Dynamical Behavior of the System

In this section, we investigate the dynamical behavior of the system (1) by analyzing the stabilities of the DFE and EE points. We analyze the local and global stability of each of these points.

#### 5.1 Local Stability of the DFE Point

We begin the analysis by presenting and then prove the following theorem:

**Theorem 5:** The disease free equilibrium point of the system (1) is locally asymptotically stable in the region  $\Gamma$  if  $R_0 < 1$  and unstable if  $R_0 > 1$ .

**Proof:**

We have to show that the trace of the Jacobian matrix  $J_{U_0}$  of the model (1) is negative and its determinant is a

positive entity. Let the trace and determinant of the Jacobian matrix be  $Tr(J_{U_0})$  and  $Det(J_{U_0})$  respectively.

$$J_{U_0} = \begin{bmatrix} -\mu_1 & \alpha_2 & -\frac{\alpha_1\Lambda}{\mu_1} & 0 \\ 0 & -(\mu_1 + \delta + \alpha_2) & \frac{\alpha_1\Lambda}{\mu_1} & 0 \\ 0 & \beta & -\mu_2 & 0 \\ 0 & 0 & \lambda & -\mu_3 \end{bmatrix}$$

Thus, we have:

$$Tr(J_{U_0}) = -2\mu_1 - \alpha_2 - \delta - \mu_2 - \mu_3, \text{ which is a negative entity.}$$

$$Det(J_{U_0}) = -\mu_3(-\mu_1^2\mu_2 - \mu_1\mu_2\delta - \mu_1\mu_2\alpha_2 + \alpha_1\beta\Lambda)$$

Now,  $Det(J_{U_0}) > 0$  if  $-\mu_1^2\mu_2 - \mu_1\mu_2\delta - \mu_1\mu_2\alpha_2 + \alpha_1\beta\Lambda < 0$

That is, 
$$\frac{\alpha_1\beta\Lambda}{\mu_1^2\mu_2 + \mu_1\mu_2\delta + \mu_1\mu_2\alpha_2} < 1$$

This implies that 
$$\sqrt{\frac{\alpha_1\beta\Lambda}{\mu_1^2\mu_2 + \mu_1\mu_2\delta + \mu_1\mu_2\alpha_2}} < \sqrt{1} = 1$$

Thus, we have

$$R_0 < 1$$

Hence the disease free equilibrium point  $U_0$  of the model system (1) is locally asymptotically stable in the region  $\Gamma$  if  $R_0 < 1$  and unstable if  $R_0 > 1$ , which implies that the HCV infection will not spread at this state. So, it can be controlled. Thus, we have proved Theorem 5.

### 5.2 Global Stability of the DFE Point

Using the method proposed by Castillo-Chavez *et al.*(2002), we begin the analysis by presenting and then prove the following theorem:

**Theorem 6:** *The disease free equilibrium state of the system (1) is globally asymptotically stable if the matrix  $A$  has negative eigenvalues and  $C$  is a Metzler matrix when the system is expressed in the format:*

$$\begin{cases} \frac{dX_N}{dt} = A(X_N - X_{U_0,n}) + BX_n \\ \frac{dX_n}{dt} = CX_n \end{cases} \quad (20)$$

where

$X_N$  is the non-transmitting class;  $X_n$  is the transmitting class,  $X_{U_0,n}$  is a class of the same size as  $X_n$  at the

DFE point  $U_0$ ;  $A, B$  and  $C$  are matrices.

**Proof:**

We need to prove that the DFE point of the system (1) is globally asymptotically stable by investigating the nature of the matrices  $A$  and  $C$  in equations in the format (20) above.

We first express the system (1) in the form (20) as follows:

$$X_N = (S, T) \Rightarrow dX_N/dt = (dS/dt, dT/dt)$$

$$X_N - X_{DFE} = (S - \Lambda/\mu_1, T)$$

$$X_n = (I, V) \Rightarrow dX_n/dt = (dI/dt, dV/dt)$$

So, we have:

$$\begin{pmatrix} f_1 = \Lambda + \alpha_2 I - \alpha_1 SV - \mu_1 S \\ f_4 = \lambda V(1 - \frac{T}{T_{\max}}) - \mu_3 T \end{pmatrix} = A \begin{pmatrix} S - \frac{\Lambda}{\mu_1} \\ T \end{pmatrix} + B \begin{pmatrix} I \\ V \end{pmatrix} \quad (21a)$$

$$\begin{pmatrix} f_2 = \alpha_1 SV - \gamma T - \mu_1 I - \delta I - \alpha_2 I \\ f_3 = \beta I - \mu_2 V \end{pmatrix} = C \begin{pmatrix} I \\ V \end{pmatrix} \quad (21b)$$

Then we solve for the matrices  $A$  and  $C$  in equation (21a) and equation (21b) respectively to obtain:

$$A = \begin{pmatrix} \frac{df_1}{dS} & \frac{df_1}{dT} \\ \frac{df_4}{dS} & \frac{df_4}{dT} \end{pmatrix} = \begin{pmatrix} -\mu_1 & 0 \\ 0 & -\mu_3 \end{pmatrix} \quad \therefore A = \begin{pmatrix} -\mu_1 & 0 \\ 0 & -\mu_3 \end{pmatrix}$$

$$C = \begin{pmatrix} \frac{df_2}{dI} & \frac{df_2}{dV} \\ \frac{df_3}{dI} & \frac{df_3}{dV} \end{pmatrix} = \begin{pmatrix} -(\mu_1 + \delta + \alpha_2) & \frac{\alpha_1 \Lambda}{\mu_1} \\ \beta & -\mu_2 \end{pmatrix} \quad \therefore C = \begin{pmatrix} -(\mu_1 + \delta + \alpha_2) & -\frac{\alpha_1 \Lambda}{\mu_1} \\ \beta & -\mu_2 \end{pmatrix}$$

We determine the eigenvalues, lambda, of  $A$  from

$$|A - \lambda I| = 0 \quad , \text{ where } I = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$$

That is, 
$$\begin{vmatrix} -\mu_1 - \lambda & 0 \\ 0 & -\mu_3 - \lambda \end{vmatrix} = 0$$

This implies that 
$$(\mu_1 + \lambda)(\mu_3 + \lambda) = 0$$
  

$$\therefore \lambda_1 = -\mu_1 \text{ and } \lambda_2 = -\mu_3$$

We find that the eigenvalues of  $A$  are  $-\mu_1$  and  $-\mu_3$ , which are negative; and  $C$  is a Metzler matrix as the entries in the leading diagonal are all negative while the others are positive. Hence the disease free equilibrium point  $U_0$  of the system (1) is globally asymptotically stable in the region  $\Gamma$  if  $R_0 < 1$  and unstable if  $R_0 > 1$ . Thus, we have proved Theorem 6.

### 5.3 Local Stability of the EE Point.

We analyze the local stability of the EE point by initially presenting and then prove the following theorem:

**Theorem 7:** *The endemic equilibrium point  $E^*$  of the system (1) is locally asymptotically stable in the region  $\Gamma$  if  $R_0 > 1$  and unstable if  $R_0 < 1$*

**Proof:**

Let the Jacobian matrix of the system (1) at the EE point  $E^*$  be  $J_{E^*}$ . Then we have:

$$J_{E^*} = \begin{bmatrix} -(\alpha_1 V^* + \mu_1) & \alpha_2 & -\alpha_1 S^* & 0 \\ \alpha_1 V^* & -(\gamma T^* + \mu_1 + \delta + \alpha_2) & \alpha_1 S^* & -\gamma I^* \\ 0 & \beta & -\mu_2 & 0 \\ 0 & 0 & \lambda(1 - \frac{T^*}{T_{\max}}) & -(\frac{\lambda V^* + \mu_3 T_{\max}}{T_{\max}}) \end{bmatrix}$$

We then find that the characteristic polynomial equation of  $J_{E^*}$  is

$$d_4 x^4 + d_3 x^3 + d_2 x^2 + d_1 x + d_0 = 0,$$

where

$$d_4 = 1;$$

$$d_3 = \frac{1}{T_{\max}} (\alpha_1 V^* T_{\max} + \mu_3 T_{\max} + \mu_2 T_{\max} + 2\mu_1 T_{\max} + V^* \lambda + \delta T_{\max} + \alpha_2 T_{\max});$$

$$d_2 = \frac{1}{T_{\max}} (\alpha_1 V^{*2} \lambda + \alpha_1 V^* \mu_1 T_{\max} + \alpha_1 V^* \delta T_{\max} + \alpha_1 V^* \mu_2 T_{\max} + \alpha_1 V^* \mu_3 T_{\max} + \mu_1 \gamma T^* \\ + \gamma T^* V^* \lambda + \gamma T^* T_{\max} \mu_3 + \gamma T^* \mu_2 T_{\max} + 2V^* \mu_1 \lambda + 2\mu_1 \mu_3 T_{\max} + T_{\max} \mu_2 \delta + \alpha_2 V^* \lambda \\ + V^* \mu_2 \lambda + V^* \lambda \delta + \delta \mu_3 T_{\max} + 2\mu_1 \mu_2 T_{\max} + \mu_2 \mu_3 T_{\max} + \alpha_2 \mu_3 T_{\max} + \alpha_2 \mu_2 T_{\max})$$

$$\begin{aligned}
 & + \mu_1 \delta T_{\max} + \mu_1 \alpha_2 T_{\max} + \mu_1^2 T_{\max} + \alpha_1 V^* \gamma T^* T_{\max} - \alpha_1 \beta S^* T_{\max} ); \\
 d_1 = & \frac{1}{T_{\max}} (\alpha_1 V^* \delta \mu_3 T_{\max} + \alpha_1 V^* \mu_1 \mu_2 T_{\max} + \alpha_1 V^* \mu_2 \mu_3 T_{\max} + \alpha_1 V^* \mu_1 \mu_3 T_{\max} \\
 & + \alpha_1 V^* \delta \mu_2 T_{\max} + \alpha_1 V^{*2} \mu_2 \lambda + \alpha_1 V^{*2} \mu_1 \lambda + \mu_1 \delta \mu_2 T_{\max} + \mu_1 \alpha_2 V^* \lambda + \mu_1 \delta V^* \lambda \\
 & + \mu_1 \delta \mu_3 T_{\max} + \mu_1 \alpha_2 \mu_3 T_{\max} + \mu_1 \beta \alpha_1 S^* T_{\max} + \mu_1 \alpha_2 \mu_2 T_{\max} + \mu_1 \gamma T^* V^* \lambda \\
 & + \mu_1 \gamma T^* \mu_3 T_{\max} + \mu_1 \gamma T^* \mu_2 T_{\max} + \gamma T^* \mu_2 V^* \lambda + \gamma T^* \mu_2 \mu_3 T_{\max} + \beta \gamma^* \lambda T_{\max} + \beta \gamma^* \lambda T^* \\
 & + \mu_1^2 V^* \lambda + \mu_1^2 \mu_3 T_{\max} - \beta \alpha_1 S^* V^* \lambda + \mu_1^2 \mu_2 T_{\max} + \alpha_2 \mu_2 \mu_3 T_{\max} + 2 \mu_1 \mu_2 \mu_3 T_{\max} \\
 & + \alpha_1 V^* \gamma T^* \mu_2 T_{\max} - \beta \alpha_1 S^* \mu_3 T_{\max} + \delta \mu_2 \mu_3 T_{\max} + \delta \mu_2 V^* \lambda + \alpha_2 \mu_2 V^* \lambda \\
 & + 2 \mu_1 \mu_2 V^* \lambda + \alpha_1 V^* \gamma T^* \mu_3 T_{\max} + \alpha_1 V^{*2} \gamma T^* \lambda ); \\
 d_0 = & \frac{1}{T_{\max}} (\alpha_1 V^* \delta \mu_2 \mu_3 T_{\max} + \alpha_1 V^* \mu_1 \mu_2 \mu_3 T_{\max} + \alpha_1 V^{*2} \delta \mu_2 \lambda + \alpha_1 V^{*2} \mu_1 \mu_2 \lambda \\
 & + \alpha_2 \mu_1 \mu_2 \mu_3 T_{\max} - \mu_1 \beta \alpha_1 S^* V^* \lambda - \mu_1 \beta \alpha_1 S^* \mu_3 T_{\max} + \mu_1 \delta \mu_2 \mu_3 T_{\max} + \mu_1 \delta \mu_2 V^* \lambda \\
 & + \mu_1 \alpha_2 \mu_2 V^* \lambda + \mu_1 \gamma T^* \mu_2 V^* \lambda + \mu_1 \gamma T^* \mu_2 \mu_3 T_{\max} - \mu_1 \beta \gamma^* \lambda T^* + \mu_1^2 \mu_2 \mu_3 T_{\max} \\
 & + \mu_1^2 \mu_2 V^* \lambda + \alpha_1 V^* \gamma T^* \mu_2 \mu_3 + \alpha_1 V^* \gamma T^* \mu_2 \mu_3 T_{\max} + \alpha_1 V^* \beta \gamma^* \lambda T_{\max} \\
 & - \alpha_1 V^* \beta \gamma^* \lambda T^* + \alpha_1 V^{*2} \gamma T^* \mu_2 \lambda + \mu_1 \beta \gamma^* T_{\max} )
 \end{aligned}$$

By using the Routh-Hurwitz criteria, as detailed by Sivanandam and Deepa (2007) and Parks (1962), the characteristic equation has eigenvalues with negative real parts if all coefficients satisfy the following inequalities:

$$d_0 > 0, d_1 > 0, d_2 > 0, d_3 > 0, d_4 > 0, d_3 d_2 - d_4 d_1 > 0, d_3 d_2 d_1 - (d_4 d_1^2 + d_3^2 d_0) > 0$$

Hence the endemic equilibrium point  $E^*$  of system (1) is locally asymptotically stable in the region  $\Gamma$  if  $R_0 > 1$  and unstable if  $R_0 < 1$ . Thus, we have proved Theorem 7.

#### 5.4 Global Stability of the EE Point

We examine the EE point for global stability. The analysis begins by constructing Lyapunov function using the approach of Edward *et al.* (2014). But, we initially present and then prove the following theorem:

**Theorem 8:** The endemic equilibrium point  $E^*$  of the system (1) is globally asymptotically stable in the region  $\Gamma$  if  $R_0 > 1$  and unstable if  $R_0 < 1$ .

**Proof:**

To prove that the EE point is globally asymptotically stable, we make use of the following constructed Lyapunov function:

$$f(S, I, V, T) = \theta_1 (S - S^* \ln \frac{S}{S^*}) + \theta_2 (I - I^* \ln \frac{I}{I^*}) + \theta_3 (V - V^* \ln \frac{V}{V^*}) + \theta_4 (T - T^* \ln \frac{T}{T^*})$$

Differentiating  $f$  with respect to  $t$  produces

$$\frac{df}{dt} = \theta_1 \left(1 - \frac{S^*}{S}\right) \frac{dS}{dt} + \theta_2 \left(1 - \frac{I^*}{I}\right) \frac{dI}{dt} + \theta_3 \left(1 - \frac{V^*}{V}\right) \frac{dV}{dt} + \theta_4 \left(1 - \frac{T^*}{T}\right) \frac{dT}{dt}$$

Substitution of the expressions for  $dS/dt$ ,  $dI/dt$ ,  $dV/dt$ ,  $dT/dt$  from the system (1) produces:

$$\begin{aligned} \frac{df}{dt} = & \theta_1 \left(1 - \frac{S^*}{S}\right) [\Lambda + \alpha_2 I - \alpha_1 S V - \mu_1 S] + \theta_2 \left(1 - \frac{I^*}{I}\right) \left[ \frac{\alpha_1 \beta S}{\mu_2} - \gamma T - (\mu_1 + \delta + \alpha_2) I \right] \\ & + \theta_3 \left(1 - \frac{V^*}{V}\right) [\beta I - \mu_2 V] + \theta_4 \left(1 - \frac{T^*}{T}\right) \left[ \lambda V - \frac{\lambda V T}{T_{\max}} - \mu_3 T \right] \end{aligned} \quad (22)$$

At the endemic equilibrium point  $E^*$ , we have

$$\Lambda = \alpha_1 S^* V^* + \mu_1 S^* - \alpha_2 I^* \quad (23)$$

$$\mu_1 + \delta + \alpha_2 = \frac{\alpha_1 \beta S^*}{\mu_2} - \gamma T^*; \quad (24)$$

$$\mu_2 = \frac{\beta I^*}{V^*}; \quad (25)$$

$$\mu_3 = \frac{\lambda V^*}{T^*} \left(1 - \frac{T}{T_{\max}}\right) \quad (26)$$

Substituting (23), (24), (25) and (26) into (22), we have:

$$\begin{aligned} \frac{df}{dt} = & \theta_1 \left(1 - \frac{S^*}{S}\right) [\alpha_1 S^* V^* + \mu_1 S^* - \alpha_2 I^* + \Lambda + \alpha_2 I - \alpha_1 S V - \mu_1 S] \\ & + \theta_2 \left(1 - \frac{I^*}{I}\right) \left[ \frac{\alpha_1 \beta S}{\mu_2} - \gamma T - \frac{\alpha_1 \beta S^*}{\mu_2} - \gamma T^* \right] I + \theta_3 \left(1 - \frac{V^*}{V}\right) \left[ \beta I - \frac{\beta I^*}{V^*} V \right] \\ & + \theta_4 \left(1 - \frac{T^*}{T}\right) \left[ \lambda V - \frac{\lambda V T}{T_{\max}} - \frac{\lambda V^*}{T^*} + \frac{\lambda V^* T}{T_{\max}} \right] \end{aligned}$$

Simplification produces

$$\begin{aligned} \frac{df}{dt} = & \theta_1 \left(1 - \frac{S^*}{S}\right) \left[ -\left(1 - \frac{S^*}{S}\right) \mu_1 S + \left(1 - \frac{I^*}{I}\right) \alpha_2 I + \left(1 - \frac{S V}{S^* V^*}\right) \alpha_1 S^* V^* \right] \\ & + \theta_2 \left(1 - \frac{I^*}{I}\right) \left[ \left(1 - \frac{S^*}{S}\right) \frac{\alpha_1 \beta}{\mu_2} S I - \left(1 - \frac{T^*}{T}\right) \gamma T \right] + \theta_3 \left(1 - \frac{V^*}{V}\right) \left[ 1 - \frac{I^* V}{I V^*} \right] \beta I \end{aligned}$$

$$+ \theta_4 \left(1 - \frac{T^*}{T}\right) \left[ \lambda V - \frac{\lambda V^*}{T^*} - \left(1 - \frac{V^*}{V}\right) \frac{\lambda VT}{T_{\max}} \right]$$

Further simplification produces

$$\begin{aligned} \frac{df}{dt} = & -\theta_1 \left(1 - \frac{S^*}{S}\right)^2 \mu_1 S + \theta_1 \left(1 - \frac{S^*}{S}\right) \left(1 - \frac{I^*}{I}\right) \alpha_2 I + \theta_1 \left(1 - \frac{S^*}{S}\right) \left(1 - \frac{SV}{S^*V^*}\right) \alpha_1 S^*V^* \\ & + \theta_2 \left(1 - \frac{I^*}{I}\right) \left(1 - \frac{S^*}{S}\right) \frac{\alpha_1 \beta SI}{\mu_2} - \theta_2 \left(1 - \frac{I^*}{I}\right) \left(1 - \frac{T^*}{T}\right) \gamma IT + \theta_3 \left(1 - \frac{V^*}{V}\right) \left(1 - \frac{I^*V}{IV^*}\right) \beta I \\ & + \theta_4 \left(1 - \frac{T^*}{T}\right) \lambda V - \theta_4 \left(1 - \frac{T^*}{T}\right) \frac{\lambda V^*}{T^*} - \theta_4 \left(1 - \frac{T^*}{T}\right) \left(1 - \frac{V^*}{V}\right) \frac{\lambda VT}{T_{\max}} \end{aligned}$$

Thus, we have  $\frac{df}{dt} = -\theta_1 \left(1 - \frac{S^*}{S}\right)^2 \mu_1 S + G(S, I, V, T)$ , where

$$\begin{aligned} G(S, I, V, T) = & \theta_1 \left(1 - \frac{S^*}{S}\right) \left(1 - \frac{I^*}{I}\right) \alpha_2 I + \theta_1 \left(1 - \frac{S^*}{S}\right) \left(1 - \frac{SV}{S^*V^*}\right) \alpha_1 S^*V^* \\ & + \theta_2 \left(1 - \frac{I^*}{I}\right) \left(1 - \frac{S^*}{S}\right) \frac{\alpha_1 \beta SI}{\mu_2} - \theta_2 \left(1 - \frac{I^*}{I}\right) \left(1 - \frac{T^*}{T}\right) \gamma IT + \theta_3 \left(1 - \frac{V^*}{V}\right) \left(1 - \frac{I^*V}{IV^*}\right) \beta I \\ & + \theta_4 \left(1 - \frac{T^*}{T}\right) \lambda V - \theta_4 \left(1 - \frac{T^*}{T}\right) \frac{\lambda V^*}{T^*} - \theta_4 \left(1 - \frac{T^*}{T}\right) \left(1 - \frac{V^*}{V}\right) \frac{\lambda VT}{T_{\max}} \end{aligned}$$

If we use a modified version of Barbalat's (1959) Lemma or follow the approaches of Mukandavire *et al.* (2009) and Edward *et al.* (2014), function  $G(S, I, V, T)$  is non-positive. That is,  $G \leq 0$  for every  $S, I, V, T > 0$ . Then,  $df/dt \leq 0$  for all  $S, I, V, T > 0$ , and  $df/dt = 0$  if and only if  $S = S^*, I = I^*, V = V^*$  and  $T = T^*$ . Thus, the largest compact invariant set in region  $\Gamma$  is the singleton  $\{E^*\}$  where  $E^*$  is the endemic equilibrium point of the system (1). By the invariant principle (La Salle, 1976), we find that  $E^*$  is globally asymptotically stable in the region  $\Gamma$  if  $R_0 > 1$  and unstable if  $R_0 < 1$ . Thus, we have proved Theorem 8

## 6. Numerical Sensitivity Analysis

In order to find a way that will best assist in lessening human morbidity and mortality due to HCV, we find it necessary to investigate the sensitivity index of  $R_0$  relating to each parameter appearing in the expression for  $R_0$  by means of the technique established by Chitnis *et al.* (2008). The sensitivity indices reveal parameters that highly influence  $R_0$  and which can then be considered for therapeutic intervention strategies. These sensitivity indices always help to express relative degree in state variable when the parametric value alters (Chitnis *et al.*, 2008).

The sensitivity indices corresponding to the parameters appearing in the expression for the basic reproductive number are computed by making use of the parametric values (PVs) itemized in Table 2. More of these PVs are estimated while others are adopted from some research literatures. We then apply the technique expounded in Definition 2 below.

**Table 2:** Parametric values (PVs) used for computing sensitivity indices of  $R_0$

Parameter	Value	Units	Source
$\alpha_1$	0.00001	virus <sup>-1</sup> ml <sup>-1</sup> day <sup>-1</sup>	Estimated
$\alpha_2$	2	day <sup>-1</sup>	Estimated
$\beta$	6	virus cell <sup>-1</sup> day <sup>-1</sup>	Estimated
$\mu_1$	0.00014	day <sup>-1</sup>	Estimated
$\mu_2$	10	day <sup>-1</sup>	Estimated
$\mu_3$	0.02	day <sup>-1</sup>	Avendano <i>et al.</i> (2002)
$\delta$	0.486	day <sup>-1</sup>	Estimated
$\Lambda$	100	cells ml <sup>-1</sup> day <sup>-1</sup>	Estimated
$\lambda$	0.0003	day <sup>-1</sup>	Avendano <i>et al.</i> (2002)
$\gamma$	0.00000001	virus cell <sup>-1</sup> day <sup>-1</sup>	Dahari <i>et al.</i> (2005)

**Definition 2:** By Chitnis *et.al.* (2008), the forward normalized sensitivity index of a variable  $p$  that depends on a parameter  $q$  is defined as

$$X_q^p = \frac{\partial p}{\partial q} \times \frac{q}{p} \quad (27)$$

Replacing  $p$  by  $R_0$  in equation (27), the expression for the sensitivity of  $R_0$  appears

$$X_q^{R_0} = \frac{\partial R_0}{\partial q} \times \frac{q}{R_0} \quad (28)$$

Replacing  $q$  by a parameter in (28), we can compute the analytical expression for the sensitivity of  $R_0$  related to each parameter using the normalized forward sensitivity index expression as follows:

$$X_{\alpha_1}^{R_0} = \frac{\partial R_0}{\partial \alpha_1} \times \frac{\alpha_1}{R_0} = 0.5; X_{\beta}^{R_0} = \frac{\partial R_0}{\partial \beta} \times \frac{\beta}{R_0} = 0.5; X_{\Lambda}^{R_0} = \frac{\partial R_0}{\partial \Lambda} \times \frac{\Lambda}{R_0} = 0.5$$

The remaining sensitivity indices are computed using the same approach. Table 3 summarizes the sensitivity indices of the basic reproductive number  $R_0$  with respect to all parameters.

**Table 3:** The sensitivity indices of  $R_0$  relating to each parameter

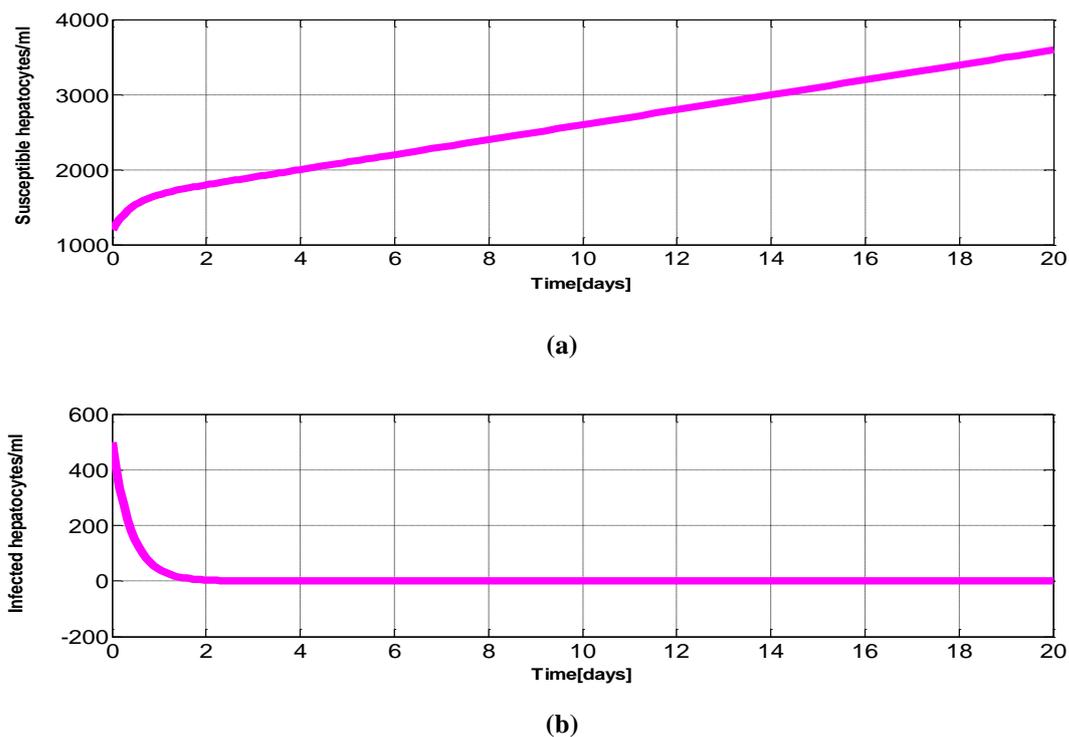
Parameter	Sensitivity index
$\mu_1$	-0.5000
$\mu_2$	-0.5000
$\alpha_1$	+0.5000
$\beta$	+0.5000
$\Lambda$	+0.5000
$\alpha_2$	-0.4022
$\delta$	-0.0977

In Table 3, we see that the parameters  $\alpha_1, \beta, \Lambda$  for the infection rate, viral replication rate and recruitment rate of susceptible hepatocytes respectively are positively sensitive parameters, which suggests that an increase in  $\alpha_1, \beta$  or  $\Lambda$  will give rise to an increase of exactly the same proportion in  $R_0$  and vice versa, as each of these parameters is directly proportional to the threshold parameter  $R_0$ . We also observe that the parameters for the natural death rate of susceptible and infected hepatocytes and natural death rate of the virus  $\mu_1$  and  $\mu_2$

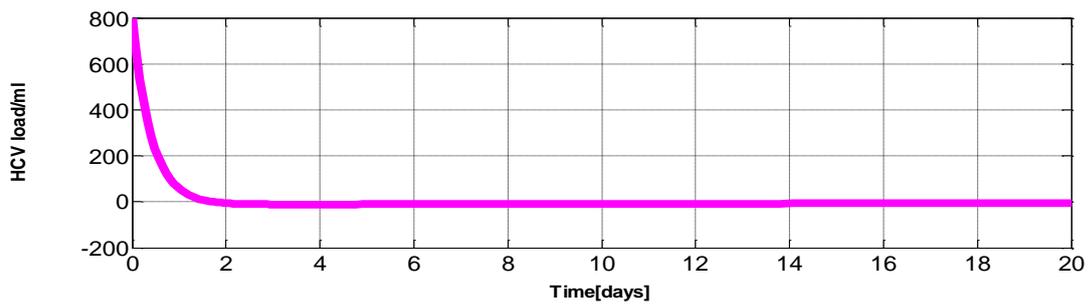
respectively are the most negatively sensitive parameters, followed by the recovery rate of infected hepatocytes  $\alpha_2$  and followed by the disease-induced death rate  $\delta$ , which is the least negatively sensitive parameter. The increase in the value of any of these parameters will decrease the value of  $R_0$  and vice versa. Thus, to eradicate or reduce intensity of the HCV morbidity, this study recommends that therapeutic interventions should be executed to reduce strictly  $R_0$  less than unity. This means therapy will lessen or stop HCV infection in the hepatic population. Specifically, antiviral drug therapy will prevent or reduce the viral replication for new infections in the population.

### 7. Numerical Simulations and Discussion

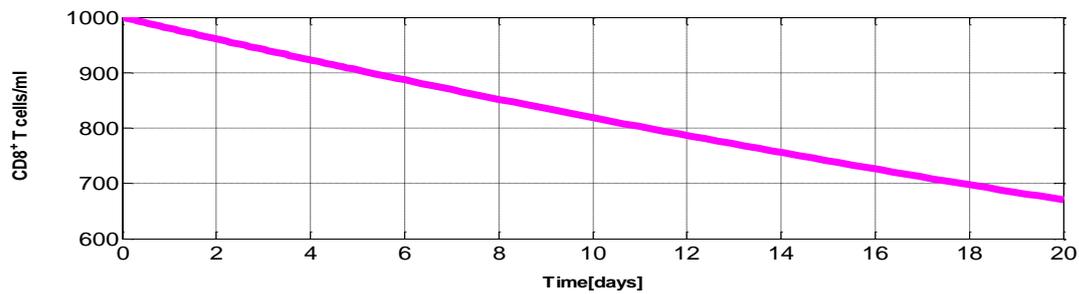
The aim of this study is to assess the interaction between the HCV and the immune system in the acute phase of infection. In order to support the analytical results, numerical simulations were performed to graphically illustrate variations in parametric values with respect to different state variables of the model and are presented in this section. To accomplish the analysis, it was found convenient to use the PVs simply for the purposes of illustrating how the model would behave at varying real situations. Table 2 shows the PVs used in the simulations.



**Figure 3:** *a* and *b* show graphs of susceptible and infected hepatocytes/ml vs. time respectively for the first 20 days of infection

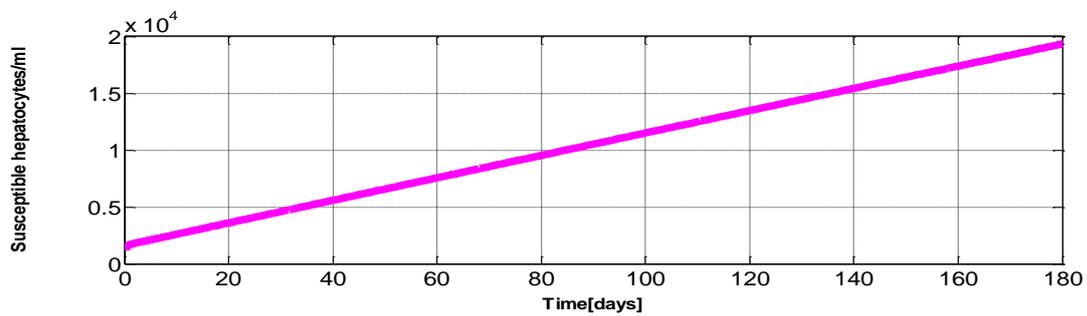


(a)

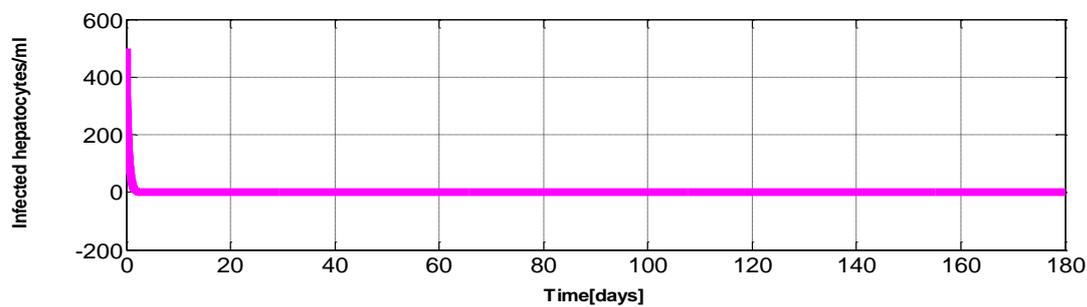


(b)

**Figure 4:** *a* and *b* show graphs of HCV load and CD8<sup>+</sup> T cells /ml vs. time respectively for the first 20 days of infection.

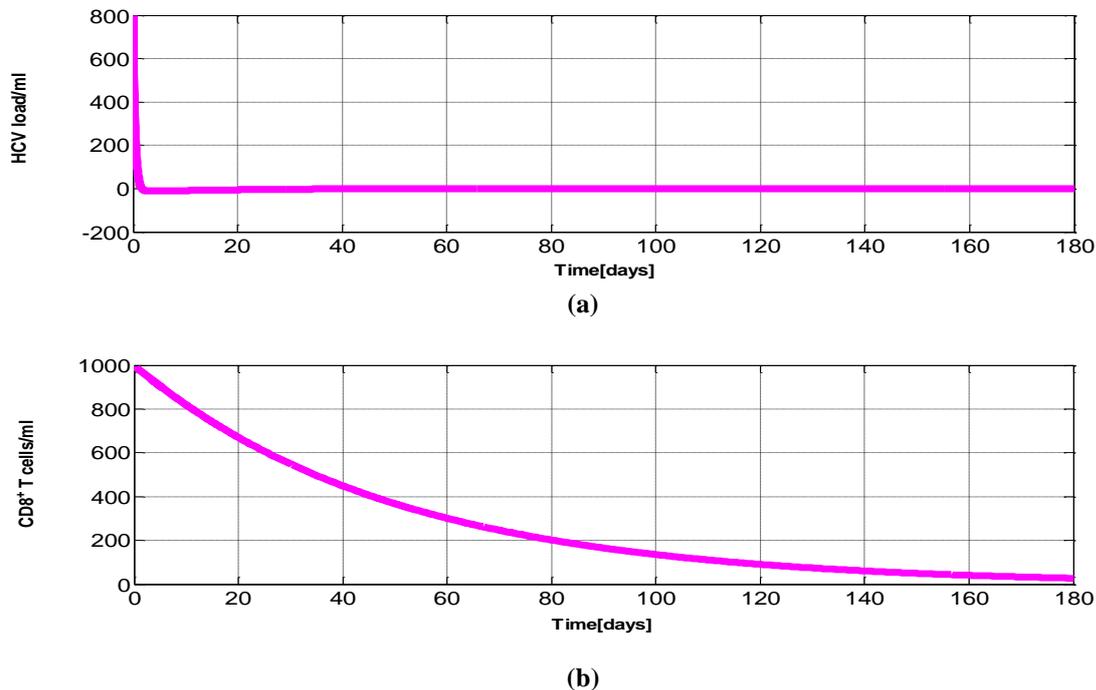


(a)



(b)

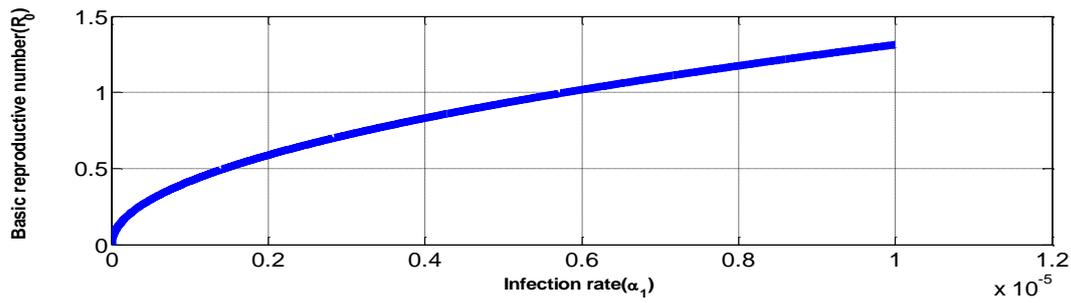
**Figure 5:** *a* and *b* show graphs of susceptible and infected hepatocytes/ml vs. time respectively for the first 180 days (6 months) of infection.



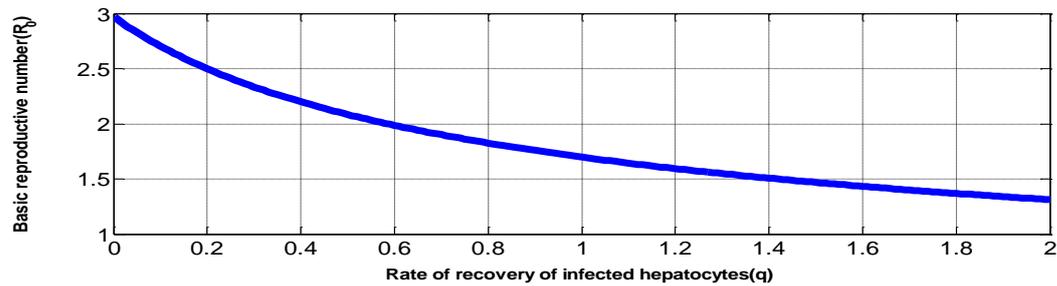
**Figure 6:** *a* and *b* show graphs of HCV load and  $CD8^+$  T cells /ml vs. time respectively for the first 180 days (6 months) of infection.

Figures 3, 4, 5 and 6 show the graphs of the susceptible and infected hepatocytes, virus and  $CD8^+$  cells for the first 20 or 180 days in the acute phase of infection, where the initial numerical values are all positive entities. It can be seen that in Fig. 4(a) and Fig.6 (a); and Fig. 3(a) and Fig.5 (a), the levels of HCV load and infected hepatocytes monotonously decrease with time and finally level off at  $V = 0$  and  $I = 0$  respectively. The decrease in the level of infected hepatocytes must be due to the spontaneous recovery, natural mortality, death due to infection and the  $CD8^+$  T cells destructive role which accounts for the decrease in the viral production as well. Also, we find that there is an increase in the level of susceptible hepatocytes with time (Fig. 3a and Fig.5a). The increase in the level of susceptible hepatocytes must be due to immigration or/and spontaneous recovery of infected hepatocytes by a noncytolytic process. Conversely, the decrease in the level of  $CD8^+$  T cells (Fig., 4b and Fig.6b) must be because of the decreased level of  $CD4^+$  T cells signals sent to the  $CD8^+$  T cells for the destructive role in the presence of HCV.

By using the parametric values itemized in Table 2, we find that  $R_0 = 1.3129$  which suggests that the disease will spread, i.e. within this acute stage of infection the HCV patient might not recover from the liver disease. Nevertheless, we can show the impact of varying the values of some parameters in the  $R_0$ . To achieve this goal, we present graphical illustrations that show the variation of  $R_0$  with respect to the rate of infection (Fig.7a), recovery rate of infected hepatocytes (Fig. 7b), rate of virus replication (Fig. 8a) and disease-induced death rate (Fig. 8b)

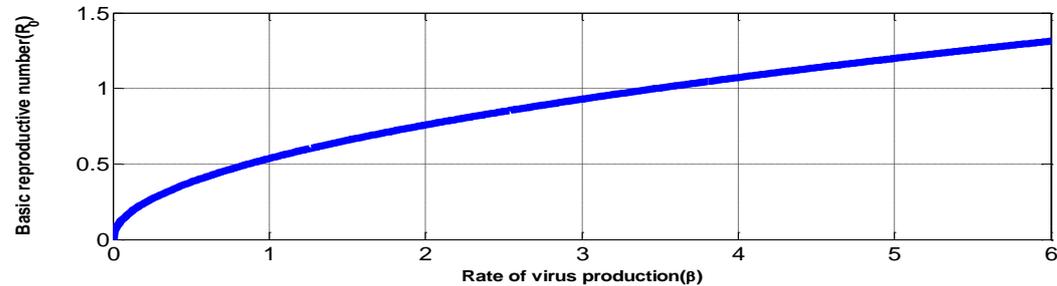


(a)

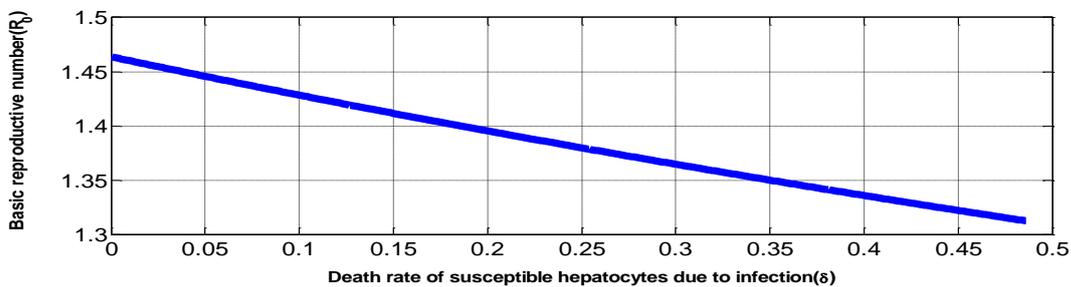


(b)

**Figure 7:** *a* and *b* show variations in the value of the basic reproductive number with respect to the infection rate and recovery rate respectively.



(a)

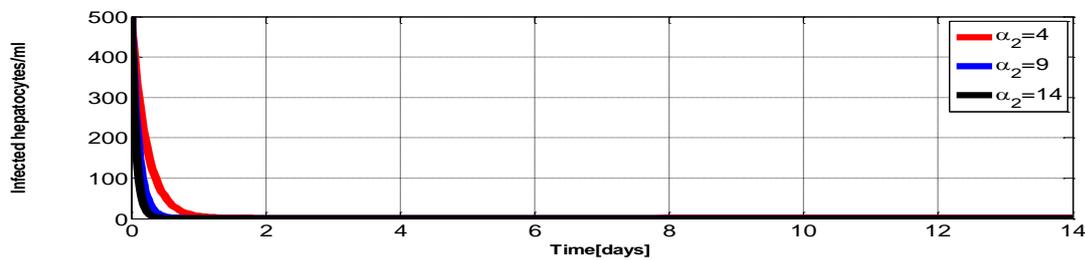


(b)

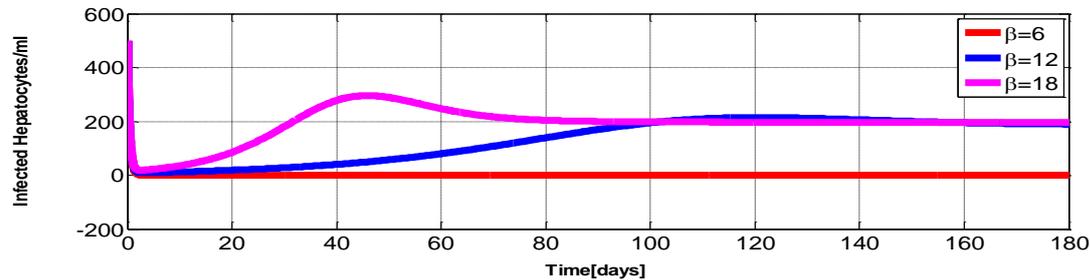
**Figure 8:** *a* and *b* show variations in the value of the basic reproductive number with respect to viral production rate and death rate due to disease respectively.

In Fig. 7(b) and Fig. 8(b), we see that the value of  $R_0$  decreases with increase in the recovery rate and disease-induced death rate, as the parameters are inversely proportional to it. Conversely, we see that an increase in the value of each parameter will give rise to the decrease in the value of  $R_0$ , implying gradual lowering of the HCV infection. Also, in Fig. 7(a) and Fig.8 (a), we observe that the value of  $R_0$  increases when the infection

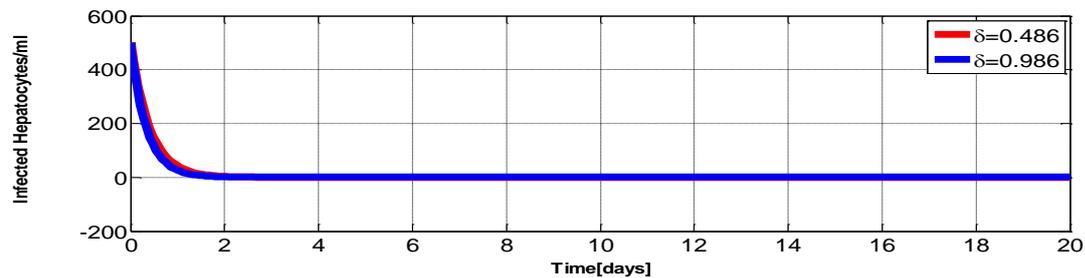
rate and virus production rate increase respectively, due to the direct proportionality between  $R_0$  and these parameters. Conversely, the decrease in the value of each of these parameters will give rise to the decrease in the value of  $R_0$ , suggesting that the HCV morbidity will decrease as well.



**Figure 9:** Graphs of infected hepatocytes/ml vs. time for the first 14 days of infection, varying recovery rate ( $\alpha_2 = 4,9,14$ ).



**Figure 10:** Graphs of infected hepatocytes/ml vs. time for the first 180 days (6 months) of infection, varying viral production rate ( $\beta = 6,12,18$ ).



**Figure 11:** Graphs of infected hepatocytes/ml vs. time for the first 20 days of infection, varying death rate due to disease ( $\delta = 0.486,0.986$ ).

The graph in Fig. 9 shows that an increase in the recovery rate decreases the number of hepatocytes. This enables the acutely HCV infected individual to clear off the virus faster in the acute stage. Nevertheless, in Fig.10 the graph indicates that the increases in the virus production rate initially causes a drastic decrease in the number of infected hepatocytes and later increases to attain an endemic equilibrium state, meaning that more hepatocytes become infected due to increased number of viruses. This implies that the recovery rate of infected hepatocytes does not have any significant effect on the HCV infection. So, the disease progresses to chronic stage. The graph in Fig. 11 shows that the increase in the disease-induced death rate reduces the number of infected hepatocytes, which subsequently levels off at  $I = 0$ .

## 8. Conclusion

This paper presents a formulated deterministic mathematical model for the interaction between HCV and immune system. From the model, we computed the disease free equilibrium point (DFP) and endemic equilibrium point (EEP). We derived the basic reproductive number  $R_0$ , which was subsequently employed to determine the scope of the disease control. We found that the DFP is both locally and globally asymptotically stable if  $R_0 < 1$  and unstable if  $R_0 > 1$ . Moreover, we found that the EEP is both locally and globally asymptotically stable if  $R_0 > 1$  unstable if  $R_0 < 1$ . We used the parametric values to determine the sensitivity induces of  $R_0$  relating to each parameter embedded in  $R_0$  and found that the infection rate, viral production rate and recruitment rate of new susceptible could be targeted for strategic intervention to eradicate or reduce intensity of the disease. Numerical simulations were performed and the results supported the analytical results.

Finally, we have seen that the analyses were performed based the knowledge acquired from findings from various HCV epidemiological studies, whereby we adopted several parametric values. The analytical and simulation results, we obtained, can be a beginning of harm-reduction strategy (HRS). The HRS is a public health strategy that could help in reducing threats of HCV transmission, rather than eliminating the infection in vivo, which should be taken as early as possible to prevent or diminish the incidence of the disease. In this paper, we recommend that antiviral drug therapy should be implemented in order to eradicate or reduce the intensity of the disease by blocking the virus replication during early phase. This will absolutely stop the disease progression to chronicity, and possibly stop mortality.

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