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MATHEMATICAL MODEL FOR THE ACUTE HEPATITIS C VIRUS INFECTION SUBJECT TO IMMUNE SYSTEM RESPONSE AND THERAPY

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Abstract:

Hepatitis C virus (HCV) is a source of chronic hepatitis C infection that can destroy the liver when proper therapeutic intervention is not executed early. For the purpose of studying the dynamics of the disease during acute infection, a deterministic mathematical model incorporating the effect of immune system and therapy has been formulated. The model is a system of non-linear ordinary differential equations. The disease-free equilibrium point E_0 during therapy has been computed. Furthermore, the basic reproductive number R_0 and effective reproductive number R_e have been computed using the next generation operator method. The sensitivity indices of R_e relating to each parameter in the model were computed. It is found that R_e is most sensitive to the drug inhibiting efficacy of viral replication parameter ε. Thus, it implies that an increase in the value of ε will reduce the rate of viral replication leading to the decrease or eradication of the HCV morbidity. By using the estimated parametric values, we found that $R_e < R_0$, which attests that therapeutic strategy is absolutely effective in reducing intensity of the disease and hence preventing evolution to chronic state.

1. Introduction

HCV is a small positive-stranded RNA microbe belonging to the *Hepacivirus* genus in the family *Flaviviridae* (Taxonomy, 2005), which mutates so rapidly that there is no vaccine (Colina *et al.*, 1999). It is the source of hepatitis C virus infection (HCVI) that can destroy the liver if no proper therapeutic strategy is implemented. It is approximated that about 130 to 170 million people are infected with HCV worldwide (Lavanchy, 2009). Usually, HCVI is categorized as acute hepatitis C infection (AHCI) and chronic hepatitis C infection (CHCI) depending on the disease evolution. The AHCI signifies the first 6 months of infection following acquisition of HCV whereas CHCI refers to a period subsequent to the AHCI phase, which is marked by the persistence of HCV RNA in the blood. This is irrespective of whether patients are symptomatic or asymptomatic during AHCI. It is also

Key words and phrases: Hepatitis c virus, Immune system, Disease-free equilibrium, Therapy, Effective reproductive number.

evident that around 20% to 50% patients with AHCI spontaneously clear the virus within 6 months (Kamal, 2008) while others progress to CHCI. It implies that more than 50% of AHCI cases undergo CHCI, which can be a source of evolution of cirrhosis and hepatocellular carcinoma to some of them. Many people with AHCI are asymptomatic, which makes the diagnosis of the disease become difficult while symptomatic patients most commonly show fatigue.

The channels of HCV transmission are primarily dependent on exposure to infected blood, which incorporate vertical transmission (Owusu-Ofori *et al.*, 2005), needle stick injuries (Xia *et al.*, 2008), intravenous drug use (IDU) (Tohme and Holmberg, 2010), sexual behaviors(Jafari *et al.*, 2010) and body piercings (Lam *et al.*, 2010). In developing countries (DCs), HCV is transmitted mainly through contact with infected blood and blood products in healthcare provisions centers. In most developed countries, it results from IDU; it can be a risk source of the transmission in the DCs as well (Aceijas and Rhodes, 2007;Nelson *et al.*, 2011).

We know that numerous antivirals have been clinically tested for therapy of HCV. The trials have revealed that therapy of CHCI with different antivirals results into different SVR rates. For instance, it was formerly treated using conventional interferon alpha that led to the SVR rate of at least 20% of patients after 48 weeks of therapy, which later was improved to the SVR of 38% to 43% of patients using interferon alpha-2b plus ribavirin combination therapy (McHutchison *et al.*, 1998; Poynard *et al.*, 1998). Combination therapy with peginterferon alpha 2a or 2b plus ribavirin combination therapy further improved the SVR rate to approximately 50% of cases (Fried *et al.*, 2002; Muir *et al.*, 2004; Kanda *et al.*, 2010), which has been the standard therapy for CHCI. Unlike AHCI, chronic hepatitis c is associated with a worsening prognosis, which requires more demanding therapy and longer therapy period leading to intolerability owing to developing side effects. Conversely, drugs prescribed for therapy of CHCI can also be assigned to people with AHCVI although interferon-based monotherapy is just sufficient to produce SVR of more than 50% of cases (Jaeckel *et al.*, 2001; Kamal *et al.*, 2006). Monotherapy is far better tolerated due to fewer side effects, relatively cheaper, more suitable and takes shorter time than combination therapies for chronic CHCI (Myers *et al.*, 2001).Hence, therapy of patients with HCV during acute period of infection significantly reduces side effects and disease development to chronic hepatitis(Alberti *et al.*, 2002).

Although this paper presents a deterministic mathematical model for the effect of therapy on dynamics of HCV *in vivo* during acute phase of infection, patients with AHCI are diverse. It is very difficult to identify patients who require therapy owing to varying rates of

spontaneous clearance of the viruses and the presence of asymptomatic cases (Busch and Shafer, 2005). Spontaneous clearance of the virus can take place either during AHCI (Kamal, 2008) or beyond this period (Grebely *et al.*, 2014).Also, some patients are entirely asymptomatic having normal or slightly elevated serum alanine aminotransferase (ALT) levels despite HCV-RNA positivity after known exposure. Others show acute illness and have high serum ALT levels and noticeable jaundice. Thus, we have considered these challenges in the development of the model, i.e. a patient can either clear the virus spontaneously or not during acute infection.

Certainly, mathematical modeling of viral dynamics with therapy provides us with understanding and quantifying biological processes that govern changes in the viral load and accompanying biomarkers such as ALT levels before and after treatment (Ribeiro *et al.*, 2003).For our case, mathematical models can help to provide answers to biological questions regarding pathogenesis, the dynamics of HCV, immune response and efficacy of drug therapy. Furthermore, we see that modeling HCV dynamics with therapy has deepened our understanding of the virus pathogenesis and guided drug development (Chatterjee *et al.*, 2012). Various models have been formulated by several researchers in order to understand the efficacy of drug therapy on the dynamics of HCV. Thus, Neumann *et al.*(1998) formulated a simple model to investigate the dynamics of HCV during therapy by adopting a model of human immunodeficiency viral infection (Wei *et al.*, 1995; Perelson *et al.*, 1996). The model had a system of three nonlinear differential equations which represented a constant population of target hepatocytes, infected hepatocytes and the virus, and it was used to approximate the rates of viral clearance and loss of infected hepatocytes by fitting to the model the decline of HCV RNA level within infected people in the first 14 days of therapy. Since then modeling of the virus dynamics has been very important in examining the HCV RNA level decay during therapy, which is very well expounded by Perelson (2002) and Perelson *et al.*(2005). However, it could not include some observed HCV RNA dynamic profiles under therapy, i.e., it assumed that there is no proliferation of target and infected cells and no spontaneous recovery of infected hepatocytes. The extended model of Dahari *et al.*(2007) incorporated proliferation of target and infected hepatocytes without spontaneous recovery of the infected hepatocytes. A model that includes proliferation and the spontaneous recovery of infected hepatocytes was used to investigate the dynamics of HCV for primary infection in chimpanzees (Dahari *et al.*, 2005).Nevertheless, these models do not include the role of immune response on the dynamics of HCV.

The Neumann *et al.*(1998) model and extended model of Dahari *et al.*(2007) assumed that the drugs had two major effects on the dynamics of HCV: reduction of infections and

blockage of virus replication. We observe that the drug blocking efficacy of virus replication increases with drug dosage (Neumann *et al.*, 1998), where at large values of blocking efficacies the drug does not directly reduce infections i.e. the drug efficacy in reducing infections becomes negligible. Thus, it is required to consider only blockage of the virus replication. In this paper, we extend the model of Ismail *et.al*, (2016) to investigate the effect of interferon alpha-2b monotherapy on the dynamics of HCV by adopting therapy regimen of Neumann *et al.*(1998).

2. Model Formulation

In this section, we formulate a deterministic model incorporating three different populations: hepatocytes population, Hepatitis C virus population and the $CD8^+$ T cells population. But, we classify the hepatocytes population as susceptible and infected classes whereby the susceptible class is a group of hepatocytes (liver cells) exposed to the HCV infection, and are equally likely to be infected, while the infected class is a group of hepatocytes infected with HCV. Moreover, the HCV population refers to a group of viruses that is responsible for the infection whereas the $CD8^+$ T cells population is a collection of T-Lymphocytes of the immune system that is liable for the destruction of the infected hepatocytes. We have extended the model proposed by Ismail*, et al.* (2016) to include the effect of antiviral monotherapy.

In order to achieve our goal, we make the following assumptions:
(1) The model is formulated to describe the dynamics of HCV and immune system during acute phase of infection; (2) susceptible hepatocytes are equally likely to be infected by the viruses and infected hepatocytes; (3) the susceptible hepatocytes are generated by proliferation of existing hepatocytes and immigration (differentiation of liver cells progenitor or bone marrow cell) at a constant rate; (4) these susceptible hepatocytes and infected hepatocytes have the same natural mortality rates; (5) the virions and the $CD8^+$ T cells have different natural death rates; (6) the $CD8^+$ T cells destroy the infected hepatocytes at a constant rate and die at a constant rate due to infection; (7) the $CD8^+$ T cells are produced at a constant rate and (8)we assume that the person with HCV infection receives highly dosed interferon alpha-2b monotherapy that blocks viral replication within infected hepatocytes. (9) Also, we assume that the person with HCV infection can either clear the virus spontaneously by a noncytolytic process or not during therapy.
All state variables and parameters are positive; they are introduced and concisely described in Table 1 and Table 2 respectively.

Table 1: State variables and their descriptions

Variable	Description
$S(t)$	The susceptible hepatocytes at time t
$I(t)$	The infected hepatocytes at time t
$V(t)$	The hepatitis c viruses at time t
$T(t)$	The CD8+ T cells at time t

For brevity, we henceforth denote the susceptible hepatocytes sub-population by S; the infected sub-population by I; HCV viral population by V and the CD8+ T cells population by T.The state variables and their descriptions are summarized in Table 1.

Table 2: Parameters and their descriptions

Parameter	Description
ω	Per capita infection rate
σ	Per capita production rate of viruses from the infected hepatocytes
β	Rate at which the CD8+ T cells destroy the infected hepatocytes
Π	Per capita production rate of susceptible hepatocytes
g	Per capita production rate of the CDB+ T cells
d	Per capita natural death rate of susceptible and infected hepatocytes
c	Per capita natural death rate of viruses
b	Per capita natural death rate of CD8+ T cells
q	Rate of spontaneous cure of infected hepatocytes by a noncytolytic process
μ	Per capita death rate infected hepatocytes due to HCV infection
ε	Fraction by which antiviral drug reduces viral production rate
$T_{\max}$	Maximum CD8+ T cells population level

Healthy hepatocytes S are constantly produced at the rate Π and die naturally at a constant rate d; the S cells are infected at the rate that is proportional to the product SV,with a constant of proportionality ω.The infected hepatocytes I have a constant natural mortality rate of d.The hepatitis C viruses V are produced from these infected cells at a constant rate σ viruses per infected cell per day, once produced they die naturally at the rate of c.Then the CD8+ T cells destroy the infected cells I at the rate proportional to the product I and T, with a constant of proportionality β. In the presence of HCV, the CD8+ T cells are instigated by the CD4+ T cells and constantly supplied at the rate g,and die naturally at a constant rate b. When the person infected with HCV receives interferon

alpha-2b monotherapy, the drug inhibits virus production from infected hepatocytes I by a fraction ε.

2.1 Model Compartment and Dynamics

If we consider the assumptions and the symbols representing the parameters and state variables from Table 1 and Table 2 respectively, we can illustrate the description of the model dynamics in the form of a compartmental diagram as in Figure 1.

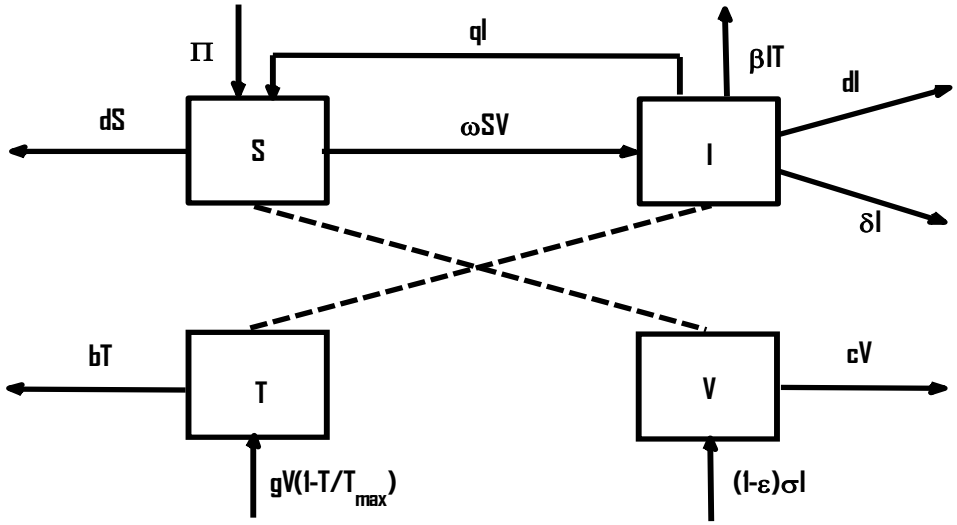

Figure 1: Compartmental diagram for the hepatitis C virus model with immune system including drug therapy.

2.2 Equations of the model

Based on the assumptions made and relationships that exist between the state variables shown in Figure 1, we formulate a system of four non-linear ordinary differential equations describing the dynamics of hepatitis c virus in the presence of drug therapy.

$$\frac{dS}{dt} = \Pi + qI - \omega SV - dS \tag{1.1}$$

$$\frac{dI}{dt} = SV - \beta IT - dI - \mu I - qI \tag{1.2}$$

$$\frac{dV}{dt} = (1-\varepsilon)\sigma I - cV \tag{1.3}$$

$$\frac{dT}{dt} = gV(1-\frac{T}{T_{\max}}) - bT \tag{1.4}$$

where the initial conditions are $S(0) > 0$, $I(0) \geq 0$, $V(0) \geq 0$ and $T(0) \geq 0$

2.3 Basic properties of the model

2.3.1 Invariant regions

Since the system of equations (1.1)-(1.4) describes modeling of susceptible hepatocytes, infected hepatocytes, HCV and the $CD8^+$ T cells with the effect of drug therapy, we assumed that all state variables and parameters used in the model are non-negative $\forall t \geq 0$. According to Figure 1, we observe that the hepatocytes population has two classes $S(t)$ and $I(t)$ which can be combined together to form $N(t)$, which denotes the total hepatocytes population. That is,

$$N(t) = S(t) + I(t) \tag{2}$$

Then we can determine the appropriate feasible region where all state variables are non-negative through the following theorem:

Theorem 1: *All forward solutions of the system (1) are contained in the region* $\Phi \in R_+^4$, $\forall t \geq 0$ *and* $\Phi = \Gamma_L \cup \Gamma_V \cup \Gamma_T \in R_+^2 \times R_+^1 \times R_+^1$, *where*

$$\Gamma_L = (S, I) \in R_+^2 : S + I \leq N$$
$$\Gamma_V = V \in R_+^1$$
$$\Gamma_T = T \in R_+^1$$

and Φ *is the positive invariant region for the whole system.*

Proof:

We prove the theorem by initially determining the invariant region within which the solution for each population are feasible $\forall t \geq 0$.

Hepatocytes population

We have to determine the invariant region Γ_L of the system (Hepatocytes) containing the feasible solutions $\forall t \geq 0$.

Let $\Gamma_L = (S, I) \in R_+^2$ be any solution of the system with non-negative initial conditions.

From (2), we have:

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} \tag{3}$$

Substituting (1.1) and (1.2) into (3) produces

$$\frac{dN}{dt} = [\Pi + qI - \omega SV - dS] + [\omega SV - \beta IT - dI - \mu I - qI]$$
$$= \Pi - Nd - \beta IT - \mu I \tag{4}$$

From (4), we have:

$$\frac{dN}{dt} \leq \Pi - Nd$$

$$\frac{dN}{dt} + dN \leq \Pi \tag{5}$$

The general solution of the first order ordinary differential inequality (5) is:

$$N(t) \leq \frac{\Pi}{d} + (N_0 - \frac{\Pi}{d}) \exp(-dt) \tag{6}$$

where N_0 is the initial hepatocytes population size.

From (6), we deduce that

$$N(t) \leq \max\{N_0, \frac{\Pi}{d}\} \tag{7}$$

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

$$\Gamma_L = \{N(t) : N(t) \leq \max\{N_0, \frac{\Pi}{d}\}\}$$

HCV population

We have to determine the invariant region Γ_V of the system (HCV) containing feasible solutions $\forall t \geq 0$. Let $\Gamma_V = V \in R_+^1$ be any solution with non-negative initial conditions.

Since we know that

From (2) and (7), we deduce that

$$I(t) \leq \max(N_0, \frac{\Pi}{d}) \Rightarrow I(t) \leq \frac{\Pi}{d} \tag{8}$$

Substitution of (8) into (1.3) produces

$$\frac{dV}{dt} \leq \frac{(1-\varepsilon)\sigma\Pi}{d} - cV$$

$$\frac{dV}{dt} + cV \leq \frac{(1-\varepsilon)\sigma\Pi}{d} \tag{9}$$

The general solution of the first order ordinary differential inequality (9) is

$$V(t) \leq \frac{(1-\varepsilon)\sigma\Pi}{cd} + (V_0 - \frac{(1-\varepsilon)\sigma\Pi}{cd}) \exp(-ct) \tag{10}$$

where V_0 is the initial viral population size.

From (10), we deduce that

$$V(t) \leq \max\{V_0, \frac{(1-\varepsilon)\sigma\Pi}{cd}\} \tag{11}$$

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

$$\Gamma_V = \{V(t) : V(t) \le \max\{V_0, \frac{(1-\varepsilon)\sigma\Pi}{cd}\}\}$$

CD8+ T cells population

We have to determine the invariant region Γ_T of the system (CD8+ T cells) containing feasible solutions $\forall t \ge 0$.

Let $\Gamma_T = T \in R_+^1$ be any solution with non-negative initial condition

From (11), we deduce that

$$V(t) \le \frac{(1-\varepsilon)\sigma\Pi}{cd} \tag{12}$$

Substitution of (12) into (1.4) produces:

$$\frac{dT}{dt} \le \frac{g(1-\varepsilon)\sigma\Pi}{cd}(1-\frac{T}{T_{\max}}) - bT$$

$$\frac{dT}{dt} + [\frac{g(1-\varepsilon)\sigma\Pi}{cdT_{\max}} + b]T \le \frac{g(1-\varepsilon)\sigma\Pi}{cd} \tag{13}$$

The general solution of the first order ordinary differential inequality (13) is

$$T(t) \le \frac{g(1-\varepsilon)\sigma\Pi T_{\max}}{g(1-\varepsilon)\sigma\Pi + bcdT_{\max}} + (T_0 - \frac{g(1-\varepsilon)\sigma\Pi T_{\max}}{g(1-\varepsilon)\sigma\Pi + bcdT_{\max}})\exp[-(\frac{g(1-\varepsilon)\sigma\Pi}{cdT_{\max}} + b)t] \tag{14}$$

From (14), we deduce that

$$T(t) \le \max\{T_0, \frac{g(1-\varepsilon)\sigma\Pi}{g(1-\varepsilon)\sigma\Pi + bcdT_{\max}}\}$$

Thus, the feasible solutions for the CD8+ T population in the system (1) are positively invariant in the region:

$$\Gamma_T = \{T(t) : T(t) \le \max\{T_0, \frac{g(1-\varepsilon)\sigma\Pi}{g(1-\varepsilon)\sigma\Pi + bcdT_{\max}}\}\}$$

Thus $\Phi = \Gamma_L \cup \Gamma_V \cup \Gamma_T \in R_+^2 \times R_+^1 \times R_+^1$, for

$$\Gamma_L = \{N(t) : N(t) \le \max\{N_0, \frac{\Pi}{d}, d > 0\},$$

$$\Gamma_V = \{V(t) : V(t) \le \max\{V_0, \frac{(1-\varepsilon)\sigma\Pi}{cd}\}\}$$

$$\Gamma_T = \{T(t) : T(t) \le \max\{T_0, \frac{g(1-\varepsilon)\sigma\Pi}{g(1-\varepsilon)\sigma\Pi + bcdT_{\max}}\}\}$$

From this, we conclude that the model system (1) is positively invariant in the region Φ.Hence it is epidemiologically and mathematically realistic.

2.3.2 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 solve each equation in the system to test for positivity. We achieve this thorough 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 (1.3), we have:

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

$$\frac{dV}{V} \geq -cdt \tag{15}$$

Integration of (15) produces

$$\ln V \geq -ct + K$$

That is, $$V(t) \geq V_0 \exp(-ct) \tag{16}$$

where V_0 is the initial viral population size.

From (16), we have:

At $t = 0$, $\exp[-c(0)] = 1$. So, $V(0) = V_0 \geq 0$. If $t > 0$, $\exp[-c(t)] > 0$ since $c > 0$. Thus, we find that $V(t) \geq V_0 \exp(-ct) \geq 0$, $\forall t \geq 0$

From (1.1), we have:

$$\frac{dS}{dt} \geq -(\omega V + d)S$$

$$\frac{dS}{S} \geq -(\omega V + d)dt \tag{17}$$

Integration of (17) produces:

$$\ln S \geq -(\omega V + d)t + K$$

That is, $$S(t) \geq S_0 \exp[-(\omega V(t) + d)t] \tag{18}$$

From (18), we have:

At $t = 0$, $\exp[-(\omega V(0) + d)(0)] = 1$. So, $S(0) = S_0 \geq 0$. If $t > 0$, then $\exp[-(\omega V(t) + d)t] > 0$ since $\omega V(t) + d > 0$. Thus, we find that $S(t) \geq S_0 \exp[-(\omega V + d)t] \geq 0$, $\forall t \geq 0$

From (1.4), we have:

$$\frac{dT}{dt} \geq -(\frac{gV + bT_{\max}}{T_{\max}})T$$

$$\frac{dT}{T} \geq -(\frac{gV + bT_{\max}}{T_{\max}})dt \tag{19}$$

Integration of (19) produces:

$$\ln T \geq -(\frac{gV + bT_{\max}}{T_{\max}})t + K$$

That is,

$$T(t) \geq T_0 \exp[-(\frac{gV + bT_{\max}}{T_{\max}})t] \quad (20)$$

From (20), we have:

At $t = 0$, $\exp[-(\frac{gV + bT_{\max}}{T_{\max}})(0) = 1$.So, $T(0) = T_0 \geq 0$.If $t > 0$ then $\exp[-(\frac{gV + bT_{\max}}{T_{\max}})t] > 0$ since $\frac{gV + bT_{\max}}{T_{\max}} > 0$.Thus, we find that $T(t) \geq T_0 \exp[-(\frac{gV + bT_{\max}}{T_{\max}})] \geq 0, \forall t \geq 0$

From (1.2), we have:

$$\frac{dI}{dt} \geq -(\beta T + d + q)I$$

$$\frac{dI}{I} \geq -(\beta T + d + q)dt \quad (21)$$

Integration of (21) produces:

$$\ln I \geq -(\beta T + d + q)t + K$$

That is,

$$I(t) \geq I_0 \exp[-(\beta T + d + q)t] \quad (22)$$

From (22), we have:

At $t = 0$, $\exp[-(\beta T(0) + d + q)(0)] = 1$.So, $I(0) = I_0 \geq 0$.If $t > 0$, then $\exp[-(\beta T(t) + d + q)t] > 0$ since $\beta T(t) + d + q > 0$ Thus, we find that $I(t) \geq I_0 \exp[-(\beta T + d + q)] \geq 0, \ \forall t \geq 0$.

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. Model Analysis

In this section, we determine the disease free equilibrium point of the system (1) and the basic reproductive number in the absence of therapy. We also determine the effective reproductive number for the purpose of examining the impact of antiviral therapy on the HCV morbidity.

3.1 Disease Free Equilibrium Point (DFE)

We determine the disease free equilibrium point by setting the equations of the system (1) equal to zero.

$$\Pi + qI - \omega SV - dS = 0 \tag{23.1}$$

$$\omega SV - \beta IT - dI - \mu I - qI = 0 \tag{23.2}$$

$$(1-\varepsilon)\sigma I - cV = 0 \tag{23.3}$$

$$gV(1-\frac{T}{T_{\max}}) - bT = 0 \tag{23.4}$$

From equations (23.1), (23.3) and (23.4), we obtain

$$S^* = \frac{\Pi + qI^*}{\omega V^* + d} \qquad I^* = \frac{cV^*}{(1-\varepsilon)\sigma} \qquad T^* = \frac{gT_{\max}V^*}{gV^* + bT_{\max}} \tag{24}$$

At the disease free equilibrium point, $V^* = 0$ .Then, from (24), we obtain

$$S^* = \frac{\Pi + q(0)}{\omega(0) + d} = \frac{\Pi}{d} \qquad I^* = \frac{c(0)}{(1-\varepsilon)\sigma} = 0 \qquad T^* = \frac{gT_{\max}(0)}{g(0) + bT_{\max}} = 0 \tag{25}$$

Hence the disease free equilibrium point of the system (1) exists and is given by

$$E_0 = (\frac{\Pi}{d}, 0, 0, 0) \tag{26}$$

According to (26), the absence of hepatitis c virus implies absence of infected hepatocytes and therefore the $CD8^+$ T cells are not activated to destroy the infected hepatocytes.

3.2 The Basic Reproduction Number, R_0

Definition 1: *The basic reproduction number , R_0, is defined as the average number of secondary infections produced when an 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).

The basic reproduction number is a very important parameter as it can be used to determine whether the disease prevails in the community or dies out. If $R_0 < 1$, the average number of new infected individuals produced by an infectious individual is less than one during its infectious period, implying that the infection cannot grow. Conversely, $R_0 > 1$ implies that the average number of new infections produced by an infectious individual greater than one, and therefore the disease spreads in the population. It is also very important in the process of analyzing sensitive parameters which drive the dynamics of the disease and stability analysis of the disease free equilibrium.

To determine the basic reproduction number, we find it important to recognize new infections from all other changes in the population. To achieve this, we apply the next generation operator proposed by Van den Driessche and Watmough (2002). Then we consider the model system (1) without therapy, i.e. $\varepsilon = 0$.

Then in the absence of therapy, we have the system (1) reduced to the system (27)

$$\begin{cases} \dfrac{dS}{dt} = \Pi + qI - \omega SV - dS \\ \dfrac{dI}{dt} = \omega SV - \beta IT - dI - \mu I - qI \\ \dfrac{dV}{dt} = \sigma I - cV \\ \dfrac{dT}{dt} = gV(1 - \dfrac{T}{T_{\max}}) - bT \end{cases} \tag{27}$$

Let $f_i(x)$ be the rate of appearance of new infection in compartment i, $v_i^-(x)$ be the rate of transfer of individuals out of compartment i and $v_i^+(x)$ be the rate of transfer of individuals into of compartment i by all other means. Furthermore, we assume that each function is continuously differentiable at least twice in the region Φ.The HCV model system comprises nonnegative initial conditions with the following equations:

$$x_I^{'} = F_i(x) = f_i(x) - y_i(x), i = 1,2,\ldots,n$$

where $v_i = v_i^- - v_i^+$

Then we consider equations (1.2) and (1.3) of the system (1) to determine the expressions for f_i and v_i as follows:

$$f_i = \begin{bmatrix} \omega SV \\ \sigma I \end{bmatrix} \qquad y_i = \begin{bmatrix} (\beta T + d + \mu + q)I \\ cV \end{bmatrix}$$

Let F be a non-negative matrix $n \times n$ and Y be a non-singular N-matrix

At the disease free equilibrium point E_0, we find that

$$F = \frac{\partial f_i(E_0)}{\partial x_j} = \begin{bmatrix} 0 & \dfrac{\omega\Pi}{d} \\ \sigma & 0 \end{bmatrix}$$

$$Y = \frac{\partial y_i(E_0)}{\partial x_j} = \begin{bmatrix} d + \mu + q & 0 \\ 0 & c \end{bmatrix}$$

Then, we have

$$Y^{-1} = \begin{bmatrix} \dfrac{1}{d + \mu + q} & 0 \\ 0 & \dfrac{1}{c} \end{bmatrix}$$

We determine the next generation matrix FV^{-1} developed by Castillo-Chavez *et al.*(2002) as

$$FY^{-1} = \begin{bmatrix} 0 & \frac{\omega\Pi}{cd} \\ \frac{\sigma}{d+\mu+q} & 0 \end{bmatrix}$$

By Van den Driessche and Watmough (2002), the basic reproductive number is a spectral radius of the next generation matrix FY^{-1}.Henceforth, to determine the basic reproductive number R_0, we compute the spectral radius (ρ) of this next generation matrix from

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

where λ_1 and λ_2 are the eigenvalues of the next generation matrix FY^{-1}

Thus, the eigenvalues, lambda, of FY^{-1} are obtained by

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

That is,

$$\begin{vmatrix} -\lambda & \frac{\omega\Pi}{cd} \\ \frac{\sigma}{d+\mu+q} & -\lambda \end{vmatrix} = 0$$

$$\lambda^2 - \frac{\omega\sigma\Pi}{cd(d+\mu+q)} = 0$$

Hence the basic reproductive number is given by

$$R_0 = \sqrt{\frac{\omega\sigma\Pi}{cd(d+\mu+q)}} \tag{28}$$

3.3 The Effective Reproduction Number, R_e

Definition 2: *The effective reproduction number, R_e, is the average number of infections caused by a single infectious individual introduced in a community where intervention strategies (in our case therapy) are administered* (Okuonghae and Korobeinikov, 2007; Okuonghae and Aihie, 2008*)*.

We compute the effective reproduction number R_e of the system (1) by applying the method used for R_0,where R_e is the spectral radius of FY^{-1} denoted by $R_e = \rho(FY^{-1})$.Thus the effective reproduction number is given by

$$R_e = \sqrt{\frac{(1-\varepsilon)\omega\sigma\Pi}{cd(d+\mu+q)}} \tag{29}$$

From (29), we have:

$$R_e = \sqrt{(1-\varepsilon)}R_0 \tag{30}$$

The drug blocking efficacy, ε, of viral replication can take any value in the interval $0 \le \varepsilon \le 1$, whereby its role can be discussed in three sub-intervals: $\varepsilon = 0, 0 < \varepsilon < 1$ and $\varepsilon = 1$.When $\varepsilon = 0$, the result in (30) reduces to the form $R_e = R_0$,which implies that drug therapy has no impact on the HCV morbidity. Conversely, if $\varepsilon = 1$, it becomes $R_e = 0$, implying that the disease vanishes due to therapy, i.e. the drug is 100% effective in exterminating the disease. But, any value of ε taken from the sub-interval $0 < \varepsilon < 1$ changes it into $R_e < R_0$.This reflects therapy efficacy to reduce the impact of the disease.

4. Numerical Sensitivity Analysis

Mathematical epidemiology is a study that helps in understanding the dynamics of an infection in order to control it by focusing on some sensitive parameters. This can be achieved by performing sensitivity analysis based on the model parameters. The sensitivity analysis describes how each parameter influences R_e.It helps to identify the most sensitive parameters. With small variations in the values of the parameters, we can identify the parameters that highly influence R_e whereby proper control measures can be taken(Chitnis *et al.*, 2008). We accomplish this by computing the sensitivity indices of R_e relating to all parameters in it. In this case, the estimated values of the parameters employed were adopted from some literatures and others were just estimated, which are altogether itemized in Table 3.

Table 3: Estimated values of parameters used to compute sensitivity indices of R_e

Parameter	Value	Unit	Source
b	0.02	day^{-1}	Avendano *et al.*(2002)
c	10	day^{-1}	Estimated
d	0.00014	day^{-1}	Estimated
g	0.0003	day^{-1}	Avendano *et al.*(2002)
q	2	day^{-1}	Estimated
β	0.00000001	virus $cell^{-1}day^{-1}$	Dahari *et al.* (2005)
μ	0.486	day^{-1}	Estimated
ε	0.96		Neumann *et al.*(1998)
σ	6	virus $cell^{-1}day^{-1}$	Estimated
ω	0.00001	$virus^{-1}ml^{-1}day^{-1}$	Estimated
Π	100	cells $ml^{-1}day^{-1}$	Estimated

The normalized forward sensitivity index refers to the ratio of relative change of a variable to the relative change in a parameter. If the variable is a differentiable function of the parameter then the sensitivity index is defined as follows:

Definition 3: *The normalized forward sensitivity index of variable* p *that depends on parameter* q *is defined as:*

$$\chi_q^p = \frac{\partial p}{\partial q} \times \frac{q}{p} \tag{31}$$

Replacing p in (31) by R_e, we obtain

$$\chi_q^{R_e} = \frac{\partial R_e}{\partial q} \times \frac{q}{R_e} \tag{32}$$

According to (32), the sensitivity indices of R_e are computed with regard to all parameters in it. This is achieved by replacing q by a parameter to obtain

$$\chi_\varepsilon^{R_e} = \frac{\partial R_e}{\partial \varepsilon} \times \frac{\varepsilon}{R_e} = -12.0000, \chi_d^{R_e} = \frac{\partial R_e}{\partial d} \times \frac{d}{R_e} = -0.5000 \text{ and so on}$$

The sensitivity indices of R_e pertaining to all parameters are computed using the same approach and then summarized in Table 4.

Table 4: Sensitivity indices of R_e relating to all parameters

Parameter	Sensitivity index
ε	-12.0000
d	-0.5000
c	-0.5000
ω	$+0.5000$
σ	$+0.5000$
Π	$+0.5000$
q	-0.4022
μ	-0.0977

According to the sensitivity indices displayed in Table 4, we observe that the parameters for infection rate ω, the viral replication rate σ and rate of recruitment of susceptible hepatocytes Π are the most positively sensitive parameters. This implies that increasing the values of these parameters will increases R_e and vice versa. For example, increasing the value of ω by 20% will increase R_e by 10% while decreasing ω by 20% will decrease R_e by 10%.

The drug blocking efficacy of virus replication ε, the natural mortality rate of susceptible and infected hepatocytes d and the natural death rate of the virus c are the most negatively sensitive parameters. This implies that increasing the values of these parameters will decrease R_e and vice versa. For example, increasing ε by 10% will decrease R_e by 120%. Also, we observe that the rate of spontaneous recovery of infected hepatocytes q and the death rate of infected hepatocytes due to infection μ are less sensitive negative parameters.

5. Numerical Simulations and Discussion

In this section we present the numerical simulations of the system (1).We performed simulations based on the estimated parametric values itemized in Table 3 and this was accomplished through the application of ode45 MATLAB's standard solver for ordinary differential equations (ODEs), which implements a Runge-Kutta technique with a variable time step for efficient computation. However, this was preceded by the assessment of the values of R_0 and R_e at $\omega = 0.00001$, $\sigma = 6$, $c = 10$, $d = 0.00014$, $\mu = 0.486$, $\varepsilon = 0.96$ and $q = 2$.We found that $0.2626 = R_e < R_0 = 1.3129$, implying that therapy reduces the HCV infection *in vivo.*

According to Fig. 2, the simulation for the basic reproduction number R_0 shows that the HCV transmission is very high without therapy, regardless of variations of spontaneous recovery of infected hepatocytes q, for $0 \le q \le 2$.In Fig.3, the numerical solution of R_e shows four different cases: (1) when $q = 0$ and $\varepsilon = 0$, R_e has the highest value, indicating the increase in the chance of disease evolution to chronic state, implying that patients who do not spontaneously clear the virus and are not subjected to treatment will get chronic HCV infection in the long run; (2) when $q = 0$ and $\varepsilon \neq 0$, R_e is still high although decreases with increasing value of ε,implying that patients who do not spontaneously clear the virus will only clear it through drug therapy. But, the drug will totally eradicate the disease with increase of blocking efficacy of the virus production; (3) when $q \neq 0$ and $\varepsilon = 0$, R_e is relatively low, implying that patients who spontaneously clear the virus and are not subjected to therapy will cure from the disease at different times depending on the rate of clearance q and (4) when $q \neq 0$ and $\varepsilon \neq 0$, R_e attains the lowest value and additionally decreases with increasing values of q and ε, implying that patients who spontaneously clear the virus and are subjected to therapy will also cure from the disease. The numerical solution based on category 4 shows a very low value of R_e, implying that the disease is eradicated very rapidly. However, this is practically not recommended as therapy of this group of patients is unnecessary due to spontaneous clearance of the virus they undergo.

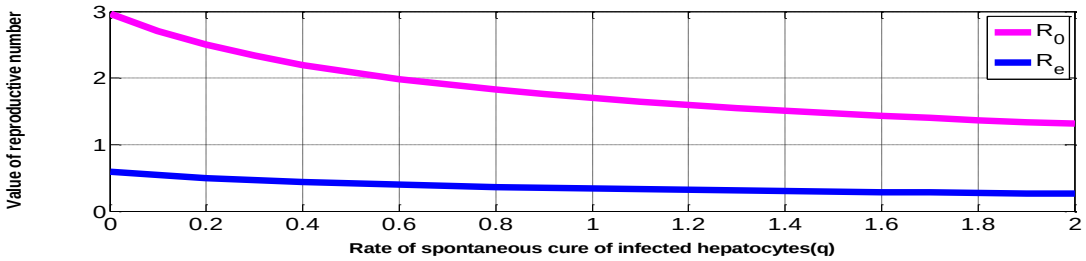

Figure 2: Relative values of reproduction numbers R_0 and R_e with respect to the rate of spontaneous recovery of infected hepatocytes (q).

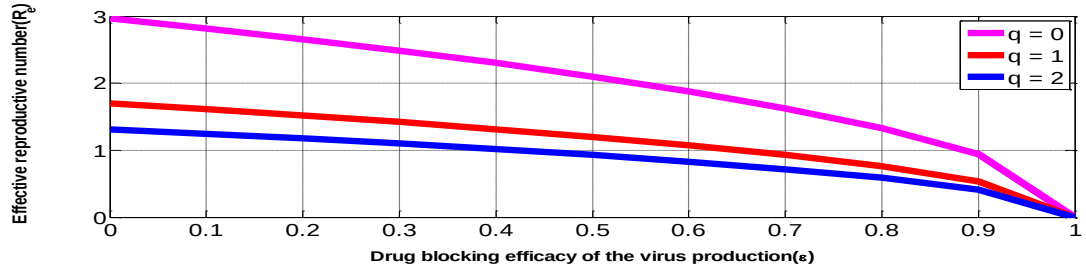

Figure 3: Value of R_e with respect to drug blocking efficacy of the virus production rate (ε), with variation in the rate of spontaneous cure of infected hepatocytes ($q = 0,1,2$)

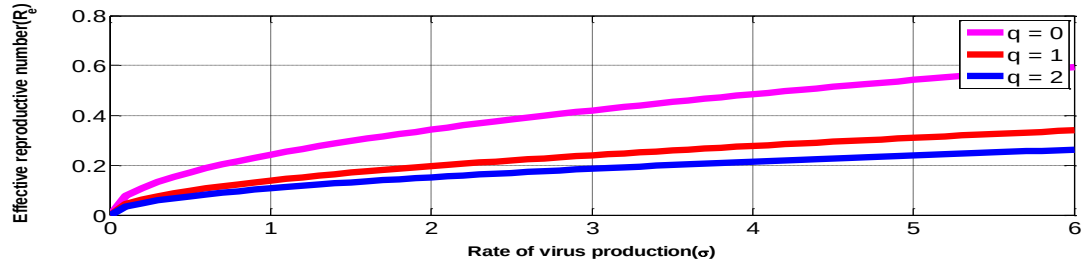

Figure 4: Value of R_e with respect to the rate of virus production rate (σ), with variation in the rate of spontaneous cure of infected hepatocytes ($q = 0,1,2$) at $\varepsilon = 0.96$

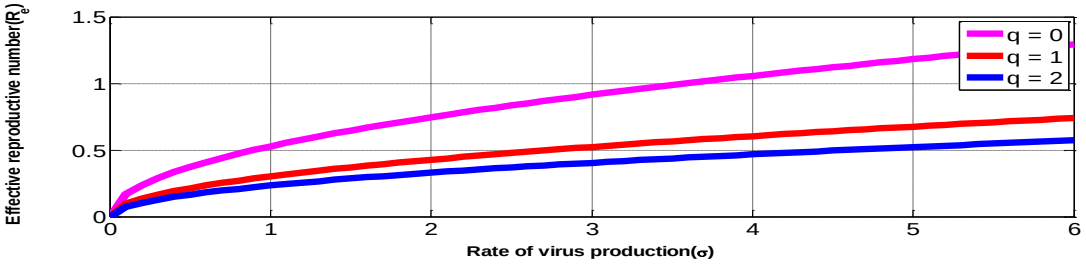

Figure 5: Value of R_e with respect to rate of virus production rate (σ), with variation in the rate of spontaneous cure of infected hepatocytes ($q = 0,1,2$) at $\varepsilon = 0.81$

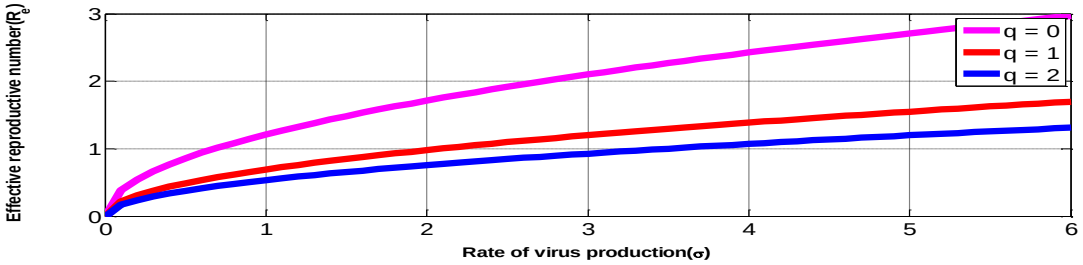

Figure 6: Value of R_e with respect to the rate of virus production rate (σ) , with variation in the rate of spontaneous cure of infected hepatocytes ($q = 0,1,2$) at $\varepsilon = 0$

Fig.4, Fig.5 and Fig.6 show that the value of R_e increases with the rate of virus production σ at $\varepsilon = 0.96$, $\varepsilon = 0.81$ and $\varepsilon = 0$ respectively, and it attains the lowest and greatest values at $q = 2$ and $q = 0$ respectively. It also reduces with increasing value of ε .This implies that patients with different rates of viral production and who do not spontaneously clear the virus can remove it by means of only therapy; this is optimal if the dug blocking efficacy is approximately 100% (e.g $\varepsilon = 96\%$). However patients with higher rates of viral production (e.g. $\sigma = 2$) cure later than those with lower rates (e.g. $\sigma = 1$).Conversely, patients who spontaneously clear the virus will do it faster with therapy. It will vanish in a short time if the drug is highly effective. Practically, therapy is necessary and so should be directed to only patients who do not spontaneously clear the virus.

6. Conclusion

In this paper, we have formulated a deterministic mathematical model on the dynamics of HCV and immune system with the effect of therapy in the acute phase of infection. We have shown that the numerical solution of the basic and effective reproductive number obtained validate that therapy has significant impact on the disease transmission, which implies that therapy reduces the number of secondary infections produced by an infectious hepatocyte during its infectious period, i.e. fewer hepatocytes are infected. From the sensitivity analysis, the parameter for the drug blocking efficacy is the most negatively sensitive parameter while the parameters for the rates of infections, virus production and recruitment of susceptible hepatocytes and mortality rate due to infection are the most positively sensitive ones. Thus, if the blocking drug efficacy of the virus production increases there is reduction of disease transmission, and eventually it dies out.

Literatures reveal that therapy of acute HCV infection is associated with challenges such as unclear criteria of identification of patients who require therapy (to exclude those who are able to spontaneously clear the virus), initiation of therapy and therapy regimens. Available drugs for therapy of chronic infection have severe side effects due to combination therapies. Nevertheless, therapy of people with acute HCV infection is necessary to prevent

evolution of the disease to chronicity, which is a fatal period of infection. Current models describing the dynamics of HCV with therapy do not consider drug types, variation of blocking efficacy with dosage and the virus genotype concurrently. For example, individuals with genotype 1 and 4 HCV infections do not respond to most antivirals while those infected with genotype 2 and 3 HCV respond quite well to these antivirals, and therefore the mathematical models are only descriptive of the dynamics of HCV with therapy for the second category of patients. Hence, more mathematical models are needed to address all these anomalies concurrently. However, our model assumes that the drug blocking efficacy of virus production increases with drug dosage administered to a patient who is a responder to the drug and can either clear the virus spontaneously or not.

Hence we recommend that more mathematical models should be formulated to describe viral dynamic profiles observed when new antiviral drugs are employed, test possible mechanisms for new biological or clinical phenomena and optimize therapy such as determining optimal drug dosages and therapy duration. The models should be used to give additional insight into the HCV pathogenesis and assist in the development of more effective therapeutic strategies. The virus genotype should be considered when modeling the HCV dynamics and immune system with therapy, as the current mathematical models assume that all patients are good responders to the available antivirals. Also, they should consider the dynamics of HCV in a patient with a graft organ such as kidney, liver or heart. Modeling the dynamics of HCV and immune system with drug therapy can be done to include co-infections such as HCV-HIV co-infection.

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