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An Intracellular Differential Equation Model For The Dynamics Of Hepatitis B Virus (Hbv) Infection With Immune Control

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ABSTRACT: We analyzed a non linear intracellul.ar ordinary differential equation model of the Hepatitis B Virus infection that considers the interaction between the hepatocyte, free virus and immune response. The non negative steady state of the model equation shows that the uninfected and the coexisting states were the only equilibrium points while the wholly infected state is not an equilibrium point. From further analysis of the stability, we observe that the steady state of the model is asymptotically stable If β which is Hepatitis B virus infection capability is weak, a_3 which is hepatitis B virus replication ability is also slow, CTL growth and production a_4 is rapid, strong and active and the CTL defense ability (b_1+b_2) is large enough to eliminate the virus from the blood and liver entirely.

Keywords: Mathematical model, HBV infection, Hepatocytes, Immune Response, Equilibrium.

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I. INTRODUCTION

Hepatitis B virus (HBV) infection can lead to cirrhosis and primary hepatocellular carcinoma (HCC) and is a major health problem worldwide. The natural history and outcome of HBV infection is different as more than 2 billion people alive today have been infected by HBV (Gourley et al, 2008). Despite the presence of hepatitis B vaccine, new HBV infections remain common. An individual can develop hepatitis B virus infection that is acute and achieve complete immune clearance of virus yielding lifelong immunity; however, an alternate fate of the host is the development of chronic hepatitis B. There are two phases of hepatitis B virus infection based on viral – host interaction, namely, the immune tolerant phase and the immune clearance (reactive) phase. After acute infection of HBV, some patients may remain HBeAg positive (a serological marker of viral replication) with high levels of serum HBV DNA (high viral replication rate), little or no symptoms, normal alanine aminotransferase (ALT) levels and minimal histological activity in the liver. This phenomenon is known as the immune tolerant phase and there is little or no inflammation or fibrosis of the liver (Pita et al, 2014).This phase is typical of infection in children and young adults. It usually lasts for 2 – 4 weeks, but can last for years in those that acquired the infection during the perinatal period (Merican et al, 2000; Pita et al, 2014). Individuals in this group are highly contagious and can transmit HBV easily. When the tolerogenic effect is lost during the immunetolerant phase, immune – mediated lysis (destruction of cells through the damage of cell contents) of infected hepatocytes become active and patients enter the second phase defined as immune clearance (reactive) phase. In this phase, the host immune system starts mounting a response against HBV, HBV DNA level decreases, ALT level increases and there is moderate to severe necro inflammatory activity in the liver (pita et al, 2014). The age of the patient at the time of infection determines whether the virus will be cleared and the infection cured during this phase. The immune clearance (reactive) phase ends with the loss of HBeAg and seroconversion to anti HBe status. The loss of HBeAg and seroconversion to anti HBe is usually associated with viral suppression by the host immune system (European association for the study of liver (EASL), 2012).

Hepatitis B virus (HBV) is a non cytopathic human hepadnavirus that causes acute and chronic hepatocullular carcinoma (Genem and Varmus, 1987). In order to find an efficient way to prevent and treat HBV infection, it is of great importance to understand the immune pathogenesis of HBV. Although molecular techniques have provided fundamental insight into the fine detail of the interaction between HBV and immune system, many biological important questions are not primarily concerned with the molecular mechanisms of immune recognition but with the population dynamics of the immune response. Mathematical models are always needed to answer these questions. Recent studies on HBV pathogenesis in animal models demonstrated

that the enhanced recruitment of virus specific CTLs into the liver cells is critical for the pathogenesis of both HBV infection and hepatocellular carcinoma (Ciupe et al, 2007; and Xuli et al, 2004). The need for treatment of hepatitis B depends on the natural history of the disease. Rates of progression to cirrhosis and hepatocellular carcinoma vary according to the state of the immune system, the age of the patient, the cerologic stage of the infection, and geographic and genetic factors (William, 2006). During HBV infection, infected individuals' Tim-3 expression is elevated on both adaptive and innate immune cells and this (Tim-3) increase inhibits the antiviral immune response, indicating that Tim-3 is a potential target for controlling HBV infection (Liu et al, 2016). A set of inhibitory surface receptor ligand pairs, or immune checkpoints regulate the activation of the innate and the adaptive immunocyte. The binding of T cell immunoglobulin domain and mucin domain -3 (Tim-3) and carcinoebryonic antigen cell adhesion molecule 1 (CEACAM1) appears to be necessary for the T cell inhibiting function of Tim-3 and this interaction has a crucial role in regulating antitumor immunity (Huang et al, 2015). The innate immune cells which are the monocytes/mocrophages, NKs and NK T cells (NKTs) constitutively express Tim-3 and this (Tim-3) is further elevated in some diseases including chronic HBV infection (Liu et al,2016). Interference of Tim-3 pathway changes the function of innate immune cells (Ju et al, 2010 and Yan et al, 2015).

II. RELATED WORKS

Since HBV is a noncytopathic virus (Ilan, 2002), that is cells infected by HBV will not be killed by virus directly, cellular function and life span of HBV – infected hepatocytes are almost the same as that of the uninfected cells in vitro (Kangxian, 2006). The death rate of noncytopathic virus infected cells in the absence of immunity equals that of uninfected target cells (Woderz, 2005). The lifespan of HBV infected cells varies greatly in vivo which is mainly due to the strength of the anti HBV CTL response (Nowak and Robert, 2000). CTL will not only kill but cure the infected hepatocytes by nonlytic effector mechanism (Bartoletti and Ferrari, 2003; and Guidotti, 2003). In a study by Yang et al (2009) it was observed that, induction of a $CD8^+$ T cell response depends on the presence of $CD4^+$ T cells. That each of these effectors, $CD4^+$ and $CD8^+$ T cells, Nk cells, fas, IFN – gamma (IFN - γ), IFN – alpha/beta receptor (IFN – α/β - R), and IFN receptor 1 (INF R1), was required to eliminate the transcriptional template from the liver. These results are consistent with a model in which $CD4^+$ T cells serve as master reguletors of the adaptive immune response to HBV; $CD8^+$ T cells are the key cellular effectors mediating HBV clearance from the liver, apparently by a fas – dependent perforin independent process in which NK cells, IFN – γ, INF R1 and IFN – α/β – R play supportive roles (Yang et al, 2009). Immediately after infection, innate immunity limits the spread of the pathogen and initiate efficient development of an adaptive immune response. Innate host responses during the early phase of viral infection are mainly characterized by the production of type 1 interferon (IFN) – α/β cytokines and the activation of natural killer (NK) cells. Production of type 1 IFNs can be triggered directly by virus replication through cellular mechanisms that detect the presence of viral RNA or DNA (Alexopoulou et al, 2001; Lund et al, 2003; Heil et al, 2004), while NK cells are activated by the recognition of stress – induced molecules and /or the modulation of the quantity of major histocompatibility complex (MHC) – class 1 molecules on the surface of infected cells (Moretta et al, 2005).

Hepatitis B virus causes liver disease that vary greatly in sensitivity from person to person (Gamen and Prince, 2004); some subjects control infection efficiently and clear the virus from the blood stream either without clinically evident liver disease or with an acute inflammation of the liver (acute hepatitis) that can resolve without long – term clinical sequelae. Other patients fail to clear the virus and develop chronic infection. Most chronically infected patients remain largely asymptomatic with possible progression to liver cancer (Alberti et al, 1999; Lok and Mcmahon, 2001). The rate of HBV chronicity is low in adult infections (5% or lower) but age and route of infection influences the outcome with exposure in neonatal life leading to a high rate of HBV persistence (Lok and Mcmahon, 2001; Gamen and Prince, 2004).

The works of Payne et al (1996) on the dynamics of hepatitis B virus infection, find that the severity of the initial phase of disease is determined by the immune response against the infected S cells, which also controls the asymptomatic/symptomatic character of persistent hepatitis whereas possible progression to persistent disease is determined by the immune response against the infected R cells. They further stated that, although the risk of oncogenesis is proportional to the number of infected R cells, we find that both cell types play a role in determining the expected duration of latency before the onset of primary hepatocellular carcinoma (PHC). The model explains the observed age dependence of the various manifestations of infections. Nowak et al,(1996) designed a simple natural mathematical model using ordinary differential equation for the viral dynamics in hepatitis B virus infection due to factors common to hepatitis B virus existence in the hepatocytes of infected individual. This does not include the importance of immune response initiated by the CTL response to viral antigen for viral clearance. Neglecting this action is an over simplification and thus this fact is included in the study of a dynamic model for the hepatitis B virus infection (Long, et al, 2008), which suggests that the clinical outcome of HBV infection is determined by host – virus interactions, especially the quality and vigor of

the antiviral immune response produced by the infected host. However, with these assumptions, the model is able to account for the difference outcomes of HBV infections.

As mathematical models have become important tool in analyzing the spread and control of infectious diseases, Okamoto (2013), used it to predict the risk of hepatitis B infection through needle/syringe sharing in mass vaccination. In his studies, it was observed that more than half of the HBV carriers in Japan born in the early 1950's might have contracted the disease by mass vaccination. Elaiw et al, (2013) presented an intracellular delay hepatitis B virus dynamic model that incorporated two types of drug therapies which are used to inhibit viral production and prevent new infections. In the current study, we provide a detailed analytical study of a mathematical model of the interaction between infective virus, hepatocytes and CTL.

III. THE MODEL EQUATIONS

The Assupmtions of the Intracellular Ordinary Differential Equation model are;

- That uninfected susceptible hepatocytes are infected after contact with the virus.
- Both the uninfected and infected hepatocytes proliferate at the same rate.
- Both the uninfected and infected hepatocytes die at the same natural rate.
- There is either cytocidal or noncytocidal immune response against infected hepatocytes.
- Some of the hepatocytes die due to the infection.
- There may be hepatic injury.

In an effort to model hepatitis B virus infection dynamics and immune response, we employed the following phenomenological model described in the flow diagram below;

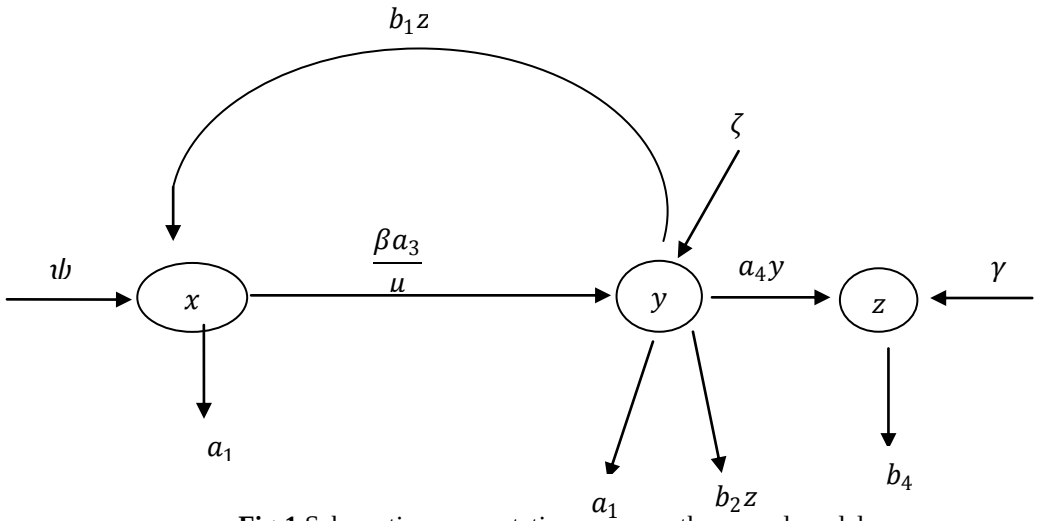

Fig:1 Schematic representation of the mathematical model.

In view of the assumptions and the flow diagram, we obtain the following system of non linear ordinary differential equations.

$$\begin{aligned}
\frac{dx}{dt} &= \psi - a_1 x - \frac{\beta a_3 xy}{\mu} + b_1 yz \\
\frac{dy}{dt} &= \zeta y + \frac{\beta a_3 xy}{\mu} - a_1 y - (b_1 + b_2) yz \qquad (3.1) \\
\frac{dz}{dt} &= \gamma + a_4 yz - b_4 z.
\end{aligned}$$

For quantitative analysis, our natural mathematical model based on ordinary differential equations contains three variables, that is, uninfected hepatocytes (x), infected hepatocytes (y), and CTL response (z). Uninfected, susceptible hepatocyte are assumed to be produced at a constant level, ψ, the natural death rate of both infected and uninfected hepatocytes are assumed to be the constant a_1. $\frac{\beta a_3 xy}{\mu}$ is assumed to be the level at which uninfected hepatocytes are being infected due to interaction with infected hepatocytes and ζy is the level at which infected hepatocyte proliferate. The elimination of virus is through the response of the cytotoxic T lymphocytes (CTL) which can be activated in two different pathways, either by killing the infected hepatocytes or by clearing the virus from within the hepatocyte without killing it. Infected hepatocytes are assumed to be

killed by the CTL response at a rate b_2yz and be cleared from within by the CTL response at a rate b_1yz. a_3y is the production level of free virus from infected hepatocytes and the free virus particles are removed at a rate μ.Two terms, γ and a_4yz were used to describe CTL rapid growth and reproduction of new cells (proliferation), where γ represents antigen independent proliferation (primary immune response) anda_4yz represents antigen dependent proliferation (secondary immune response). γ is small, and is the response to the first exposure to antigen which is mediated by lymphocytes, called naïve lymphocytes that are seeing antigen for the first time and they are "immunologically inexperienced". We also assume that CTL decay at constant rate b_4.

3.2: Equilibrium State Analysis

The possible steady states are:

❖Hepatocytes are not infected – the uninfected state,

❖All the hepatocytes are infected – wholly infected state, and

❖The coexisting state i.e, the infected and uninfected hepatocytes coexist.

By defining three non linear functions:

$$\begin{aligned} f_1(x,y,z) &= \psi - a_1x - \frac{\beta a_3xy}{\mu} + b_1yz \\ f_2(x,y,z) &= \zeta y + \frac{\beta a_3xy}{\mu} - a_1y - (b_1+b_2)yz \\ f_3(x,y,z) &= \gamma + a_4yz - b_4z. \end{aligned} \tag{3.2}$$

Equation (4.1) becomes

$$\begin{aligned} \frac{dx}{dt} &= f_1(x,y,z) \\ \frac{dy}{dt} &= f_2(x,y,z) \\ \frac{dZ}{dt} &= f_3(x,y,z). \end{aligned} \tag{3.3}$$

A point $(\hat{x},\hat{y},\hat{z})$ is called a steady state of the system (3.3) if it is a constant solution of the equations.

$$\begin{aligned} f_1(\hat{x},\hat{y},\hat{z}) &= 0 \\ f_2(\hat{x},\hat{y},\hat{z}) &= 0 \\ f_3(\hat{x},\hat{y},\hat{z}) &= 0. \end{aligned} \tag{3.4}$$

Proposition 1: The possible steady states are as follows

(i) $\left(\psi/a_1, 0, \gamma/b_4\right)$

(ii) $(0,\ \hat{y}_1,\ \hat{z}_1)$

(iii) $(\hat{x}_2,\ \hat{y}_2,\ \hat{z}_2)$.

Proof:

$$\begin{aligned} \psi - a_1x - \frac{\beta a_3xy}{\mu} + b_1yz &= 0 \\ \zeta y + \frac{\beta a_3xy}{\mu} - a_1y - (b_1+b_2)yz &= 0 \\ \gamma + a_4yz - b_4z &= 0 \end{aligned} \tag{3.5}$$

from $\gamma + a_4yz - b_4z = 0$, we have

$$\gamma = b_4z - a_4yz$$

$$\gamma = (b_4 - a_4y)z \qquad \therefore z = \frac{\gamma}{b_4 - a_4y}.$$

From $\zeta y + \frac{\beta a_3xy}{\mu} - a_1y - (b_1+b_2)yz = 0$, we obtain

$$\left(\zeta + \frac{\beta a_3x}{\mu} - a_1 - (b_1+b_2)z\right)y = 0$$

$$y = \frac{0}{\zeta + \frac{\beta a_3x}{\mu} - a_1 - (b_1+b_2)z} \qquad \therefore y = 0$$

$$\Longrightarrow z = \frac{\gamma}{b_4}.$$

From $\psi - a_1x - \frac{\beta a_3xy}{\mu} + b_1yz = 0$, we get

$$\psi - a_1x = 0 \Longrightarrow x = \frac{\psi}{a_1}.$$

We investigate the linear stability by considering small perturbations to the system in the vicinity of the steady state $(\hat{x},\hat{y},\hat{z})$ i.e, we consider a region close to the steady state and

let $x = \hat{x} + X, y = \hat{y} + Y, z = \hat{z} + Z.$

Expanding $f_1, f_2 and\ f_3$ in Taylor series expansions about $(\hat{x}, \hat{y}, \hat{z})$ then retaining only the linear terms, we obtain the following linear system. This implies that we differentiate equation (3.1) each with respect to $\hat{x}, \hat{y}, \hat{z}$ respectively to obtain the linear system below.

$$\frac{dX}{dt} = \left[-a_1 - \frac{\beta a_3 \hat{y}}{\mu}\right] X + \left[-\frac{\beta a_3 \hat{x}}{\mu} + b_1 \hat{z}\right] Y + [b_1 \hat{y}] Z$$
$$\frac{dY}{dt} = \left[\frac{\beta a_3 \hat{y}}{\mu}\right] X + \left[\zeta + \frac{\beta a_3 \hat{x}}{\mu} - a_1 - (b_1 + b_2)\hat{z}\right] Y - [(b_1 + b_2)\hat{y}] Z \qquad (3.6)$$
$$\frac{dZ}{dt} = [a_4 \hat{z}] Y + [a_4 \hat{y} - b_4] Z.$$

This can further be represented thus;

$$\begin{bmatrix} \frac{dX}{dt} \\ \frac{dY}{dt} \\ \frac{dZ}{dt} \end{bmatrix} = G \begin{bmatrix} X \\ Y \\ Z \end{bmatrix} \qquad (3.7)$$

where G denotes the Jacobian matrix of the model system evaluated at $(\hat{x}, \hat{y}, \hat{z})$.

Proposition 2: Suppose $a_1, a_3, b_1, b_2, b_4, \gamma, \zeta, \psi, \beta, \mu > 0$.

(i) The steady state $\left(\psi/_{a_1}, 0, \gamma/_{b_4}\right)$ of system (3.3) is asymptotically stable if $\zeta + \frac{\beta a_3 \psi}{a_1 \mu} < a_1 + \frac{(b_1 + b_2)\gamma}{b_1}$, and

(ii) Unstable if $\zeta + \frac{\beta a_3 \psi}{a_1 \mu} > a_1 + \frac{(b_1 + b_2)\gamma}{b_1}$.

Proof:

1. The uninfected state $\left(\boldsymbol{\psi/_{a_1}}, \mathbf{0}, \boldsymbol{\gamma/_{b_4}}\right)$.

This state satisfies $\frac{dX}{dt} = \frac{dY}{dt} = \frac{dZ}{dt} = 0$. Substituting $\hat{x} = \frac{\psi}{a_1}$, $\hat{y} = 0, \hat{z} = \frac{\gamma}{b_4}$ into equation (3.6) we obtain the lineariized equations as

$$\frac{dX}{dt} = -a_1 X + \left[-\frac{\beta a_3 \psi}{a_1 \mu} + \frac{b_1 \gamma}{b_4}\right] Y$$
$$\frac{dY}{dt} = \left[\zeta + \frac{\beta a_3 \psi}{a_1 \mu} - a_1 - (b_1 + b_2)\frac{\gamma}{b_4}\right] Y$$
$$\frac{dZ}{dt} = \left[\frac{a_4 \gamma}{b_4}\right] Y - b_4 Z.$$

$$G = \begin{bmatrix} -a_1 & -\frac{\beta a_3 \psi}{a_1 \mu} + \frac{b_1 \gamma}{b_4} & 0 \\ 0 & \zeta + \frac{\beta a_3 \psi}{a_1 \mu} - a_1 - (b_1 + b_2)\frac{\gamma}{b_4} & 0 \\ 0 & \frac{a_4 \gamma}{b_4} & -b_4 \end{bmatrix} \qquad (3.8)$$

Then, the characteristic equation is $|G - \lambda I| = 0$ which gives

$$\begin{vmatrix} -a_1 - \lambda & -\frac{\beta a_3 \psi}{a_1 \mu} + \frac{b_1 \gamma}{b_4} & 0 \\ 0 & \zeta + \frac{\beta a_3 \psi}{a_1 \mu} - a_1 - (b_1 + b_2)\frac{\gamma}{b_4} - \lambda & 0 \\ 0 & \frac{a_4 \gamma}{b_4} & -b_4 - \lambda \end{vmatrix} = 0. \qquad (3.9)$$

The characteristic equation of the matrix G is

$$U_0(\lambda) = \lambda^3 + (d_1 + k_1)\lambda^2 + (d_2 + k_2)\lambda + d_3 + k_3 = 0 \qquad (3.10)$$

Expanding (4.9) by finding the determinant we obtain

$$\Longrightarrow [-a_1 - \lambda] \begin{vmatrix} \zeta + \frac{\beta a_3 \psi}{a_1 \mu} - a_1 - (b_1 + b_2)\frac{\gamma}{b_4} - \lambda & 0 \\ \frac{a_4 \gamma}{b_4} & -b_4 - \lambda \end{vmatrix}$$

$$-\left[-\frac{\beta a_3\psi}{a_1\mu}+\frac{b_1\gamma}{b_4}\right]\begin{vmatrix}0 & 0\\ 0 & -b_4-\lambda\end{vmatrix}+[0]\begin{vmatrix}0 & \zeta+\frac{\beta a_3\psi}{a_1\mu}-a_1-(b_1+b_2)\frac{\gamma}{b_4}-\lambda\\ 0 & \frac{a_4\gamma}{b_4}\end{vmatrix}=0$$

$$\Rightarrow[-a_1-\lambda]\left[\left(\zeta+\frac{\beta a_3\psi}{a_1\mu}-a_1-(b_1+b_2)\frac{\gamma}{b_4}-\lambda\right)(-b_4-\lambda)\right]=0$$

$$\Rightarrow(\lambda+a_1)(\lambda+b_4)\left(\lambda-\left(\zeta+\frac{\beta a_3\psi}{a_1\mu}-a_1-(b_1+b_2)\frac{\gamma}{b_4}\right)\right)=0 \qquad (3.11)$$

$$\lambda_1=-a_1,\qquad \lambda_2=-b_4,\qquad \lambda_3=+\zeta+\frac{\beta a_3\psi}{a_1\mu}-a_1-(b_1+b_2)\frac{\gamma}{b_4}.$$

Since $a_1>0, b_4>0, if\ \zeta+\frac{\beta a_3\psi}{a_1\mu}<a_1+\frac{(b_1+b_2)\gamma}{b_4}, \lambda_{1,2,3}<0\ and\ x,y,z\to 0$. There will always be stability with respect to perturbations in x,y,z. The left hand side of the equation represents the ability of HBV, ζ represents the multiplication ability of infected hepatocytes, a_1 represents the death rate of both infected and uninfected hepatocytes, a_3 represents the production ability of HBV from infected hepatocytes, β represents the infective ability of HBV and μ represents the death rate of HBV while ψ represents the production ability of uninfected susceptible hepatocytes. The right hand side of the equation represents the ability of the immune system, b_1 represents the ability of CTL to destroy the HBV without destroying the infected hepatocyte (nonlytic ability) and b_2 represents the ability of CTL to destroy both the virus and the infected hepatocyte (lytic ability). Also $\frac{\gamma}{b_4}$ is the initial value of CTLs, while a_1 represents the death rate of both infected and uninfected hepatocytes.If the right hand side of $\zeta+\frac{\beta a_3\psi}{a_1\mu}<a_1+\frac{(b_1+b_2)\gamma}{b_4}$ is larger than the left side, it means that the immune system is strong enough to eliminate the infection.

For the case of $\zeta+\frac{\beta a_3\psi}{a_1\mu}>a_1+\frac{(b_1+b_2)\gamma}{b_4}$, there will always be instability with respect to perturbation in x,y,z. That is to say that, HBV can invade the body and exist for a long time.

2. All hepatocytes are infected $(\mathbf{0},\ \hat{\boldsymbol{y}}_1,\ \hat{\boldsymbol{z}}_1)$.

In this case, if we substitute this into equation (4.2), we observe that $\frac{dX}{dt}=\psi+b_1\hat{y}_1\hat{z}_1$, as $\psi,b_1,y,z>0,\frac{dX}{dt}>0,(0,\ \hat{y}_1,\ \hat{z}_1)$ cannot be an equilibrium point because the rate of production of susceptible uninfected hepatocyte, (ψ) and the rate at which the infected hepatocyte is being repaired by the CTL,(b_1yz) without damage are all greater than zero.

3. Uninfected and infected hepatocytes coexisting steady state $(\hat{\boldsymbol{x}}_2,\ \hat{\boldsymbol{y}}_2,\ \hat{\boldsymbol{z}}_2)$.

From$\frac{dX}{dt}=\frac{dY}{dt}=\frac{dZ}{dt}=0$, we can get

$$\begin{aligned}\psi-a_1\hat{x}_2-\frac{\beta a_3\hat{x}_2\hat{y}_2}{\mu}+b_1\hat{y}_2\hat{z}_2&=0\\ \zeta y+\frac{\beta a_3\hat{x}_2\hat{y}_2}{\mu}-a_1\hat{y}_2-(b_1+b_2)\hat{y}_2\hat{z}_2&=0\\ \gamma+a_4\hat{y}_2\hat{z}_2-b_4\hat{z}_2&=0.\end{aligned} \qquad (3.12)$$

From which we obtain,

$$\begin{aligned}\hat{x}_2&=\frac{\psi\mu+b_1\mu\hat{y}_2\hat{z}_2}{a_1\mu+\beta a_3\hat{y}_2}\\ \hat{y}_2&=\frac{b_4\hat{z}_2-\gamma}{a_4\hat{z}_2}\\ \hat{z}_2&=\frac{\zeta\mu+\beta a_3\hat{x}_2-a_1\mu}{(b_1+b_2)\mu}\end{aligned} \qquad (3.13)$$

Substituting equation (3.13) into (3.6) gives the linearized equations

$$\begin{aligned}\frac{dX}{dt}&=\left[-a_1-\frac{\beta a_3\hat{y}_2}{\mu}\right]X+\left[-\frac{\beta a_3\hat{x}_2}{\mu}+b_1\hat{z}_2\right]Y+[b_1\hat{y}_2]Z\\ \frac{dY}{dt}&=\left[\frac{\beta a_3\hat{y}_2}{\mu}\right]X+\left[\zeta+\frac{\beta a_3\hat{x}_2}{\mu}-a_1-(b_1+b_2)\hat{z}_2\right]Y-[(b_1+b_2)\hat{y}_2]Z\\ \frac{dZ}{dt}&=[a_4\hat{z}_2]Y+[a_4\hat{y}_2-b_4]Z.\end{aligned} \qquad (3.14)$$

From (3.14) we obtain that the characteristic determinant is

$$|G_2 - \lambda I| = \begin{vmatrix} -a_1 - \frac{\beta a_3 \hat{y}_2}{\mu} - \lambda & -\frac{\beta a_3 \hat{x}_2}{\mu} + b_1 \hat{z}_2 & b_1 \hat{y}_2 \\ \frac{\beta a_3 \hat{y}_2}{\mu} & \zeta + \frac{\beta a_3 \hat{x}_2}{\mu} - a_1 - (b_1 + b_2)\hat{z}_2 - \lambda & -(b_1 + b_2)\hat{y}_2 \\ 0 & a_4 \hat{z}_2 & a_4 \hat{y} - b_4 - \lambda \end{vmatrix}.$$

The characteristic equation of matrix G_2 is given by$|G - \lambda I| = 0$ which gives us:

$$\begin{vmatrix} -a_1 - \frac{\beta a_3 \hat{y}_2}{\mu} - \lambda & -\frac{\beta a_3 \hat{x}_2}{\mu} + b_1 \hat{z}_2 & b_1 \hat{y}_2 \\ \frac{\beta a_3 \hat{y}_2}{\mu} & \zeta + \frac{\beta a_3 \hat{x}_2}{\mu} - a_1 - (b_1 + b_2)\hat{z}_2 - \lambda & -(b_1 + b_2)\hat{y}_2 \\ 0 & a_4 \hat{z}_2 & a_4 \hat{y} - b_4 - \lambda \end{vmatrix} = 0$$

and it can be represented thus,

$$U_1(\lambda) = \lambda^3 + (d_1 + k_1)\lambda^2 + (d_2 + k_2)\lambda + d_3 + k_3 = 0. \tag{3.15}$$

The expansion of the characteristic equation of matrix G_2 as in Appendix B yields

$$\begin{aligned} d_1 &= \zeta + b_4 + b_2 \hat{z}_2 + \frac{b_1 \hat{z}_2}{\mu} + 2a_1 + \frac{\beta a_3 \hat{y}_2}{\mu} \\ k_1 &= -a_4 \hat{y}_2 - \frac{\beta a_3 \hat{x}_2}{\mu} \\ d_2 &= 2b_2 b_4 \hat{z}_2 + b_1 b_4 \hat{z}_2 + 2a_1 b_4 + b_1 b_2 \hat{z}_2 + a_1 b_1 \hat{z}_2 + a_1^2 + a_1 b_1 \hat{y}_2 \hat{z}_2 + \zeta a_1 + \zeta b_4 \\ &\quad + \frac{\zeta \beta a_3 \hat{y}_2}{\mu} + \frac{\beta a_3 a_4 \hat{x}_2 \hat{y}_2}{\mu} + \frac{\beta a_3 b_4 \hat{y}_2}{\mu} + \frac{\beta a_3 b_2 \hat{y}_2 \hat{z}_2}{\mu} + \frac{\beta a_3 b_1 \hat{y}_2 \hat{z}_2}{\mu} + \frac{\beta a_1 a_3 \hat{y}_2}{\mu} \\ k_2 &= -a_4 b_1 \hat{y}_2 \hat{z}_2 - 2a_1 a_4 \hat{y}_2 - \zeta a_4 \hat{y}_2 - \beta a_3 b_1 \hat{y}_2 \hat{z}_2 \\ &\quad - \frac{\beta a_3 b_4 \hat{x}_2}{\mu} - \frac{\beta a_3 a_4 \hat{y}_2^2}{\mu} - \frac{\beta^2 a_3^2 \hat{x}_2 \hat{y}_2}{\mu^2} - \frac{\beta a_1 a_3 \hat{x}_2}{\mu} \\ d_3 &= a_1^2 b_4 + a_1 b_1 b_4 \hat{z}_2 + a_1 b_2 b_4 \hat{z}_2 + \beta \mu a_3 a_4 b_1 \hat{y}_2^2 \hat{z}_2 + \zeta a_1 b_4 + \frac{\zeta \beta a_3 b_4 \hat{y}_2}{\mu} \\ &\quad + \frac{\beta a_1 a_3 a_4 \hat{x}_2 \hat{y}_2}{\mu} + \frac{\beta^2 a_3^2 a_4 \hat{x}_2 \hat{y}_2^2}{\mu^2} + \frac{\beta a_1 a_3 b_4 \hat{y}_2}{\mu} + \frac{\beta a_3 b_1 b_4 \hat{y}_2 \hat{z}_2}{\mu} + \frac{\beta a_3 b_2 b_4 \hat{y}_2 \hat{z}_2}{\mu} \\ &\quad + \frac{\beta^2 a_3^2 b_4 \hat{x}_2 \hat{y}_2}{\mu} \\ k_3 &= -a_1^2 a_4 \hat{y}_2 - \beta a_3 b_1 b_4 \hat{y}_2 \hat{z}_2 - \zeta a_1 a_4 \hat{y}_2 - \frac{\zeta \beta a_3 a_4 \hat{y}_2^2}{\mu} - \frac{\beta a_1 a_3 b_4 \hat{x}_2}{\mu} \\ &\quad - \frac{\beta^2 a_3^2 b_4 \hat{x}_2 \hat{y}_2}{\mu^2} - \frac{\beta a_1 a_3 a_4 \hat{y}_2^2}{\mu} - \frac{\beta a_3 a_4 b_1 \hat{y}_2^2 \hat{z}_2}{\mu} - \frac{\beta^2 a_3 a_4 \hat{x}_2 \hat{y}_2}{\mu}. \end{aligned} \tag{3.16}$$

By the Routh-Hurwitz criterion, Lina (2005) it follows that all roots of the characteristic equation (3.15) have negative real part if and only if

$$\begin{aligned} &d_1 + k_1 > 0 \Rightarrow d_1 > -k_1, \qquad d_3 + k_3 > 0 \Rightarrow d_3 > -k_3, \\ &(d_1 + k_1)(d_2 + k_2) - (d_3 + k_3) > 0 \implies (d_1 + k_1)(d_2 + k_2) > (d_3 + k_3). \end{aligned} \tag{3.17}$$

Therefore, from (3.16) we have that all roots of (3.15) will have negative real part if and only if

$$b_4 + b_2 \hat{z}_2 + \frac{b_1 \hat{z}_2}{\mu} + 2a_1 + \frac{\beta a_3 \hat{y}_2}{\mu} > a_4 \hat{y}_2 + \frac{\beta a_3 \hat{x}_2}{\mu},$$

$$\begin{bmatrix} a_1^2 b_4 + a_1 b_1 b_4 \hat{z}_2 + a_1 b_2 b_4 \hat{z}_2 + \beta \mu a_3 a_4 b_1 \hat{y}_2^2 \hat{z}_2 \\ + \frac{\beta a_1 a_3 a_4 \hat{x}_2 \hat{y}_2}{\mu} + \frac{\beta^2 a_3^2 a_4 \hat{x}_2 \hat{y}_2^2}{\mu^2} + \frac{\beta a_1 a_3 b_4 \hat{y}_2}{\mu} \\ + \frac{\beta a_3 b_1 b_4 \hat{y}_2 \hat{z}_2}{\mu} + \frac{\beta a_3 b_2 b_4 \hat{y}_2 \hat{z}_2}{\mu} + \frac{\beta^2 a_3^2 b_4 \hat{x}_2 \hat{y}_2}{\mu} \end{bmatrix} > \begin{bmatrix} a_1^2 a_4 \hat{y}_2 + \beta a_3 b_1 b_4 \hat{y}_2 \hat{z}_2 + \frac{\beta a_1 a_3 b_4 \hat{x}_2}{\mu} \\ + \frac{\beta^2 a_3^2 b_4 \hat{x}_2 \hat{y}_2}{\mu^2} + \frac{\beta a_1 a_3 a_4 \hat{y}_2^2}{\mu} \\ + \frac{\beta a_3 a_4 b_1 \hat{y}_2^2 \hat{z}_2}{\mu} + \frac{\beta^2 a_3 a_4 \hat{x}_2 \hat{y}_2}{\mu} \end{bmatrix}$$

and

$$\begin{bmatrix} b_4 + b_2\hat{z}_2 + \frac{b_1\hat{z}_2}{\mu} + 2a_1 + \frac{\beta a_3\hat{y}_2}{\mu} \\ -a_4\hat{y}_2 - \frac{\beta a_3\hat{x}_2}{\mu} \end{bmatrix} \begin{bmatrix} 2b_2b_4\hat{z}_2 + b_1b_4\hat{z}_2 + 2a_1b_4 + b_1b_2\hat{z}_2 + a_1b_1\hat{z}_2 \\ +a_1^2 + a_1b_1\hat{y}_2\hat{z}_2 + \frac{\beta a_3a_4\hat{x}_2\hat{y}_2}{\mu} + \frac{\beta a_3b_4\hat{y}_2}{\mu} \\ + \frac{\beta a_3b_2\hat{y}_2\hat{z}_2}{\mu} + \frac{\beta a_3b_1\hat{y}_2\hat{z}_2}{\mu} + \frac{\beta a_1a_3\hat{y}_2}{\mu} \\ -a_4b_1\hat{y}_2\hat{z}_2 - 2a_1a_4\hat{y}_2 - \beta a_3b_1\hat{y}_2\hat{z}_2 - \frac{\beta a_3b_4\hat{x}_2}{\mu} \\ -\frac{\beta a_3a_4\hat{y}_2^2}{\mu} - \frac{\beta^2a_3^2\hat{x}_2\hat{y}_2}{\mu^2} - \frac{\beta a_1a_3\hat{x}_2}{\mu} \end{bmatrix}$$

$$> \begin{bmatrix} a_1^2b_4 + a_1b_1b_4\hat{z}_2 + a_1b_2b_4\hat{z}_2 + \beta\mu a_3a_4b_1\hat{y}_2^2\hat{z}_2 \\ + \frac{\beta a_1a_3a_4\hat{x}_2\hat{y}_2}{\mu} + \frac{\beta^2a_3^2a_4\hat{x}_2\hat{y}_2^2}{\mu^2} + \frac{\beta a_1a_3b_4\hat{y}_2}{\mu} + \frac{\beta a_3b_1b_4\hat{y}_2\hat{z}_2}{\mu} \\ + \frac{\beta a_3b_2b_4\hat{y}_2\hat{z}_2}{\mu} + \frac{\beta^2a_3^2b_4\hat{x}_2\hat{y}_2}{\mu} - a_1^2a_4\hat{y}_2 - \beta a_3b_1b_4\hat{y}_2\hat{z}_2 \\ -\frac{\beta a_1a_3b_4\hat{x}_2}{\mu} - \frac{\beta^2a_3^2b_4\hat{x}_2\hat{y}_2}{\mu^2} - \frac{\beta a_1a_3a_4\hat{y}_2^2}{\mu} - \frac{\beta a_3a_4b_1\hat{y}_2^2\hat{z}_2}{\mu} - \frac{\beta^2a_3a_4\hat{x}_2\hat{y}_2}{\mu} \end{bmatrix}.$$

We observe that there will be stability with respect to perturbation in $(\hat{x}, \hat{y}, \hat{z})$. In this case, the HBV can invade the body and cause disease. Cuipe et al, (2007) showed that about 99% of the hepatocytes will be infected since viral production rate is going to be higher in cells infected with CCCDNA thereby causing active liver disease and cirrhosis. This will eventually lead to liver failure and hepatocellular carcinoma, but sometimes the patient will die of the severe liver dysfunction.

IV. ANALYSIS OF RESULT

to show the qualitative behavior of the three variable, uninfected hepatocytes, (x), infected hepatocyte, (y), CTL response, (z), when the production of the free virus is under control, we numerically solve system (3.1), that is;

using fifth oder Runge-Kutta-Fehlberg method with $a_1 = 0.002, \gamma = 3E-5, a_3 = 200, a_4 = 0.1, b_1 = 1E3, b_2 = 5E2, \psi = 1, b_4 = 0.2, \zeta = 0.04, \mu = 0.58, \beta = 1\ , x_0 = 1, y_0 = 0, z_0 = 1E-8.$

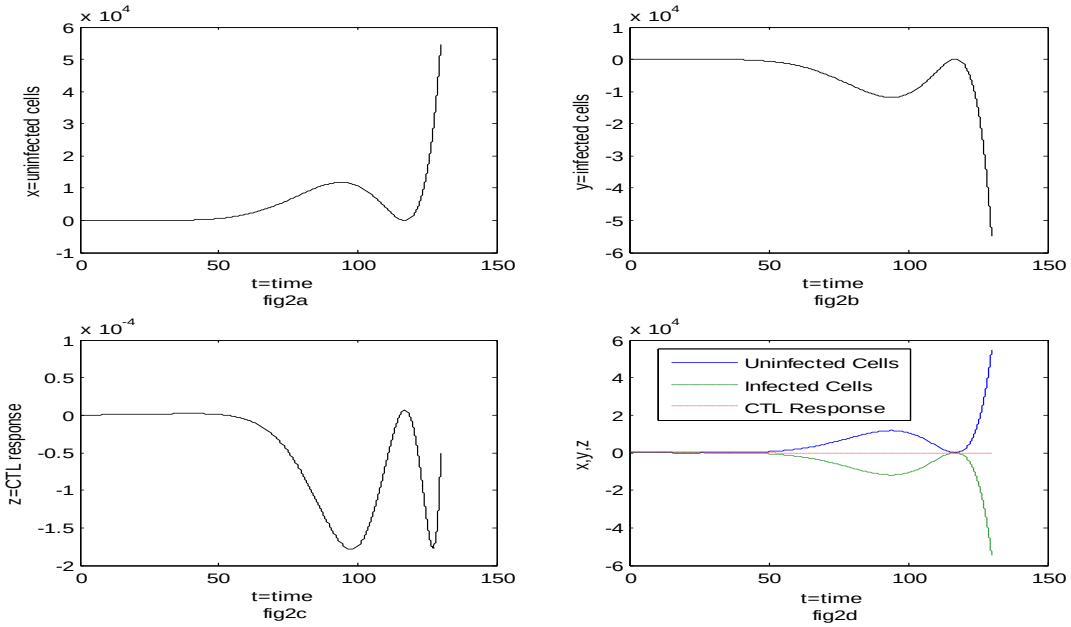

Figure (2a – 2d): Numerical simulation of the model system (3.1) where $a_1 = 0.002, \gamma = 3E-5, a_3 = 200, a_4 = 0.1, b_1 = 1E3, b_2 = 5E2, \psi = 1, b_4 = 0.2, \zeta = 0.04, \mu = 0.58, \beta = 1\ , x_0 = 1, y_0 = 0, z_0 = 1E-8$ $(Long\ et\ al, 2008)$, $with\ time\ ranging\ from\ 0\ to\ 130.$

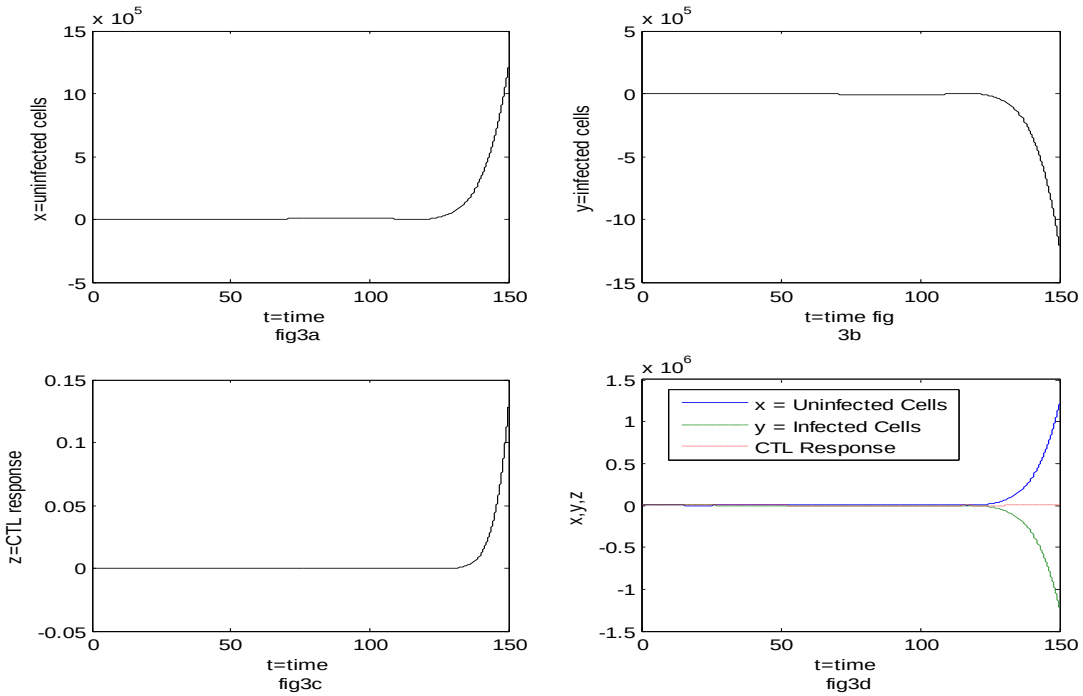

Figure (3a – 3d): Numerical simulation of the model system (3.1) where $a_1 = 0.002, \gamma = 3E-5, a_3 = 200,$ $a_4 = 0.1, b_1 = 1E3, b_2 = 1E2, \psi = 1, b_4 = 0.2, \zeta = 1, \mu = 0.58, \beta = 3E-5\,, x_0 = 1, y_0 = 0, z_0 = 1E-8,$ $with\ \ time\ ranging\ from\ 0\ to\ 150 days.\ (Acute\ Hepatitis)$

From figure (7a – 7c), we observed that the density of the three variables oscillate as time passes. This is because CTL response is clearing the virus from the infected liver cells where as the viral particles are resisting the clearance. In this case, the immunity is primarily mediated by humoral antibodies against HBsAg and antibodies to HBsAg are protective. These antibodies bind with the surface antigen of the virus and prevent it from interacting with the receptors on the hepatocytes and this neutralizes the infectivity of HBV. To overcome the infection, the immune system produces antibodies which attacks and eliminates the three viral antigens that make up hepatitis B virus. Certainly, if the infected individuals immune system is healthy (strong and active), it will employ enough antibodies to effectively fight each of the antigens thereby resolving the infection (naturally eliminate or clear the virus) before six months as predicted by the simulation and the individual will recover fully from acute hepatitis B. Also, the body's immune system attacks liver cells that are infected with the virus (HBV). This two-fold immune response eradicates the virus and the viral antigens from the body and blood stream and frees the liver of its infected cells either by curing or killing them. This is finally illustrated in figure (8a – 8c), that is to say that as CTL responses were able to overcome the viral resistance, the density of the uninfected hepatocytes started increasing and that of the infected hepatocytes decreases continually. This focuses on the density of the hepatitis B virus infected cells and CTL response near the initial point to show the interaction between virus and immune response. This was clearly demonstrated in figures 7d and 8d respectively and it verify the suggestion that the clinical outcome of HBV infection is determined by the host – virus interaction that is the potency and the active strength of the antiviral immune response by the infected host. The stronger the immune response, the greater the chances of clearing (eliminating) the virus from the liver and finally recover from the infection.

As the immune system is able to clear the virus within six months, after infection, it results in short term inflammation of the liver before the immune system is able to remove the virus from the body. This is known as acute hepatitis. Some patients with acute hepatitis successfully control the virus. This is because, the immune response produced by these patients is polyclonal,(immunoglobulin molecules that react against a specific antigen) and multi-specific and this enables them to eliminate the virus from the liver and blood entirely. After the removal of the virus from the liver and blood, if the maximum damage to the liver and maximum concentration of free virus are both low, the disease may come and go without any symptoms. But if otherwise, severe clinical symptoms will be observed (Long et al, 2008).

In summary, we have the qualitative analysis and simulation results suggested as;

If the cellular immune response satisfies $\zeta + \frac{\beta\psi a_3}{a_1\mu} < a_1 + \frac{(b_1+b_2)\gamma}{b_4}$, the immune system is strong enough to eliminate the infection. But if $\zeta + \frac{\beta\psi a_3}{a_1\mu} > a_1 + \frac{(b_1+b_2)\gamma}{b_4}$, chronic hepatitis appears because the immune system cannot clear the infection.

If β which is Hepatitis B virus infection capability (i.e, the level at which uninfected hepatocytes are being infected) is large (strong) and a_3 which is hepatitis B virus replication ability is also large (fast),then most of the hepatocytes in the liver will be infected and this will eventually result to massive liver necrosis due to the strong CTL response.

If β which is Hepatitis B virus infection capability (i.e, the level at which uninfected hepatocytes are being infected) is small (weak), a_3 which is hepatitis B virus replication ability is also small (slow), CTL growth and production a_4 is rapid, strong and active and the CTL defense ability $(b_1 + b_2)$ is large enough to eliminate the virus from the blood and liver entirely, then the outcome will be acute hepatitis. The disease may come and go unnoticed if the maximum damage and maximum concentration of the free virus are low. But if the maximum damage caused to the liver and maximum concentration of the free virus are both high, the disease will persist and the patient observes severe clinical symptoms.

If the CTL defense ability $(b_1 + b_2)$ against HBV is small (weak) and the growth and production of CTL a_4 is small (weak), then the infected hepatocytes cannot be cleared entirely. This will finally result to chronic hepatitis B virus infection with little or no clinical signs.

V. SUMMARY AND CONCLUSION

In summary, we have the qualitative analysis and simulation results suggested as;

If the cellular immune response satisfies $\zeta + \frac{\beta\psi a_3}{a_1\mu} < a_1 + \frac{(b_1+b_2)\gamma}{b_4}$, the immune system is strong enough to eliminate the infection. But if $\zeta + \frac{\beta\psi a_3}{a_1\mu} > a_1 + \frac{(b_1+b_2)\gamma}{b_4}$, chronic hepatitis appears because the immune system cannot clear the infection.

If β which is Hepatitis B virus infection capability (i.e, the level at which uninfected hepatocytes are being infected) is large (strong) and a_3 which is hepatitis B virus replication ability is also large (fast),then most of the hepatocytes in the liver will be infected and this will eventually result to massive liver necrosis due to the strong CTL response.

If β which is Hepatitis B virus infection capability (i.e, the level at which uninfected hepatocytes are being infected) is small (weak), a_3 which is hepatitis B virus replication ability is also small (slow), CTL growth and production a_4 is rapid, strong and active and the CTL defense ability $(b_1 + b_2)$ is large enough to eliminate the virus from the blood and liver entirely, then the outcome will be acute hepatitis. The disease may come and go unnoticed if the maximum damage and maximum concentration of the free virus are low. But if the maximum damage caused to the liver and maximum concentration of the free virus are both high, the disease will persist and the patient observes severe clinical symptoms.

If the CTL defense ability $(b_1 + b_2)$ against HBV is small (weak) and the growth and production of CTL a_4 is small (weak), then the infected hepatocytes cannot be cleared entirely. This will finally result to chronic hepatitis B virus infection with little or no clinical signs.

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