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Research article

A dynamic model of hepatitis B virus with drug-resistant treatment

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Abstract: In this paper, the problem of reducing the effectiveness of drug resistance treatment due to mutation of hepatitis B virus is investigated, a model of hepatitis B virus with drug resistance treatment is established, and the existence conditions of four equilibrium points in the model are provided. The effect of drug resistance caused by virus mutation on drug treatment is simulated. It is found that drug efficacy decreases with the increase in mutation rate. Without considering the value of mutation rate, the continuous usage of drugs can meet the clinical treatment standard, while stopping treatment will cause the virus to rebound.

Keywords: drug resistance; dynamics model of hepatitis B virus; equilibrium point; stability; numerical simulation
Mathematics Subject Classification: 34K20, 92B05, 92D25

1. Introduction

Viral hepatitis B is a kind of liver disease caused by a virus infection, which is called hepatitis B for short. According to the World Health Organization (WHO), about 350 million people in the world suffer from chronic hepatitis B and C, of which nearly 100 million are Chinese. Hepatitis B is one of the major infectious diseases under control in China.

At present, the first choice for hepatitis B treatment is nucleotide drugs. Clinical statistics show that drug resistance develops after long-term use [1]. Boglione and Lucio et al. analyzed the blood drug concentration and HBV DNA clinical data of 40 patients taking entecavir (ETV), and found that with the increase of blood drug concentration, the decline rate of HBV DNA slowed down, and the two showed a negative correlation, which provided a scientific basis for the rational selection of treatment regimen for viral infection [2]. In [3], by studying the mechanism of HBV mutation and the resistance of several nucleotide drugs, only when the mutation degree was high, the mutant strain

would greatly reduce the sensitivity to drugs, which provided a new idea for the study of the treatment scheme of drug-resistant viruses. Mao Richeng et al. collected the clinical data from lamivudine-resistant hepatitis B patients during entecavir monotherapy, and detected the proportion and dynamic changes of HBV DNA resistant strains. They found that entecavir resistance was obtained in long-term entecavir monotherapy and drug-resistant strains could disappear when the treatment with entecavir was continued. This research work provided a theoretical basis for the mechanism study of treatment of drug-resistant hepatitis B virus [4]. It is of practical significance to further analyze the influence of drug resistance on virus control by using the dynamics model of the hepatitis B virus to study the law of hepatitis B transmission. Bonhoeffer et al. established a dynamic model of the drug-resistant virus according to the mechanism of antiviral treatment of HIV or HBV, and studied the dynamic change of virus population. They found that drug resistance would change the treatment effect, and concluded that the treatment had a certain impact on the control of hepatitis B in a certain period of time [5]. Zhang et al. established an HBV model with anti-drug resistance under intermittent treatment by studying the dynamic characteristics of HBV under the conventional hepatitis B treatment scheme, analyzed the change rule of HBV, and proved the effectiveness of intermittent antiviral treatment [6]. Wang et al. considered the antiviral treatment with the combination of reverse transcriptase inhibitors and protease inhibitors, and established a virus dynamics model with the general form of target cell density, drug resistance and intracellular delay incorporating antiretroviral therapy. They proved the global asymptotic stability of the disease-free and drug-resistant steady states, and simulated the impact of target cells and delayed replication of cells on HIV control. Their results provided a theoretical basis for the use of combination antiretroviral therapy [7]. In this paper, the drug's effectiveness is reduced due to the development of drug resistance, and a dynamic model of hepatitis B virus with drug resistance and drug treatment is established. The existence and stability of the equilibrium point are discussed. Numerical simulation proves the rationality of the model. We analyze the effect of drug efficacy and drug resistance on the control of hepatitis B, and give suggestions on the treatment plan of hepatitis B in theory.

2. Dynamic model of hepatitis B virus with drug-resistant treatment

Clinically, different doses of drugs are used to treat HBV for hepatitis B patients. The experimental data are shown in Table 1.

Table 1. The dose of entecavir and mean $\log_{10}$ reduction in HBV DNA.

The dose of entecavir (mg)	0.05	0.1	0.5	1
Mean $\log_{10}$ reduction in HBV DNA(copies/ml)	2.21	2.29	2.81	2.55

We find that with the increase of drug doses, the number of HBV DNA in the body of hepatitis B patients does not decrease rapidly, indicating that the efficacy does not play a role in inhibiting HBV with the increase of drug doses [8]. The plasma concentrations in patients are inversely related to HBV DNA decrease. It can be considered that the rate of drug clearance of HBV is related to the average steady-state plasma concentration C_N of nucleoside drugs, which is recorded as $f(C_N)$ [2].

In [9], drug-resistant strains of hepatitis B patients with HBV DNA positive after lamivudine treatment were monitored. The statistical data are shown in Table 2, and the trend chart is shown in Figure 1.

Table 2. Mutation rate and duration of lamivudine treatment.

Treatment time （month）	The total number of cases	The number of cases where the mutation rate is less than 10%	The number of cases where the mutation rate is between 10% and 50%	The number of cases where the mutation rate is greater than 50%	The number of cases with viral mutations as a proportion of the total number of observed cases
<6	15	0	0	2 （Mutation rates are 80% and 100%, respectively）	0.13
6–12	42	4	12	7	0.55
12–24	56	3	8	24	0.63
>24	57	0	5	52（The mutation rates are all 100%）	1

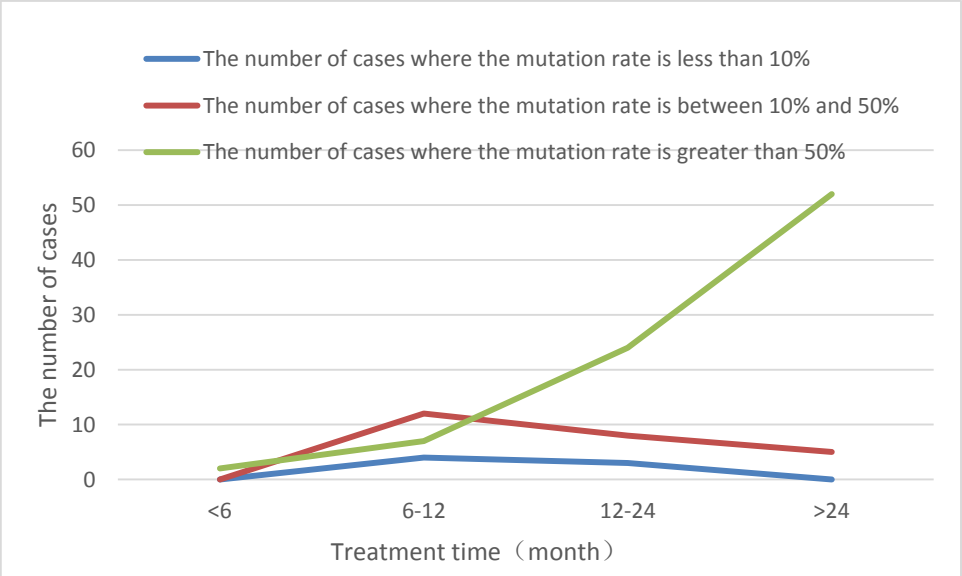


Figure 1. Relationship between mutation rate and treatment time of lamivudine.

The results in Table 2 and Figure 1 show that the mutation rate increases with the extension of the duration of drug treatment and reaches 100%. The mutation rate is considered as an increasing function of treatment time. Therefore, with the increase of treatment time, the mutation rate gradually increases from 0 to 1.

Patients who take nucleosides for a long time will produce mutant strains in the body. The mutant strains reduce the interaction space with the drug by changing their own molecular structure, so as to reduce the inhibition effect of the drug on them [3]. The results of the study indicate that the susceptibility to drugs will be greatly reduced when the drug-resistant mutations occur simultaneously in different locations of the HBV genome [3]. Moreover, drug-resistant mutations increase as a result of drug screening, which will lead to the decrease of drug inhibition. This means that the mutation rate increases and the inhibitory effect of the drug is weakened. Thus, the inhibition

rate of the drug to the resistant virus is related to the mutation rate u of the virus, which is recorded as $\beta(u)$. We can assume $\beta(u)=1-u$.

Anti-HBV drugs are targeted at the virus in the infected cells, and they play the antiviral effect in a single target to different degrees, but they have a high ability to screen drug-resistant virus [10]. These drug-resistant viruses are present in drug-resistant infected hepatocytes and rapidly replicate to produce new drug-resistant HBV. The number of drug-resistant HBV produced from infectious hepatocyte with drug-sensitive HBV due to the lack of proofreading activity of reverse transcriptase is relatively small and can be ignored. Therefore, it is believed that drug-sensitive HBV and drug-resistant HBV are produced from drug-sensitive infected hepatocytes and drug-resistant infected hepatocytes respectively.

According to the above analysis, the following dynamic model of HBV with drug resistance is established

$$\begin{cases} T'(t)=\lambda-K_sV_s(t)T(t)-K_rV_r(t)T(t)-\alpha T(t) \\ T_s'(t)=(1-u)K_sV_s(t)T(t)-\alpha T_s(t) \\ V_s'(t)=N_s\alpha T_s(t)-\delta V_s(t)-f(C_N)V_s \\ T_r'(t)=uK_sV_s(t)T(t)+K_rV_r(t)T(t)-\alpha T_r(t) \\ V_r'(t)=N_r\alpha T_r(t)-\delta V_r(t)-\beta(u)f(C_N)V_r \end{cases} \tag{1}$$

Here T, T_s, V_s, T_r and V_r respectively represent the number of uninfected hepatocytes at time t, the number of hepatocytes infected with drug-sensitive HBV, the number of drug-sensitive HBV, the number of hepatocytes infected with drug-resistant HBV, and the number of drug-resistant HBV; λ is the growth rate of uninfected hepatocytes; α and δ are the death rates of hepatocytes and viruses; K_s and K_r respectively denote the infection rate of drug-sensitive HBV and drug-resistant HBV on uninfected hepatocytes; N_s and N_r respectively denote the total number of viruses produced by drug-sensitive infected hepatocytes and drug-resistant infected hepatocytes during their life cycle; The mutation rate between drug-sensitive hepatocytes and drug-resistant hepatocytes is given by u; $f(C_N)$ is the rate at which drug therapy causes the decrease of HBV; C_N denotes denotes the average steady-state plasma concentration of nucleoside drugs in a patient; $\beta(u)$ denotes the inhibition rate of drug therapy on drug-resistant HBV; All parameters are positive. Suppose that $f(C_N)$ is a bounded function. The higher the mutation rate, the lower the inhibition rate of drug to the drug-resistant virus. Suppose $\beta(u)=1-u$.

Let $$N=T+T_s+\frac{1}{2N_s}V_s+T_r+\frac{1}{2N_r}V_r$$

Calculating the derivative of N, we get

$$N'\le\lambda-mN$$

where $m=\min\left\{\frac{\alpha}{2},\delta+\beta(u)f(C_N)\right\}$. Thus, for any $\varepsilon>0$, let $M=\frac{\lambda}{m}+\varepsilon$. The final feasible region of model (1) is

$$\Gamma=\left\{(T,T_s,V_s,T_r,V_r)\,|\,0\le T+T_s+\frac{1}{2N_s}V_s+T_r+\frac{1}{2N_r}V_r\le M\right\}$$

3. Existence of equilibrium point

The equilibrium point of model (1) satisfies the following system of equations

$$\begin{cases}\lambda-K_sV_sT-K_rV_rT-\alpha T=0\\(1-u)K_sV_sT-\alpha T_s=0\\N_s\alpha T_s-\delta V_s-f(C_N)V_s=0\\uK_sV_sT+K_rV_rT-\alpha T_r=0\\N_r\alpha T_r-\delta V_r-\beta f(C_N)V_r=0\end{cases}\tag{2}$$

From the first, the second and the fourth equations in formula (2), we get

$$T=\frac{\lambda}{\alpha}-T_s-T_r\tag{3}$$

From the third and the fifth equations in formula (2), we get

$$T_s=\frac{(\delta+f(C_N))V_s}{N_s\alpha},\quad T_r=\frac{(\delta+\beta f(C_N))V_r}{N_r\alpha}\tag{4}$$

Substituting the first equation in formula (4) into the second equation in formula (2), we get

$$V_s\left((1-u)K_sT-\frac{\delta+f(C_N)}{N_s}\right)=0\tag{5}$$

Let
$$R_s=\frac{\lambda N_sK_s(1-u)}{\alpha(\delta+f(C_N))},\quad R_r=\frac{\lambda N_rK_r}{\alpha(\delta+\beta f(C_N))}\tag{6}$$

The types of equilibrium points are as follows:

(1) When $V_s=V_r=0$, from formula (3) and formula (4), we get the disease-free equilibrium point $E_0=(T_0,0,0,0,0)$, where $T_0=\lambda/\alpha$.

(2) When $V_r=0$, from the first equation of formula (5) and formula (2), we get

$$T=\frac{\delta+f(C_N)}{K_sN_s(1-u)}=\frac{\lambda}{\alpha R_s},\quad T_s=\frac{(\delta+f(C_N))V_s}{N_s\alpha},\quad V_s=\frac{\frac{\lambda}{T}-\alpha}{K_s}=\frac{\alpha}{K_s}(R_s-1)\tag{7}$$

(3) When $V_s=0$, from the fourth equation in formula (3) and formula (2), we get

$$T=\frac{\delta+\beta f(C_N)}{K_rN_r},\quad T_r=\frac{(\delta+\beta f(C_N))V_r}{N_r\alpha},\quad V_r=\frac{\frac{\lambda}{T}-\alpha}{K_r}=\frac{\alpha}{K_r}(R_r-1)\tag{8}$$

(4) When $V_s\cdot V_r\neq 0$, from formula (4) and formula (5), we get

$$T=\frac{\delta+f(C_N)}{K_sN_s(1-u)}=\frac{\lambda}{\alpha R_s},\quad T_s=\frac{\lambda(1-u)(1-\frac{1}{R_s})(1-\frac{R_r}{R_s})}{\alpha(u+(1-u)(1-\frac{R_r}{R_s}))} \tag{9}$$

$$T_r==\frac{uT_s}{(1-u)(1-\frac{R_r}{R_s})},\quad V_s=\frac{N_s\alpha}{\delta+f(C_N)}T_s,\quad V_r=\frac{N_r\alpha}{\delta+\beta f(C_N)}T_r$$

According to the above analysis, we have established the following theorem:

Theorem 1. *(1) Model (1) has a disease-free equilibrium point* $E_0=(T_0,0,0,0,0)$.

(2) If $R_s>1$ *and* $R_r<1$, *there exists a drug-sensitive type virus equilibrium point* $E_s=(T_1,T_{s1},V_{s1},0,0)$ *in model (1), where* T_1,T_{s1},V_{s1} *satisfy Eq 7.*

(3) If $R_s<1$ *and* $R_r>1$, *there exists a drug-resistance type virus equilibrium point* $E_r=(T_2,0,0,T_{r2},V_{r2})$ *in model (1), where* T_2,T_{r2},V_{r2} *satisfy Eq 8.*

(4) If $R_s>R_r$ *and* $R_s>1$, *there exists a double virus equilibrium point* $E^*=(T^*,T_s^*,V_s^*,T_r^*,V_r^*)$ *in model (1), where* $T^*,T_s^*,V_s^*,T_r^*,V_r^*$ *satisfy Eq 9.*

Note: when $u=0$, E^* degenerates to the boundary equilibrium point E_s.

4. Stability analysis of equilibrium

Theorem 2. *If* $R_s<1-u$ *and* $R_r<1$, E_0 *is globally asymptotically stable; If* $R_s>1$ *and* $R_r>1$, E_0 *is unstable.*

Proof. Define the Lyapunov function

$$L_0=T_s+\frac{K_sT_0}{\delta+f(C_N)}V_s+T_r+\frac{K_rT_0}{\delta+\beta f(C_N)}V_r$$

Calculating the derivative of L_0, we get

$$\begin{aligned}L_0'&=((1-u)K_sV_sT-\alpha T_s)+\frac{K_sT_0}{\delta+f(C_N)}(N_s\alpha T_s-\delta V_s-f(C_N)V_s)+(uK_sV_sT\\&+K_rV_rT-\alpha T_r)+\frac{K_rT_0}{\delta+\beta f(C_N)}(N_r\alpha T_r-\delta V_r-\beta f(C_N)V_r)\\&\le K_sV_sT_0-\alpha T_s+\frac{K_sT_0N_s\alpha T_s}{\delta+f(C_N)}-K_sV_sT_0+K_rV_rT_0-\alpha T_r+\frac{K_rT_0N_r\alpha T_r}{C+\beta f(C_N)}-K_rV_rT_0\\&=(\frac{R_s}{1-u}-1)\alpha T_s+(R_r-1)\alpha T_r\end{aligned}$$

If $R_s<1-u$ and $R_r<1$, then $L_0'\le 0$. In particular, $L_0'=0$ only if $T_s=T_r=0$. According to the LaSalle's invariant principle [11], E_0 is the global asymptotic stable point of model (1).

The characteristic equation corresponding to model (1) is

$$f(\lambda)=(-\alpha-\lambda)(\lambda^2+a_1\lambda+a_2)(\overline{\lambda}+b_1\overline{\lambda}+b_2)$$

where

$$a_1=\alpha+\delta+\beta f(C_N),\ a_2=\alpha(\delta+\beta f(C_N))(1-R_r)$$

$$b_1=\alpha+\delta+f(C_N),\ b_2=\alpha(\delta+f(C_N))(1-R_s)$$

If $R_s>1$ or $R_r>1$, then $a_2<0$ or $b_2<0$. Hence, $f(\lambda)$ has positive eigenvalue and E_0 is unstable.

Theorem 3. *If $R_s>1$ and $R_r<1$, E_s is globally asymptotically stable.*

Proof. From the first equation of model (1), it is easy to obtain $T\le T_0$. If there is no drug resistance, then $u=0$. The comparison equations corresponding to the fourth and fifth equations of model (1) are

$$\begin{cases}T_r'=K_rV_rT_0-\alpha T_r\\ V_r'=N_r\alpha T_r-\delta V_r-\beta f(C_N)V_r\end{cases}\tag{10}$$

It can be obtained that $(0,0)$ is the equilibrium point of Eq 10, and its corresponding determinant and trace of the coefficient matrix are

$$|J|=\alpha(\delta+\beta f(C_N))(1-R_r),\quad trJ=-\alpha-\delta-\beta f(C_N)$$

When $R_r<1$, $|J|<0$ and $trJ<0$. Therefore, $(0,0)$ is the stable equilibrium point of model (10). The corresponding limit equation [12] of model (1) is

$$\begin{cases}T'=\lambda-\alpha T-K_sV_sT\\ T_s'=K_sV_sT-\alpha T_s\\ V_s'=N_s\alpha T_s-\delta V_s-f(C_N)V_s\end{cases}\tag{11}$$

Introducing a function $g(x)=x-1-\ln x\ge 0\ (x>0)$, $g(x)=0$ only if $x=1$.

Define the Lyapunov function

$$L_s=T_1g(\frac{T}{T_1})+T_{s1}g(\frac{T}{T_{s1}})+\frac{V_{s1}}{N_s}g(\frac{V_s}{V_{s1}})$$

Calculating the derivative of L_s, we get

$$\begin{aligned}L_s'=&\lambda-\alpha T-\lambda\cdot\frac{T_1}{T}+K_sV_sT_1+\alpha T_1-K_sV_sT\cdot\frac{T_{s1}}{T_s}+\alpha T_{s1}\\ &-\frac{\delta+f(C_N)}{N_s}V_s-\alpha T_s\cdot\frac{V_{s1}}{V_s}+\frac{\delta+f(C_N)}{N_s}V_{s1}\end{aligned}\tag{12}$$

According to Eq 7, when $u=0$,

$$\lambda=K_sV_{s1}T_1+\alpha T_1,\alpha T_{s1}=K_sV_{s1}T_1,N_s\alpha T_{s1}=(\delta+f(C_N))V_{s1}\tag{13}$$

Substituting Eq 13 into Eq 12, we get

$$L_s' = -\frac{\alpha(T-T_1)^2}{T} - K_s V_{s1} T_1 (\frac{T_1}{T} + \frac{V_{s1} T_s}{T_{s1} V_s} + \frac{V_s T T_{s1}}{T_1 V_{s1} T_s} - 3)$$
$$= -\frac{\alpha(T-T_1)^2}{T} - K_s V_{s1} T_1 (g(\frac{T_1}{T}) + g(\frac{V_s T_s}{T_{s1} V_s}) + g(\frac{V_s T T_{s1}}{T_1 V_{s1} T_s}))$$

Thus, $L_s' \le 0$. $L_s' = 0$ only if $\frac{T_1}{T} = \frac{V_s T_s}{T_{s1} V_s} = \frac{V_s T T_{s1}}{T_1 V_{s1} T_s} = 1$. According to the LaSalle's invariant principle, E_s is the global asymptotic stable point of model (1).

Theorem 4. *If* $R_s \le (1-u)R_r$ *and* $R_r > 1$, E_r *is globally asymptotically stable.*

Proof. Define the Lyapunov function

$$L_r = T_2 g(\frac{T}{T_2}) + T_s + \frac{K_s T_2}{\delta + f(C_N)} V_s + T_{r2} g(\frac{T_r}{T_{r2}}) + \frac{K_r T_2 V_{r2}}{C + \beta f(C_N)} g(\frac{V_r}{V_{r2}})$$

Calculating the derivative of L_r, we get

$$\begin{aligned} L_r' = {} & (1-\frac{T_2}{T})(\lambda - K_s V_s T - K_r V_r T - \alpha T) - ((1-u) K_s V_s T - \alpha T_s) \\ & + \frac{K_s T_2}{\delta + f(C_N)} (N_s \alpha T_s - \delta V_s - f(C_N) V_s) + (1-\frac{T_{r2}}{T_r})(u K_s V_s T + K_r V_r T - \alpha T) \\ & + \frac{K_r T_2}{\delta + \beta f(C_N)} (1-\frac{V_{r2}}{V_r})(N_r \alpha T_r - \delta V_r - \beta f(C_N) V_r) \end{aligned} \quad (14)$$

From formula (8), there are equations at E_r

$$\lambda = K_r V_{r2} T_2 + \alpha T_2, \quad \alpha T_{r2} = K_r V_{r2} T_2, \quad (\delta + \beta f(C_N)) V_{r2} = N_r \alpha T_{r2} \quad (15)$$

Substituting formula (15) into formula (14), we get

$$\begin{aligned} L_r' = {} & -\frac{\alpha(T-T_2)^2}{T} + (\frac{K_s N_s \alpha T_2}{\delta + f(C_N)} - \alpha) T_s + (\frac{K_r N_r \alpha T_2}{\delta + \beta f(C_N)} - \alpha) T_r - \frac{T_2}{T} K_r V_{r2} T_2 \\ & - \frac{T_{r2}}{T_r} K_r V_r T - \frac{K_r N_r \alpha T_r T_2}{\delta + \beta f(C_N)} \frac{V_{r2}}{V_r} + 3 K_r V_{r2} T_2 - u K_s V_s T \frac{T_{r2}}{T_r} \\ = {} & -\frac{\alpha(T-T_2)^2}{T} + (\frac{R_s}{(1-u)R_r} - 1) \alpha T_s - u K_s V_s T \frac{T_{r2}}{T_r} \\ & - K_r V_{r2} T_2 (g(\frac{T_2}{T}) + g(\frac{V_r T T_{r2}}{V_{r2} T_2 T_r}) + g(\frac{T_r V_{r2}}{T_{r2} V_r})) \end{aligned}$$

When $R_s < (1-u)R_r$, $L_r' \le 0$. $L_r' = 0$ only if $\frac{T_2}{T} = \frac{V_r T T_{r2}}{V_{r2} T_2 T_r} = \frac{T_r V_{r2}}{T_{r2} V_r} = 1$ and $T_s = V_s = 0$. According to the LaSalle's invariant principle, E_r is the global asymptotic stable point of the model (1).

Consider differential equation

$$x' = f(x) \tag{16}$$

where $f(x) \in R^n$ is a C^1 function and $D \subset R^n$ is a simply connected open set. Let $x(t, x_0)$ denote the solution of Eq 16 with the initial condition $x(0, x_0) = x_0$. We assume:

(H1) There exists a compact absorbing set $K \subset D$;

(H2) The system (16) has a unique equilibrium point $\bar{x}$ in D.

Lemma 1. [13] *Assume that (H1) and (H2) hold and there are a Lyapunov function $L(x)$, a bounded function $G(x)$, and positive constants a_1, g and a_2 such that*

(1) $a_1|x| \le L \le a_2|x|$,

(2) $L'(x) \le (G'(x) - g)L(x)$,

then the equilibrium point $\bar{x}$ of model (16) is globally asymptotically stable.

Theorem 5. *If $R_s > R_r > 1$, model (1) is uniformly persistent.*

Proof. When $R_s > R_r > 1$, there are only two equilibrium points E_0 and E^* in model (1). According to Theorem 2, E_0 is unstable. Only the track with an initial value on the T axis approach E_0 along the T axis, and the other tracks will move away from E_0. So $\{E_0\}$ is the largest compact invariant set on $\partial\Gamma$. There is a constant a, and the solutions of model (1) starting from the interior of Γ satisfy the following conditions

$$\lim_{t\to\infty} \sup \max\{T, T_s, V_s, T_r, V_r\} > a$$

Therefore, the solutions of model (1) will not run out of $\partial\Gamma$, This shows that $W^s(\{E_0\}) \cap \overset{\circ}{\Gamma} = \phi$, where $W^s(\{E_0\}) = \{(T, T_s, V_s, T_r, V_r) \in \Gamma, \omega(T, T_s, V_s, T_r, V_r) \subset \{E_0\}\}$.

Thus, when $R_s > R_r > 1$, model (1) is uniformly persistent [14].

Adding the first, the second, and the fourth equations in model (1), we get

$$T' + T_s' + T_r' = \lambda - \alpha(T + T_s + T_r)$$

From the limit theory, we get $T + T_s + T_r = \dfrac{\lambda}{\alpha}$ approximately. Reducing the dimension of model (1), we get

$$\begin{cases} T'(t) = \lambda - K_s V_s(t) T(t) - K_r V_r(t) T(t) - \alpha T(t) \\ T_s'(t) = (1-u) K_s V_s(t) T(t) - \alpha T_s(t) \\ V_s'(t) = N_s \alpha T_s(t) - \delta V_s(t) - f(C_N) V_s \\ V_r'(t) = N_r \alpha (\dfrac{\lambda}{\alpha} - T(t) - T_s(t)) - \delta V_r(t) - \beta f(C_N) V_r \end{cases} \tag{17}$$

Same as the method of formula (2), find the positive equilibrium point of model (17) as follows

$$T_e=\frac{\lambda}{\alpha R_s},\quad T_{se}=\frac{\lambda(1-u)(1-\frac{1}{R_s})(1-\frac{R_r}{R_s})}{\alpha\left(u+(1-u)(1-\frac{R_r}{R_s})\right)}$$
$$V_{se}=\frac{\alpha N_s}{\delta+f(C_N)}T_{se},\quad V_{re}=\frac{\alpha u(1-\frac{1}{R_s})}{R_rK_r\left(u+(1-u)(1-\frac{R_r}{R_s})\right)} \tag{18}$$

Model (17) has a positive equilibrium point $E_e=(T_e,T_{se},V_{se},V_{re})$, where T_e,T_{se},V_{se},V_{re} satisfy Eq 18.

At this time, we get

$$T_{re}=\frac{\lambda}{\alpha}-T_e-T_{se}=\frac{uT_{se}}{(1-u)(1-\frac{R_r}{R_s})} \tag{19}$$

By comparing formula (9), formula (18) and formula (19), we know that E^* and E_e are the same point. To prove that E^* is stable, we just have to prove that E_e is stable.

Theorem 6. *If* $R_s>R_r>1$, E_e *is globally asymptotically stable.*

Proof. Let $x=(T,T_s,V_s,V_r)$, the Jacobian matrix of model (17) is

$$J(x)=\begin{pmatrix}-K_sV_s-K_rV_r-\alpha & 0 & -K_sT & -K_rT\\ (1-u)K_sV_s & -\alpha & (1-u)K_sT & 0\\ 0 & \alpha N_s & -(\delta+f(C_N)) & 0\\ -\alpha N_r & -\alpha N_r & 0 & -(\delta+\beta f(C_N))\end{pmatrix}$$

According to the method in [13], the third additive compound matrix can be calculated as follows:

$$J^{[3]}(x)=\begin{pmatrix}A_{11} & 0 & 0 & -K_rT\\ 0 & A_{22} & (1-u)K_sT & K_sT\\ \alpha N_r & \alpha N_s & A_{33} & 0\\ -\alpha N_r & 0 & (1-u)K_sV_s & A_{44}\end{pmatrix}$$

where

$$A_{11}=-K_sV_s-K_rV_r-2\alpha-(\delta+f(C_N)),A_{22}=-K_sV_s-K_rV_r-2\alpha-(\delta+\beta f(C_N))$$
$$A_{33}=-K_sV_s-K_rV_r-\alpha-(\delta+f(C_N))-(\delta+\beta f(C_N))$$
$$A_{44}=-\alpha-(\delta+f(C_N))-(\delta+\beta f(C_N))$$

and the associated linear compound system is

$$\begin{cases} X' = A_{11}X - K_r TW \\ Y' = A_{22}Y + (1-u)K_s TZ + K_s TW \\ Z' = \alpha N_r X + \alpha N_s Y + A_{33}Z \\ W' = -\alpha N_r X + (1-u)K_s V_s Z + A_{44}W \end{cases} \tag{20}$$

Choose a Lyapunov function

$$V = \max(V_1, V_2, V_3, V_4)$$

where

$$V_1 = V_r|X|, V_2 = V_s|Y|, V_3 = T_s|Z|, V_4 = T|W|$$

It is known from Theorem 5 that model (17) is uniformly persistent. There exist two positive constants c_1 and c_2 such that

$$c_1(|X|+|Y|+|Z|+|W|) \le V \le c_2(|X|+|Y|+|Z|+|W|)$$

Next, we calculate the right derivative of V along the trajectory of the compound system (20). We will separate the discussion for the several cases below.

Case Ⅰ: $V = V_1$, then $V_2, V_3, V_4 \le V_1$ and

$$\begin{aligned} D_+V_1 &= V_r D_+|X| + V_r'|X| \\ &= V_r|X|(\frac{V_r'}{V_r} + A_{11} + \frac{K_r T|W|}{|X|}) \\ &= V_r|X|(\frac{V_r'}{V_r} - K_s V_s - K_r V_r - 2\alpha - (\delta + f(C_N)) + \frac{K_r T|W|}{|X|}) \\ &\le V_r|X|(\frac{V_r'}{V_r} - K_s V_s - 2\alpha - (\delta + f(C_N)) \\ &\le V_r|X|(\frac{V_r'}{V_r} - 2\alpha - (\delta + f(C_N)) \\ &\le V_r|X|(G_1' - g_1) \end{aligned} \tag{21}$$

where $G_1 = \ln V_r$, $g_1 = 2\alpha + C + f(C_N)$

Case Ⅱ: $V = V_2$, then $V_1, V_3, V_4 \le V_2$ and

$$\begin{aligned} D_+V_2 &= V_s'|Y| + V_s D_+|Y| \\ &= V_s'|Y| + V_s(A_{22}|Y| + (1-u)K_s T|Z| + K_s T|W|) \\ &= V_s|Y|(\frac{V_s'}{V_s} - K_r V_r - 2\alpha - (\delta + \beta f(C_N)) + \frac{(1-u)K_s T V_s}{T_s}) \\ &= V_s|Y|(\frac{V_s'}{V_s} + \frac{T_s'}{V_s} - K_r V_r - \alpha - (\delta + \beta f(C_N))) \\ &\le V_s|Y|(\frac{V_s'}{V_s} + \frac{T_s'}{V_s} - \alpha - (\delta + \beta f(C_N))) \\ &= V_s|Y|(G_2' - g_2) \end{aligned} \tag{22}$$

where $G_2 = \ln V_s + \ln T_s$, $g_2 = \alpha + \delta + \beta f(C_N)$

Case Ⅲ: $V = V_3$, then $V_1, V_2, V_4 \le V_3$ and

$$\begin{aligned} D_+V_3 &= T_s'|Z| + T_s D_+|Z| \\ &\le T_s|Z|(\frac{T_s'}{T_s} + \frac{\alpha N_r T_s}{V_r} + \frac{\alpha N_s T_s}{V_s} + A_{33}) \\ &\le T_s|Z|(\frac{T_s'}{T_s} + \frac{V_s'}{V_s} - \frac{V_r'}{V_r} + A_{33} + (\delta + f(C_N)) - (\delta + \beta f(C_N)) + \frac{\lambda N_r}{V_r}) \\ &= T_s|Z|(\frac{T_s'}{T_s} + \frac{V_s'}{V_s} - \frac{V_r'}{V_r} + f(T, T_s, V_s, V_r)) \end{aligned} \tag{23}$$

where

$$\begin{aligned} f(T, T_s, V_s, V_r) &= A_{33} + (\delta + f(C_N)) - (\delta + \beta f(C_N)) + \frac{\lambda N_r}{V_r} \\ &= -K_s V_s - K_r V_r - \alpha - 2(\delta + \beta f(C_N)) + \frac{\lambda N_r}{V_r} \end{aligned} \tag{24}$$

From Eq 17, we get

$$\frac{\alpha N_s T_s}{V_s} = \frac{V_s'}{V_s} + \delta + f(C_N), \quad \frac{\alpha N_r T_s}{V_r} \le -\frac{V_r'}{V_r} + \frac{\lambda N_r}{V_r} - (\delta + \beta f(C_N))$$

Because of model (1) is uniformly persistent, the proper lower bound is chosen so that the polynomial function $f(T, T_s, V_s, V_r)$ take negative values. In other words, there exists a positive constant m such that $f(T, T_s, V_s, V_r) \le -m$.

Substituting Eq 24 into Eq 23 yields

$$D_+V_3 \le V_3(G_3' - m) \tag{25}$$

where $G_3' = \ln T_s + \ln V_s - \ln V_r$.

Case Ⅳ: $V = V_4$, then $V_1, V_2, V_3 \le V_4$ and

$$\begin{aligned} D_+V_4 &= T'|W| + TD_+|W| \\ &\le T|W|(\frac{T'}{T} + A_{44} + \frac{\alpha N_r T}{V_r} + \frac{(1-u)K_s V_s T}{T_s}) \\ &\le T|W|(\frac{T'}{T} + A_{44} + \frac{T_s'}{T_s} + \alpha - \frac{V_r'}{V_r} + \frac{\lambda N_r}{V_r} - (\delta + \beta f(C_N))) \\ &= V_4(\frac{T'}{T} + \frac{T_s'}{T_s} - \frac{V_r'}{V_r} + f(T, T_s, V_s, V_r)) \end{aligned} \tag{26}$$

where

$$\begin{aligned} f(T, T_s, V_s, V_r) &= A_{44} + \alpha + \frac{\lambda N_r}{V_r} - (\delta + \beta f(C_N)) \\ &= -(\delta + f(C_N)) - 2(\delta + \beta f(C_N)) + \frac{\lambda N_r}{V_r} \end{aligned} \tag{27}$$

From Eq 17, we get

$$\frac{(1-u)K_sV_sT}{T_s}=\frac{T_s'}{T_s}+\alpha,\quad \frac{\alpha N_rT}{V_r}\le-\frac{V_r'}{V_r}+\frac{\lambda N_r}{V_r}-(\delta+\beta f(C_N))$$

In a way similar to Case Ⅲ, we can obtain the estimates $f(T,T_s,V_s,V_r)\le -m$.

Substituting Eq 27 into Eq 26 yields

$$D_+V_4\le V_4(G_4'-m) \tag{28}$$

where $G_4'=\ln T+\ln T_s-\ln V_r$.

From Eqs 21, 22, 25 and 28, we get

$$D_+V\le(G'-g)V$$

where $G=\max\{G_1,G_2,G_3,G_4\}$, $g=\min\{g_1,g_2,m\}$

From Lemma 1, the positive equilibrium point of model (1) is the global asymptotic stability point.

5. Numerical simulation

5.1. Numerical simulation of no drug resistance

5.1.1. Parameter selection

(1) Some fixed parameters in model (1) are derived from [15], as shown in Table 3:

Table 3. Values of some parameters.

symbol	instructions	Value	Value
λ	the growth rate of uninfected hepatocytes	2.527×10^{5}	$day^{-1}(ml)^{-1}$
α	the death rate of hepatocytes	0.012	day^{-1}
δ	the death rate of viruses	0.67	day^{-1}
K_s	the infection rate of sensitive HBV on uninfected hepatocytes	3.8×10^{-8}	$day^{-1}(ml)^{-1}$
K_r	the infection rate of drug-resistant HBV on uninfected hepatocytes	1.2×10^{-8}	$day^{-1}(ml)^{-1}$
N_s	the total number of viruses produced by sensitive infected hepatocytes during their life cycle	2	—
N_r	the total number of viruses produced by drug-resistant hepatocytes during their life cycle	2	—

(2) Estimate of $f(C_N)$

The parameter $f(C_N)$ is related to the efficacy of the selected therapeutic agent. In this paper, $f(C_N)$ is estimated based on the data from hepatitis B patients treated with entecavir (ETV). In [2], the steady-state blood concentration and HBV DNA level of 40 hepatitis B patients receiving ETV treatment of 0.5mg/day were given. By using the numerical approximation algorithm, we get

$$f(C_N) = \frac{C_N}{C_N - 0.4000} \tag{29}$$

5.1.2. Numerical simulation of HBV under drug therapy

In order to further verify the simulation effect of model (1), the data of actual clinical treatment cases are selected for comparative analysis. Zhou Hongping et al. reported the experimental monitoring data of 194 patients with chronic hepatitis B taking ETV 0.5mg/day for antiviral therapy, and provided the logarithm values of HBV DNA before and after treatment at 4, 12, 24, 48 and 72 weeks, respectively [16], as shown in Table 4. According to the method in [17], the average steady-state blood drug concentration of ETV per unit time can be calculated as $C_N = 0.42$ ng/ml. Assuming that there are no drug-resistant cells and viruses at the beginning and during the treatment, we know that $u = 0$, which implies that $\beta = 1$. Considering the limit Eq 11, we substitute the parameter values in Table 3 and Eq 29 into model (11) for numerical simulation. The initial value is selected as follows

$$T(0) = 1.675 \times 10^7, \quad T_s(0) = 2.79 \times 10^8, \quad V_s(0) = 10^7 \tag{30}$$

The obtained simulation data and simulation curves are shown in Table 4 and Figure 2:

Table 4. Logarithms of HBV DNA at 4, 12, 24, 48 and 72 weeks before and after treatment (log10 copies/ml).

HBV	Before treatment	4 weeks	12 weeks	24 weeks	48 weeks	72 weeks
Clinical data	6.99	4.71	4.25	3.96	3.84	3.39
Simulation data	7.00	5.05	4.76	4.34	3.59	2.64

Before treatment, the basic reproduction numbers can be calculated as $R_s = 2.389$ and $R_r = 0.754$. After treatment, the basic reproduction numbers are $R_s = 0.074$ and $R_r = 0.023$. Then we know from Theorem 2 that E_0 is the global asymptotic stable point, which means the number of viruses will continue to decline after 72 weeks of treatment. The virus will be eliminated if the treatment lasts longer, which is consistent with Figure 2.

Figure 2 shows that from the start of treatment to 4 weeks of treatment, the number of drug-sensitive HBV decreases rapidly and then slowly after the first week. Clinical data shows that the difference between the number of HBV DNA after 4 weeks of ETV treatment and that before treatment is 2.28log10 copies/ml. The difference of HBV DNA quantity between 12 weeks and 24 weeks is 0.29log10 copies/ml, and there is small change of HBV DNA quantity between 12 weeks and 24 weeks. It can be seen that the simulated curve is consistent with the change of the actual HBV

DNA quantity. According to the data in Table 4, it can be calculated that the standard error is 0.4368, so the simulated value is close to the actual value. The parameters of model (11) are selected reasonably and the simulation results are feasible.

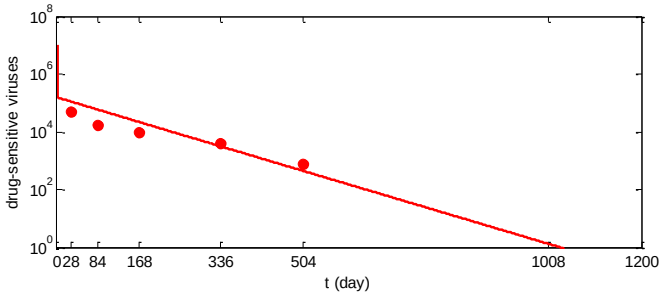


Figure 2. Simulations of 72 weeks of continuous treatment.
*Note: Solid line: the dynamic route of the model (11). Dots: the clinical data.

5.2. Numerical simulation of occurrence of drug resistance

The experiment in [3] shows that HBV mutations can change the effectiveness of HBV treatment. The effects of HBV mutation rate u on the time required for HBV to reach the expected standard after treatment and the possibility of HBV rebound after stopping treatment are analyzed by numerical simulation.

5.2.1. Effect of time required for HBV clearance to reach 1 copies/ml

Clinically, we call HBV DNA-negative when the number of HBV is lower than 10^3 copies/ml. At this time, HBV DNA cannot be detected by PCR, which means that HBV DNA is lower than the detection limit [18]. However, in practical treatment, when the monitoring of HBV DNA is below the lower detection limit, the drug is not stopped immediately for most of the cases. Instead, the liver function is further checked and the HBV DNA is continuously monitored multiple times to check whether it is still lower than the lower detection limit. Since it is takes a long time to completely eliminate HBV through treatment [19], the treatment is stopped when the number of viruses reaches 1 copies/ml, and the effects of different mutation rates on the course of virus clearance are compared through numerical simulation.

It is assumed that the patient has drug-resistant cells and viruses in the body before treatment, and the initial values are set as:

$$T(0)=1.9\times10^7,\quad T_s(0)=2.79\times10^8,\quad T_r(0)=2.79\times10^7$$

$$V_s(0)=10^7,\quad V_r(0)=10^6$$

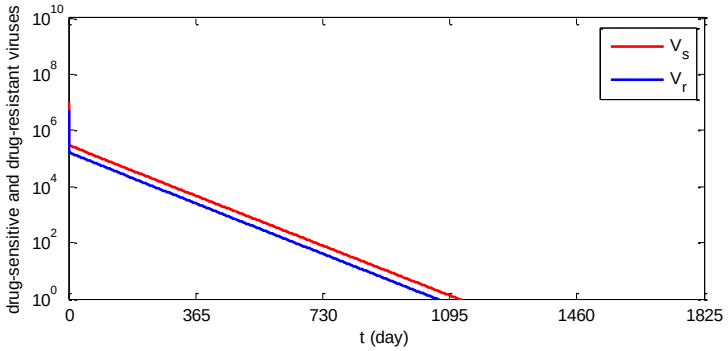
The parameters in model (1) are the same as those in Table 3. At this point, let $K_r=1.9\times10^{-8}$. When the values of u and β are different, R_s and R_r can be calculated according to formula (6), as shown in Table 5.

It can be seen from Table 5 that the basic reproduction number is less than 1 under drug treatment and it is not affected by the value of mutation rate. From Theorem 2, the solutions of the

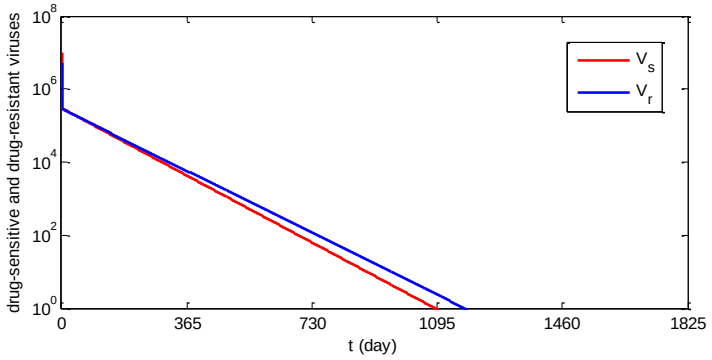
model in the above three cases tend to be the disease-free equilibrium point. The simulation results are shown in Figure 3(a)–(c):

Table 5. u , β , the corresponding basic reproduction number and HBV change image.

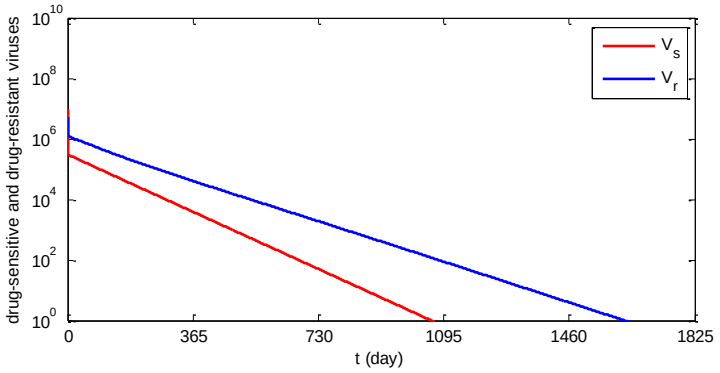
Serial number	u	β	R_s	R_r	Corresponding images of HBV changes
Case 1	0.1	0.9	0.066	0.041	Figure 3(a)
Case 2	0.5	0.5	0.037	0.072	Figure 3(b)
Case 3	0.9	0.1	0.007	0.289	Figure 3(c)



(a)



(b)



(c)

Figure 3. Simulation of continuous treatment for 5 years. (a) $u = 0.1$, (b) $u = 0.5$, (c) $u = 0.9$.

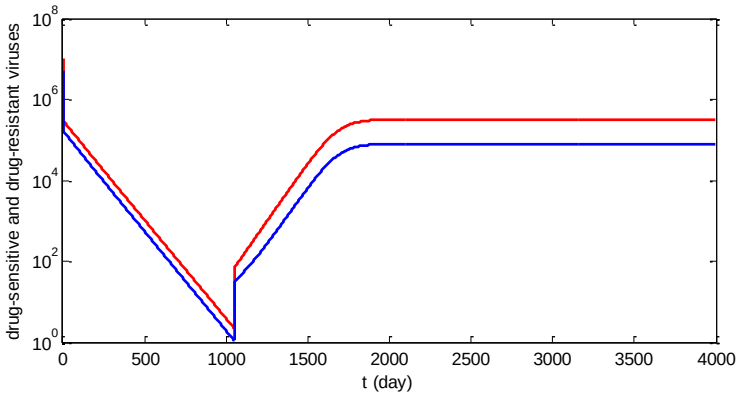
As can be seen in Figure 3(a), when $u = 0.1$, the mutation rate is low. The decline rate of the number of drug-sensitive HBV and drug-resistant HBV is similar, and it will take 3.04 years and 2.94 years respectively to reach 1copies/ml. In Figure 3(b), when $u = 0.5$, the mutation rate is relatively high, the decline rate of drug-sensitive HBV is faster than that of drug-resistant HBV, and it will take 2.97 years and 3.18 years to reach 1 copies/ml respectively. In Figure 3(c), when $u = 0.9$, the mutation rate is high, the decline rate of drug-sensitive HBV is much faster than that of drug-resistant HBV, and it will take 2.90 years and 4.45 years to reach 1 copies/ml respectively. As can be seen from Figure 3(b),(c), with the increase of mutation rate, the time to clear drug-sensitive HBV is shortened. Although the time to clear drug-resistant HBV will be prolonged, HBV will be cleared in general. The simulation results prove the research results of Mao Richeng et al. [4], and Theorem 2 is verified. After the emergence of entecavir resistance, continued entecavir treatment can clear the drug-resistant virus, although the treatment time is longer.

5.2.2. Effect of mutation rate on HBV rebound after drug withdrawal

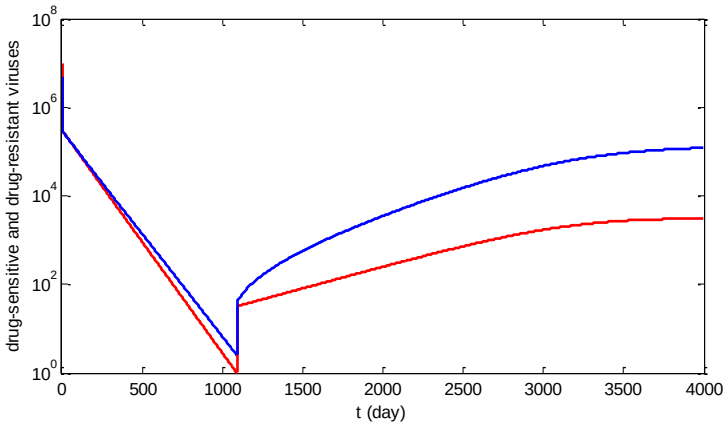
Model (1) is employed to numerically simulate the changes of drug-sensitive HBV and drug-resistant HBV after drug withdrawal. It is also used to analyze the possibility of HBV rebound. The model parameters and initial values are the same as those in section 5.2.1, and model (1) is simulated. After the treatment is stopped, model (1) is converted to the model as follows

$$\begin{cases} T'(t) = \lambda - K_s V_s(t) T(t) - K_r V_r(t) T(t) - \alpha T(t) \\ T_s'(t) = (1-u) K_s V_s(t) T(t) - \alpha T_s(t) \\ V_s'(t) = N_s \alpha T_s(t) - \delta V_s(t) \\ T_r'(t) = u K_s V_s(t) T(t) + K_r V_r(t) T(t) - \alpha T_r(t) \\ V_r'(t) = N_r \alpha T_r(t) - \delta V_r(t) \end{cases}$$

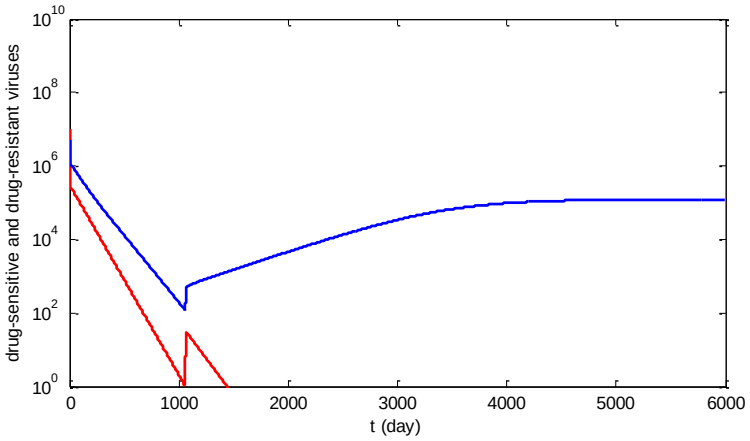
The simulation results are shown in Figure 4(a)–(c).



(a)



(b)



(c)

Figure 4. Virus decline in response to drug treatment and relapse after stopping the treatment Red line: the dynamic route of the number of drug-sensitive viruses. Blue line: the dynamic route of the number of drug-resistant viruses. (a) $u = 0.1$, (b) $u = 0.5$, (c) $u = 0.9$.

As can be seen in Figure 4(a), if the mutation rate is low and the drug is stopped when the number of HBV DNA drops to the normal range, the drug-sensitive HBV and the drug-resistant HBV will rebound rapidly at the same rate, and finally, exceed the detection limit (10^3 copies/ml). The results of Figure 4(b) show that when the mutation rate is relatively high, the rebound speed of drug-resistant HBV is faster than that of drug-sensitive HBV, and finally it will exceed the detection limit. Figure 4(c) shows that when the mutation rate is high, the drug-sensitive HBV will rebound rapidly and then decrease. Although the rebound rate of drug-resistant HBV is slow, the number of drug-resistant HBV will eventually exceed the detection limit. According to the comparison in Figure 4(a)–4(c), the virus will rebound after drug withdrawal. Meanwhile, different mutation rates lead to different time period for the virus to exceed the threshold.

6. Conclusions

In this paper, an HBV model with drug resistance and drug treatment was established. The threshold values of disease-free equilibrium, drug-sensitive type virus equilibrium, drug-resistance type virus equilibrium and double virus equilibrium stability were given. The number of drug-sensitive viruses in patients treated for 72 weeks was simulated, and the simulation results were consistent with clinical data, which verifies the rationality of model (1). According to the degree of drug resistance, the dynamic characteristics of the virus after stopping treatment when the number of HBV DNA is below the lower limit of detection (10^3 copies/ml) were simulated. The research results had the following recommendations for the treatment of hepatitis B patients:

1. When the degree of virus resistance in the patient's body is high, a combined drug regimen can be appropriately adopted. At present, adefovir dipivoxil combined with entecavir in the treatment of lamivudine resistance has been studied in China [20,21]. Combined medicine can not only reduce the mutation rate of lamivudine resistance, but also increase the inhibition rate of the drug to the virus, so as to shorten the time of clearing resistant HBV.

2. Even if the number of HBV DNA in patients is lower than the detection limit, no matter whether the level of drug resistance, stopping treatment immediately will cause virus rebound. In order to clear more virus and prevent the virus from rebounding, 1–3 years of consolidation therapy is recommended.

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Conflict of interest

The authors declare there is no conflict of interest.

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