An Improved Optimal Control Model of HIV Based on Treatment and Screening

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Abstract. In this paper, an optimal control model based on an improved HIV model is considered. Using of condom, screening of unaware infectives and incentive for treatment of the infected are used as the control items. Base on the same objective functional to minimize the unaware individuals and the cost of three kinds control at a given stage, we give four different optimal strategies with four different control suppose. By comparing the optimal strategies and dynamic trend of our model, we find that the dynamic trends are almost the same and the three different controls play different role, but simulation also shows that the screening control of unaware infectives play a relative small role when compare with the control of condom use and incentive control for treatment.

Introduction

Acquired Immunity Deficiency Syndrome(AIDS) is the disease that has affected the whole world in the 20 years since it was first detected. It is caused by Human Immunodeficiency Virus(HIV). 34.3 million People live with HIV infection today and more than 24 million are in the developing world [1].

Mathematical models of transmission dynamics of HIV play an important role in better understanding of epidemiological patterns for disease control as they provide short and long term prediction of HIV and AIDS incidence[2,3,4,5,6,7,8]. On the other hand, optimal control theory has been applied extensively in HIV models [9, 10, 11, 12, 13, 14, 15]. H. R. Joshi [15] built optimal control model about HIV based on an ordinary differential equation. The optimal drug strategies are determined for various stages of initiation of treatment. Later, the HIV models become more and more complicated because more factors were considered, such as activated and resting CD4+cells were contained. Further more, two major categories of anti-retroviral drugs to combat HIV are reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs), then the RTI control variable and the PI control variable were joined into the system[16]. In paper [8], a HIV model was given as follows:

$$\begin{cases} \dfrac{dS}{dt} = Q_0 - \beta_H S - \mu S, \\[2mm] \dfrac{dI_1}{dt} = \beta_H S - (\theta + \delta + \mu)I_1, \\[2mm] \dfrac{dI_2}{dt} = \theta I_1 - (\delta + \mu + \pi)I_2, \\[2mm] \dfrac{dH}{dt} = \pi I_2 - (\sigma\delta + \mu)H, \\[2mm] \dfrac{dA}{dt} = \delta I_1 + \delta I_2 + \sigma\delta H - (\alpha + \mu)A. \end{cases} \qquad (1)$$

where $S(t)$ is the susceptible individuals, the unaware infective individuals is denoted by $I_1(t)$, $I_2(t)$ represent the aware infective individuals by screening but not be on treatment, the individuals who are on treatment are stood for by $H(t)$ and $A(t)$ represents the AIDS population.

$$\beta_H = \frac{(1-u_1)(\beta_1 c_1 I_1 + \beta_2 c_2 I_2 + \beta_3 c_3 A + \beta_h c_h H)}{N}$$, where $u_1 (0 \le u_1 \le 1)$ is the condom use control, $N(t) = S(t) + I_1(t) + I_2(t) + H(t) + A(t)$ is the number of the total human population at time t, the parameters $\beta_i (i = 1, 2, 3, h)$ are the probabilities for susceptible individuals with unaware infectives, infectives have been aware, AIDS individuals and HIV positive individuals on treatment respectively. Q_0 is the constant rate of immigration of the susceptible, μ represents the natural mortality rate, θ measures the rate at which unaware infectives are detected by a screening method to become aware infectives, π measures the rate at which the already aware infective individuals receive treatment, δ is the rate by which all the individuals with HIV develop AIDS, σ is the modification parameter due to treatment, α is the AIDS related death rate.

Paper [8] pointed that effective control of the disease may be too costly when constant controls are considered as it requires treatment at higher levels for all time and then gave a time dependent controls model is as follows:

$$\begin{cases} \dfrac{dS}{dt} = Q_0 - \beta_H S - \mu S, \\[2mm] \dfrac{dI_1}{dt} = \beta_H S - (u_2 \theta + \delta + \mu) I_1, \\[2mm] \dfrac{dI_2}{dt} = u_2 \theta I_1 - (\delta + \mu + u_3 \pi) I_2, \\[2mm] \dfrac{dH}{dt} = u_3 \pi I_2 - (\sigma \delta + \mu) H, \\[2mm] \dfrac{dA}{dt} = \delta I_1 + \delta I_2 + \sigma \delta H - (\alpha + \mu) A. \end{cases} \qquad (2)$$

where $u_2 (0 \le u_2 \le 1)$ is the control on screening of unaware infectives, $u_3 (0 \le u_3 \le 1)$ is the control on treatment of infectives. Paper [8] also gave some simulations to compare the function of different controls, but $u_2 = 0$ in model (2) means that there is no screening of unaware infectives, and it neglects the rate at which unaware infectives are detected to become aware infectives without screening method. As for u_3, since $0 \le u_3 \le 1$, it seems unreasonable because the already aware infective individuals have their own right to choose to be treated or not. So in order to find the optimal screening method, and considering the corresponding intervention to treatment, we gave another optimal control model with screening method and intervention to treatment as follows:

$$\begin{cases} \dfrac{dS}{dt} = Q_0 - \beta_H S - \mu S, \\[2mm] \dfrac{dI_1}{dt} = \beta_H S - ((1+u_2)\theta + \delta + \mu) I_1, \\[2mm] \dfrac{dI_2}{dt} = (1+u_2)\theta I_1 - (\delta + \mu + (1+u_3)\pi) I_2, \\[2mm] \dfrac{dH}{dt} = (1+u_3)\pi I_2 - ((1-\varepsilon u_3)\delta + \mu) H, \\[2mm] \dfrac{dA}{dt} = \delta I_1 + \delta I_2 + (1-\varepsilon u_3)\delta H - (\alpha + \mu) A. \end{cases} \qquad (3)$$

where u_2 represents the passive screening, and θ represents the active screening by individuals, u_3 represents the incentive control for treatment, we use $(1-\varepsilon u_3)\delta$ to reflect the effect to progression rate of HIV positive individuals on treatment to AIDS population by the control u_3. This paper intend to search for the optimal control strategy and compare the role of each control.

The organization of the paper is as follows. In section 2, the optimal control problem is proposed, the existence of the optimal control system is proved. Section 3 simulates the different

cases based on four kinds of control. Section 4 draws the conclusion.

The existence of the optimal control

Our optimal goal is to minimize the number of unaware infectives and the cost of applying the control u_1, u_2 and u_3, so we choose the objective functional $J(u_1, u_2, u_3)$ as follows:

$$J(u_1, u_2, u_3) = \min_{u_1, u_2, u_3} \int_{t_0}^{t_f} (aI_1 + b_{11}u_1^2 + b_{22}u_2^2 + b_{33}u_3^2)\, dt . \tag{4}$$

where $U = \left\{ (u_1, u_2, u_3) \mid u_i \text{ measurable}, \ a_i \le u_i \le b_i, t \in \left[t_0, t_f \right], \text{for } i = 1, 2, 3 \right\}$ is the control set. which a_i and b_i $(i = 1, 2, 3)$ stand for the minimum and maximum effect. The term a represents the weight of I_1 and the positive constants b_{11}, b_{22}, b_{33} takes into account financial constraints. We will prove the existence of (u_1, u_2, u_3) satisfy that: $\min_{(u_1, u_2, u_3)} J(u_1, u_2, u_3) = J(u_1^*, u_2^*, u_3^*)$.

To use an existence result, we must check the following properties [17]:
1. The set of controls and corresponding state variables is non-empty.
2. The control U set is convex and closed.
3. The state system is bounded in the state and control variables.
4. The integrand of the objective functional is concave on U.
5. There exists constants $\eta_1, \eta_2 > 0$, and $\beta > 1$ such that the integrand $L(I_1, u_1, u_2, u_3)$ of the objective functional satisfies:

$$L(I_1, u_1, u_2, u_3) \ge \eta_1 \left(|u_1|^2 + |u_2|^2 + |u_3|^2 \right)^{\beta/2} - \eta_2 .$$

In order to verify these conditions, we use a result by [18] to give the existence of solutions of model (3) with bounded coefficients, which gives condition 1. We note that the solutions are bounded. Our control set satisfies condition 2. Equation (3) satisfies condition 3 is easily to verified, using the boundedness of the solutions.

Note that the integrand of our objective functional is concave. Also we have the last condition needed: $aI_1 + b_{11}u_1^2 + b_{22}u_2^2 + b_{33}u_3^2 \ge \eta_1 \left(|u_1|^2 + |u_2|^2 + |u_3|^2 \right) - \eta_2$.

where η_1 depends on the upper bound on I_1; and $\eta_2 \ge 0$ since $b_{11}, b_{22}, b_{33} > 0$. We conclude there exists an optimal control pair.

The Hamiltonian function, defined by using the dynamic constraint (3) and the Lagrangian $L = aI_1 + b_1 u_1^2 + b_2 u_2^2 + b_3 u_3^2$ is as follows:

$$H^* = L + \lambda^T f = aI_1 + b_{11}u_1^2 + b_{22}u_2^2 + b_{33}u_3^2 + \lambda_1 (Q_0 - \beta_H S - \mu S) + \lambda_2 (\beta_H S - ((1 + u_2)\theta_1$$
$$+ \delta + \mu)I_1) + \lambda_3 ((1 + u_2)\theta_1 I_1 - (\delta + \mu + u_3 \pi)I_2) + \lambda_4 (u_3 \pi I_2 - ((1 - \varepsilon u_3)\delta + \mu)H)$$
$$+ \lambda_5 (\delta I_1 + \delta I_2 + (1 - \varepsilon u_3)\delta H - (\alpha + \mu)A)$$

Using Pontryagin's minimum principle, the necessary conditions (in terms of the Hamiltonian) for U^* to be an optimal control is as following:

$$1° \begin{cases} \dfrac{dS}{dt} = Q_0 - \beta_H S - \mu S, \\[2mm] \dfrac{dI_1}{dt} = \beta_H S - ((1 + u_2)\theta + \delta + \mu)I_1, \\[2mm] \dfrac{dI_2}{dt} = (1 + u_2)\theta I_1 - (\delta + \mu + (1 + u_3)\pi)I_2, \\[2mm] \dfrac{dH}{dt} = (1 + u_3)\pi I_2 - ((1 - \varepsilon u_3)\delta + \mu)H, \\[2mm] \dfrac{dA}{dt} = \delta I_1 + \delta I_2 + (1 - \varepsilon u_3)\delta H - (\alpha + \mu)A. \end{cases}$$

$2°\quad S(t_0)=S_0; I_1(t_0)=I_{10}; I_2(t_0)=I_{20}; H(t_0)=H_0; A(t_0)=A_0.$

$$3°\quad \begin{bmatrix}\dot\lambda_1\\\dot\lambda_2\\\dot\lambda_3\\\dot\lambda_4\\\dot\lambda_5\end{bmatrix}=-\begin{bmatrix}\dfrac{\partial H^*}{\partial S} & \dfrac{\partial H^*}{\partial I_1} & \dfrac{\partial H^*}{\partial I_2} & \dfrac{\partial H^*}{\partial H} & \dfrac{\partial H^*}{\partial A}\end{bmatrix}^T ,$$

$4°\quad \lambda_i(t_f)=0,\quad i=1,2,3,4,5.$

$$5°\quad \begin{bmatrix}\dfrac{\partial H^*}{\partial u_1}\\[2mm]\dfrac{\partial H^*}{\partial u_2}\\[2mm]\dfrac{\partial H^*}{\partial u_3}\end{bmatrix}=\begin{bmatrix}2b_{11}u_1+(\lambda_1-\lambda_2)\dfrac{\beta_1c_1SI_1+\beta_1c_1SI_2+\beta_1c_1SA+\beta_1c_1SH}{S+I_1+I_2+H+A}\\[2mm]2b_{22}u_2-\theta_1I_1(\lambda_2-\lambda_3)\\[2mm]2b_{33}u_3-\pi I_3\lambda_3+\pi I_3\lambda_4+\varepsilon\delta H\lambda_4-\varepsilon\delta H\lambda_5\end{bmatrix}=0.$$

So we get the optimal control:

$$\begin{cases}u_1^*=\max\left\{a_1,\min\left\{(\lambda_2-\lambda_1)\dfrac{\beta_1c_1SI_1+\beta_1c_1SI_2+\beta_1c_1SA+\beta_1c_1SH}{2b_{11}(S+I_1+I_2+H+A)},b_1\right\}\right\},\\[4mm]u_2^*=\max\left\{a_2,\min\left\{\dfrac{\theta_1I_1(\lambda_2-\lambda_3)}{2b_{22}},b_2\right\}\right\},\\[4mm]u_3^*=\max\left\{a_3,\min\left\{\dfrac{\pi I_2(-\lambda_3+\lambda_4)-\delta H(\lambda_5-\lambda_4)}{2b_{33}},b_3\right\}\right\}.\end{cases}$$

The optimal control system thus, is a coupled forward state equation and a backward adjoint equation, along with the regular control. This problem, being nonlinear and coupled in nature, needs to be solved using concurrent and iterative numerical procedures. In this paper, the optimal strategy is simulated by solving the state and adjoint systems and the transversality conditions based on Runge-Kutta fourth order scheme and the steepest gradient method [19].

Simulation and discussions

Table 1 : The parameter values we used

Parameters	Value	Reference
β_1	0.8	[8]
β_2	0.55	[8]
β_3	0.32	[8]
β_h	0.15	[8]
μ	0.2	[8]
α	1	[8]
Q_0	2000	[8]
δ	0.1	[8]
θ	0.002	[8]
π	0.66	[8]
σ	0.002	[8]
c_1	0.1	[8]
c_2	0.1	[8]
c_3	0.1	[8]
ε	0.002	Assumed

In this section, we simulate the optimal control of model (3) and compare the four cases of condom use, screening of unaware infectives and incentive control for treatment on the transmission dynamics of the disease. The parameter values we used are given in Table 1.

The cost coefficients $a = 800, b_{11} = 35, b_{22} = 95, b_{33} = 175$ and the initial condition is taken to be $S(0) = 800, I_1(0) = 100, I_2(0) = 100, H(0) = 100, A(0) = 100.$ Efficacy u_1, u_2, u_3 can theoretically lie between 0 and 1. The minimum effect a_i $(i = 1, 2, 3)$ is set to be 0, which corresponds to no control function. However, the maximum effect is taken to be less than 1, for the control can't be completely effective and, so the maximum effect b_i $(i = 1, 2, 3)$ is set to be 0.98.

We investigate and compare numerical results in the following scenario:

Case 1 The three kinds of control efforts on condom use (u_1), screening of unaware infectives (u_2) and treatment (u_3) are made to be optimized, the simulation results are shown in Figure 1 and Figure 2.
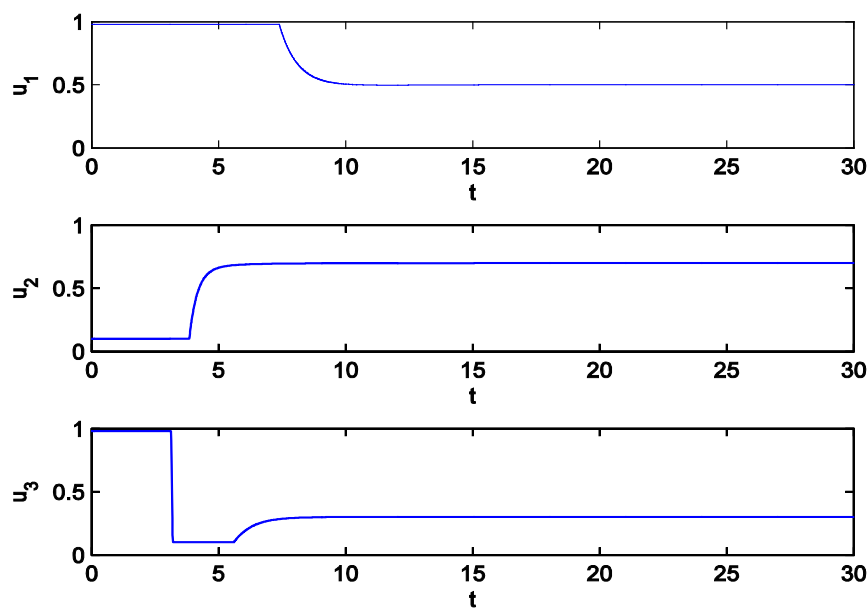

Figure 1 The optimal control strategy of u_1, u_2, u_3
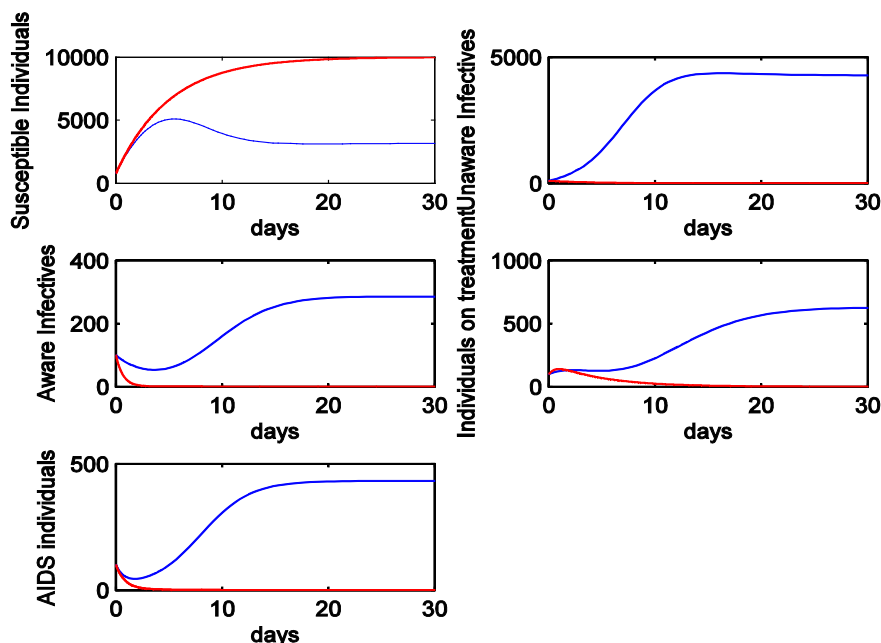

Figure 2   The comparison between the optimal control and no control

We use red curve to represent the dynamic trend with optimal control and blue curve to

represent the dynamic trend with no control. From Figure 2 we know that the optimal control can make the susceptible individuals far more than that with no control, while the other four kinds of individuals in our model much less than that with no control, which show that the HIV has been effectively controlled based on the our optimal control strategy. But since our optimal goal is to minimize the number of unaware infectives and the cost of applying the control, so when the condom use and Incentives for treatment keep the maximum level at the beginning stage, the level of screening of unaware infectives should be kept at a low level.

In the following part, we choose one of the three controls(u_1, u_2, u_3) to be zero to simulate the corresponding optimal control and compare their effect on the dynamics trend of the five kinds of individuals in our model.

Case 2: The treatment control (u_3) is set to zero and optimal control result of u_1 and u_2 are given in Figure 3. The dynamics trend of the five kinds of individuals with and without control are given in Figure 4.
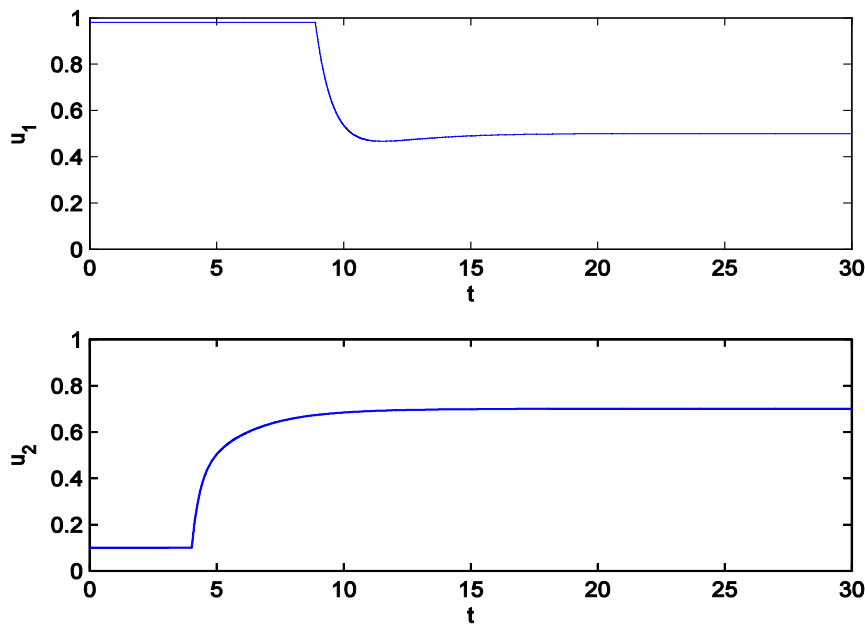

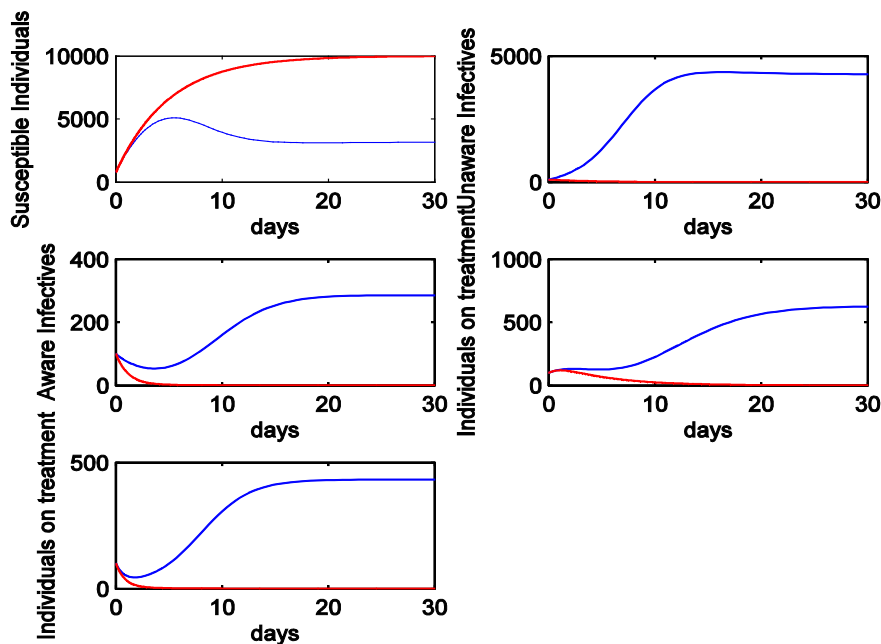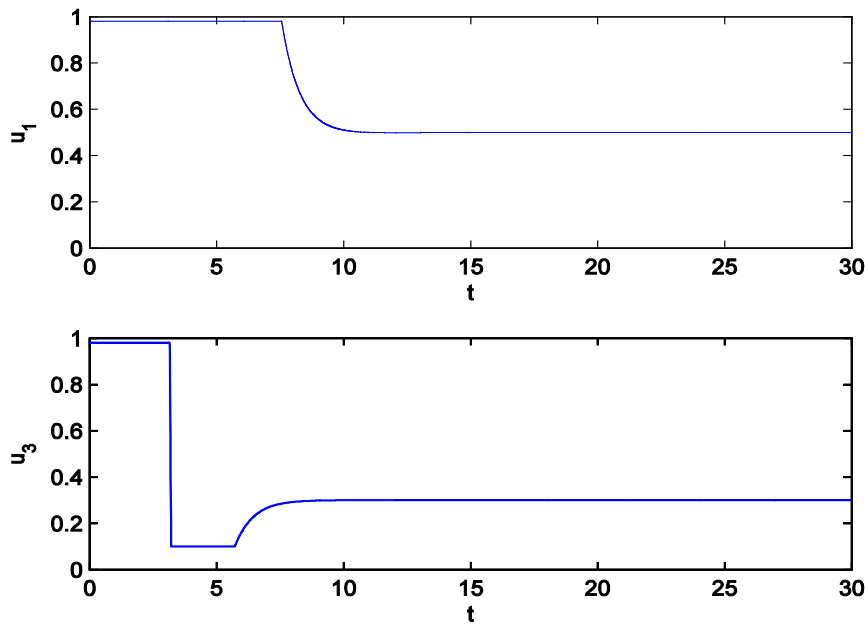Figure 3   The optimal control strategy of u_1, u_2

Figure 4 The comparison between the optimal control u_1, u_2 and no control.

Case 3: The control on screening of unaware infectives (u_2) is set to zero and the optimal control result of u_1 and u_3 are given in Figure 5. The dynamics trend of the five kinds of individuals with and without control are given in Figure 6.

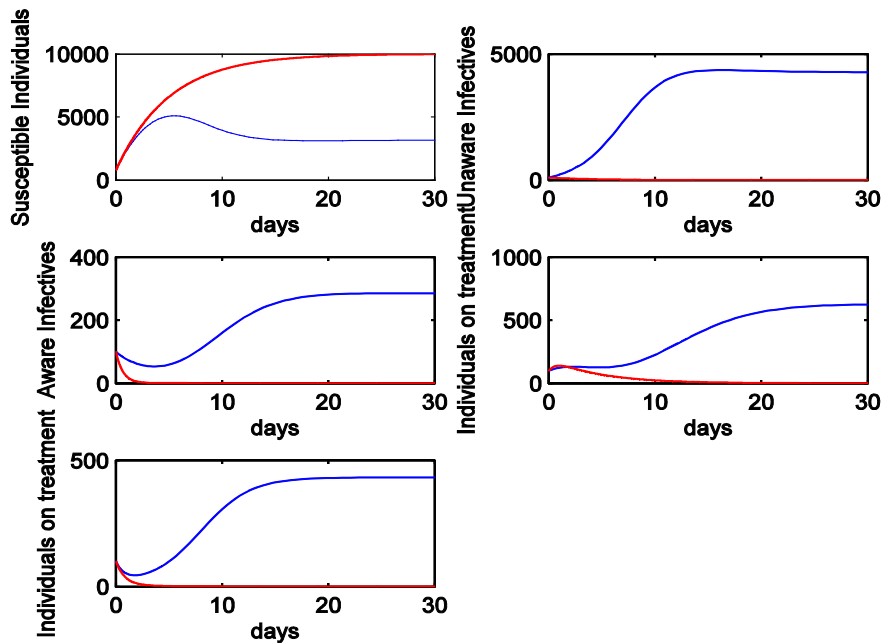Figure 5　The optimal control strategy of u_1, u_3

Figure 6 The comparison between the optimal control u_1, u_3 and no control.

Case 4: The control on condom use (u_1) is set to be zero and the optimal control result of u_2 and u_3 are given in Figure 7. The dynamics trend of the five kinds of individuals with and without control are given in Figure 8.

By comparing Figure 1 with Figure 3, we find that when incentives for treatment is zero(Case 2), the control of condom use should take longer time to keep maximum effect. But form Figure 1 and Figure 5, no obvious difference can be seen when screening of unaware infectives is zero(Case 3), which shows that the screening of unaware infectives(u_2) has almost no impact on u_1 and u_3. Similarly, when the control of condom use is zero (Case 4), the screening of unaware infectives and

drug treatment should take longer time than Case 1. As to the dynamics trend, there are no obvious differences within Figure 2, Figure 4, Figure 6 and Figure 8. From the above analysis, we found that the screening control of unaware infectives play a relative small role, the more effective control should be the control of condom use and incentive control for treatment.
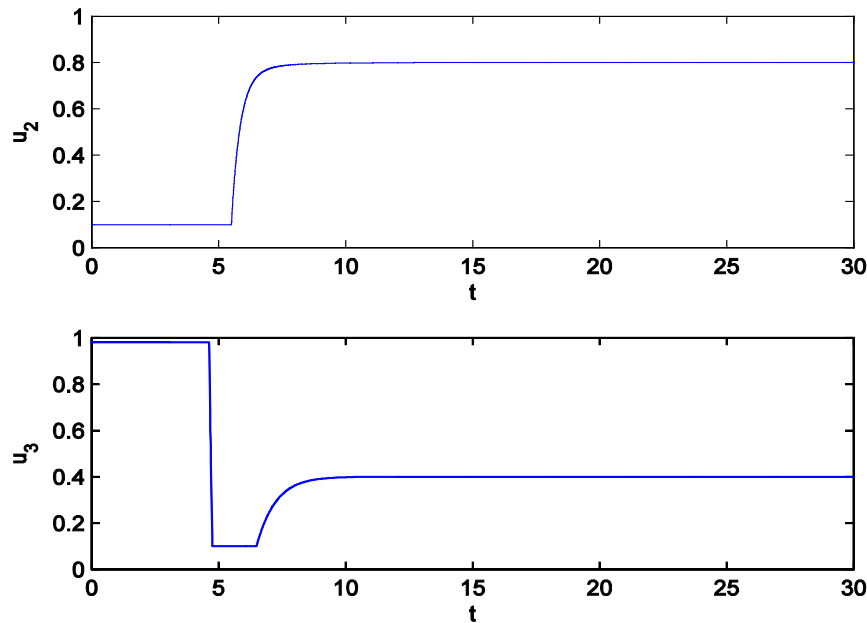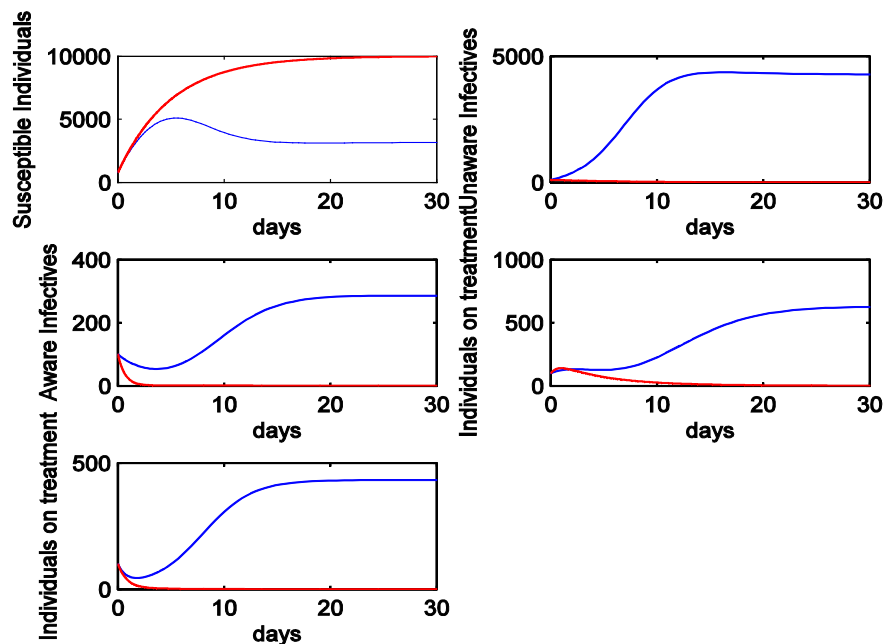

Figure 7　The optimal control strategy of u_2, u_3.

Figure 8　The comparison between the optimal control u_2, u_3 and no control.

Conclusion

In this paper, we modified the optimal control for HIV model. The conditions for optimal control of the disease with effective use of condoms, incentive control for treatment and screening of infectives were analyzed. We find that if the objective functions are same, the dynamic trends of the five kinds of individuals in our model are almost the same whether or not one of the control is set to be zero. By setting one of the three controls to be zero, we found that the three different controls play different role, when incentives for treatment is zero(Case 2), the control of condom

use should take longer time to keep maximum effect, when the control of condom use is zero (Case 4), the screening of unaware infectives and drug treatment should take longer time, but simulation showed that the screening control of unaware infectives play a relative small role when compare with the control of condom use and incentive control for treatment, so in order to minimize the cost of applying the control, the screening control of unaware infectives can be weakened while the other two controls should be encouraged.

It should be pointed that the true situation must be more complex and varied than what we have described, but the analytical results could give structures for treatment that could prove foundational for future practice. We believe that the analysis and simulation presented in this paper, can play some role in developing an improved HIV treatment regimen.

Acknowledgments

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