

OPTIMAL CONTROL ANALYSIS OF HIV/AIDS EPIDEMIC MODEL WITH AN ANTIRETROVIRAL TREATMENT

UMMU HABIBAH, RIRIT ANDRIA SARI

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MATHEMATICS DEPARTMENT AND RESEACH GROUP OF BIOMATHEMATICS, FACULTY OF MATHEMATICS AND NATURAL SCIENCE, BRAWIJAYA UNIVERSITY, JL. VETERAN MALANG 65145, INDONESIA. ummu_habibah@ub.ac.id

ABSTRACT. A mathematical model of HIV/AIDS is governed by a system of ordinary differential equations in the presence of an antiretroviral treatment (ARV). The theory of optimal control is applied to an epidemic model of HIV/AIDS which an ARV is used as a control strategy in order to prevent the spread of HIV/AIDS. The optimality system is derived by applying the Pontryagin's Minimum Principle. We analyze the boundedness and positivity of solutions, and an existence of the optimal control. Numerical simulations are conducted to obtain numerical solution of the optimally system.

Key words and phrases: Optimal control analysis; HIV/AIDS; Antiretroviral (ARV) treatment.

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1. INTRODUCTION

AIDS is one of the infectious diseases caused by the human immunodeficiency virus (HIV), which suppresses the T cells of the immune system in the body. T cells have important ability to attack infections. Recently, HIV / AIDS has spread rapidly in Indonesia and has become a big problem. According to [3], there are 640.443 HIV-infected individual in Indonesia.

Mathematical models contribute significantly to understanding HIV-infected behavior. In 2009, the dynamical analysis of HIV / AIDS epidemic models along with treatment had studied [5]. The population was divided into four compartments: susceptible (S), HIV infection (I), AIDS (A), and symptomatic (J). In 2014, the study developed by studying dynamical analysis of HIV / AIDS epidemic models with density dependence of incidence, which is a function of the total population. In 2016, an HIV / AIDS epidemic model treated as a SIATR model constructed and analyzed the dynamically. As a result, the endemic occurred since the basic reproduction number $R_0 > 1$ [2]. This means that efforts to treat individuals infected with HIV have not been effective. Therefore, it is important to apply optimal control analysis to minimize the HIV-infected subpopulation and the cost related to the application of control strategy. In 2015, mathematical models that represent the nonlinear dynamics of immune tumors investigated [9]. They used the boundedness of the solution to derive the existence and uniqueness of optimal controls, and demonstrated numerical simulations. In 2018, optimal control theory applied to HIV/AIDS model with two control strategies, ARV and highly active antiretroviral therapy (HAART) [6]. Unfortunately, they did not analyze the boundedness and positivity of the solutions. In the analysis control optimal, prove the existence of optimal control is important part that guarantees the global minimum value of the system.

In this research we study optimal control analysis including proof of the boundedness and positivity of solutions, and an existence of the optimal control using the model in [2], which is by changing the constant value of the rate of infected individual received treatment to be a control variable as function of time. The control strategy in this problem is an ARV that is used as control strategy in order to minimize HIV/AIDS infection individual and the cost related to the treatment. An optimal control problem is solve by the Minimum-Pontryagin Principle. Numerical simulation is applied by the method of sweep backward and forward.

2. OPTIMAL CONTROL FORMULATION

In this section we introduce the HIV/AIDS epidemic model with treatment modified from the model [2], with an antiretroviral (ARV) treatment as a control variable depends on time. The HIV/AIDS epidemic model is

$$\dot{S} = \Lambda - \beta I S - \mu_1 S - dS,$$

$$\dot{I} = \beta I S + \alpha_1 T - dI - k_1 I - u(t) I,$$

$$\dot{A} = k_1 I - (\delta_1 + d) A + \alpha_2 T,$$

$$\dot{T} = u(t) I - \alpha_1 T - (d + \delta_2 + \alpha_2) T,$$

$$\dot{R} = \mu_1 S - dR,$$

where S(t) is the number of susceptible patients, I(t) is the number of HIV-positive individuals in the stage of HIV infection, A(t) is the number of individuals with full-blown AIDS but not receiving ARV, T(t) is the number of individuals being treated and R(t) is the number of individuals who have changed their sexual habits sufficiently [2].

The following parameters are represented as following. A is recruitment rate, d is the natural death rate, β is the contact rate between the susceptible and infected populations, k_1 is the rate at individuals leave the infection class and become with full-blown AIDS, that is proportion of the

I becoming with full-blown AIDS, δ_1 and δ_2 are the disease-induced dead rate for individuals in compartments A(t) and T(t). u(t) is the control variable that shows the rate of individuals with HIV receive treatment. The spread of HIV/AIDS disease can be controlled by giving the ARV to the individuals with HIV in order to minimize the number of individual with HIV to be AIDS. The treatment for population with HIV infection is expressed as u(t). This research is proposed to minimize the population with HIV infection, full-blown AIDS and the cost related to the implementation of control strategy. The functional objective is

(2.2)
$$J(u(t)) = \int_0^{t_f} \left(w u^2(t) + I(t) + A(t) \right) dt,$$

where w represents weight of an ARV. We determine optimal control $u(t)^*$ such that

(2.3)
$$J(u^*(t)) = \min\{J(u(t)) : u(t) \in U\},\$$

with a set of a control function U as following

(2.4)
$$U = \{u(t) : 0 \le u(t) \le 1, t \in [0, t_f]\},\$$

where t is time and t_f represents the final time for the control strategy of HIV/AIDS.

We analyze an optimal control problem by following the approach in [10] and [8] which is the boundedness and positivity of solutions, and an existence of the optimally system for the optimal control of HIV/AIDS model were derived in tumor model. It makes sense when we apply that steps into HIV/AIDS model to prove the boundedness and positivity of solutions, and an existence of the optimal control. The first is we analyze the boundedness of the solutions.

Boundedness of Solutions. To analyze the boundedness of the solution we should determine the upper bounds of the solutions are called the super solutions. We agree that the super solutions of the system are

(2.5)

$$\begin{split}
\bar{S} &= \Lambda, \\
\dot{\bar{I}} &= \beta I S + \alpha_1 T, \\
\dot{\bar{A}} &= k_1 I + \alpha_2 T, \\
\dot{\bar{T}} &= u(t) I, \\
\dot{\bar{R}} &= \mu_1 S,
\end{split}$$

which are bounded on a finite time interval, and the sub-solutions are zero. Equation (2.5) shows the boundedness of the system. Furthermore we establish the positivity of the solutions.

Positivity of Solutions. Our goal is to investigate the subpopulations of HIV/AIDS infection. It is reasonable to set non-negative value for all the variables and parameters of the model (2.1). The system of equation (2.1) has initial condition $S(0) \ge 0$, $I(0) \ge 0$, $A(0) \ge 0$, $T(0) \ge 0$ and $R(0) \ge 0$. Domain of the system of equation (2.1) is $D = \{(S, I, A, T, R) \in \Re^5_+\}$.

The system of equation (2.1) is well-posed such that solutions with nonnegative initial conditions remain nonnegative for all $0 < t < \infty$ is shown by the following theorem. It makes the variable of the system, biologically meaningful.

Theorem 2.1. The region $D \subset \Re^5_+$ is positively invariant with respect to the system of equation (2.1 and non-negative solution exists for all time $0 < t < \infty$.

Proof. Let $D \subset \Re^5_+$ with $D = \{(S, I, A, T, R) \in \Re^5_+ : R \leq \Lambda/c_1\}$, then the solutions of S(t), I(t), A(t), T(t), R(t) of system (2.1) are positive $\forall t \ge 0$. For example, we choose and solve the susceptible variable with linear term of the system (2.1) that is

(2.6)
$$\dot{S} \leqslant \Lambda - (\mu_1 - d)S = \Lambda - lS,$$

with $l = \mu_1 + d$. By solving 2.6, we yield

$$(2.7) S \leqslant \frac{\Lambda}{l} + je^{-lt},$$

we take $t \to \infty$ to give $S \leq \frac{\Lambda}{l}$. Hence $S(t) > 0, \forall t > 0$. Again we can show I(t) > 0, A(t) > 0, T(t) > 0 and $R(t) > 0, \forall t > 0$.

Existence of Optimally System.

Theorem 2.2. Given the functional objective in (2.2). There exist an optimal control $u(t)^* \in U$ such that equation (2.2 is satisfied if the following conditions are hold

- (1) The control set U and the state variables (I(t), A(t), T(t)) and R(t), are not empty.
- (2) The control set U is convex and closed.
- (3) The right hand side of the state system (2.1) is bounded above by linear function in the form state and control variables.
- (4) The integrand of the functional objective in (2.2) is convex on U and bounded below by $-w_2 + w_1 u^2$ with $w_1, w_2 > 0$.

Proof. We prove each condition following:

- (1) By applying Theorem (1), the system (2.1) has bounded coefficients and the solutions on the finite time interval $0 < t < \infty$. To show the existence of the solution of the system (2.1), we can apply the result of [7].
- (2) The control set U is closed and convex by definition.
- (3) The right hand side of the system (2.1) must be continuous. The denominators of all fractions of the right hand side of the system consists solely of positive entities. We let $\vec{G}(t, \vec{x})$ be right hand side of the system (2.1) without control variable

(2.8)
$$\vec{F}(t,\vec{x}) = \vec{G}(t,\vec{x}) + \begin{bmatrix} \Lambda \\ 0 \\ 0 \\ uI \\ 0 \end{bmatrix},$$

with $\vec{x} = \begin{bmatrix} S & I & A & T & R \end{bmatrix}^T$. Using the boundedness of the solutions, we get

$$(2.9) |\vec{F}(t,\vec{x})| \le \left| \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ \beta_1 & 0 & 0 & \alpha_1 & 0 \\ 0 & k_1 & 0 & \alpha_2 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \nu & 0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} S \\ I \\ A \\ T \\ R \end{bmatrix} \right| + \left| \begin{bmatrix} \Lambda \\ 0 \\ 0 \\ uI \\ 0 \end{bmatrix} \right| \le w_1(|\vec{x}| + |u|),$$

where w_1 depends on the coefficients of the system. Therefore, the right side of the state equation is bounded above by a sum of the state and control variable.

(4) We will prove the integrand of the functional J is convex on U. Functional J(u) is convex when satisfies

(2.10)
$$f(\theta u_1 + (1 - \theta)u_2) \leqslant \theta f(u_1) + (1 - \theta)f(u_2).$$

for all $u_1, u_2 \in [0, 1]$ [1], and for all $\theta \in [0, 1]$ with a given function

(2.11)
$$f(u) = wu^2 + I + A.$$

We will prove (2.10) as following. By simple algebra, the left hand side of (2.10) can be written as

(2.12)
$$f(\theta u_1 + (1-\theta)u_2) = w(\theta u_1 + (1-\theta)u_2)^2 + I + A,$$

and the right hand side of (2.10) can be written as

(2.13)
$$\theta f(u_1) + (1-\theta)f(u_2) = w(\theta u_1^2 + (1-\theta)u_2^2) + I + A.$$

From equation (2.12) and (2.13), we compare the term $(\theta u_1 + (1 - \theta)u_2)$ and $(\theta u_1^2 + (1 - \theta)u_2^2)$ to get inequality

(2.14)
$$(\theta u_1 + (1-\theta)u_2)^2 \leqslant (\theta u_1^2 + (1-\theta)u_2^2)$$

furthermore, by simple algebra we can write equation the left hand side of (2.14) as following

(2.15)
$$(\theta u_1 + (1-\theta)u_2)^2 = (u_1 - u_2)\theta)^2 + u_2^2 - 2u_2^2\theta(1 - u_1/u_2),$$

and the right side of (2.14) can be written as

(2.16)
$$\theta u_1^2 + (1-\theta)u_2^2 = \theta u_1^2 + u_2^2 - \theta u_2^2,$$

by choosing $\theta \in [0,1]$, $u_1, u_2 \in [0,1]$, we agree $((u_1 - u_2)\theta)^2 \leq \theta u_1^2$ and obviously $-2u_2^2\theta(1-u_1/u_2) \leq (-\theta u_2^2)$. Hence, we get

(2.17)
$$(\theta u_1 + (1-\theta)u_2)^2 = (u_1 - u_2)\theta^2 + u_2^2 - 2u_2^2\theta(1 - u_1/u_2), \\ \leqslant \theta u_1^2 + u_2^2 - \theta u_2^2, \\ = \theta u_1^2 + (1-\theta)u_2^2.$$

From equation (2.17) we conclude the integrand of functional J is convex on U.

Furthermore, we prove the integrand of functional J is bounded. For example, there is $w_1 > w$, and remember I and A bounded in the interval [0, 1] such that

(2.18)
$$w\bar{u}^2 + I + A \leqslant w\bar{u}^2 + I_{max} + A_{max}$$

where I_{max} and A_{max} depend on upper bound of I and A. Hence U is in the interval $0 \le u \le 1$. Since $u^2 = |u|^2$, we have

(2.19)
$$w\bar{u}^2 + I + A \leqslant w|\bar{u}|^2 + I_{max} + A_{max},$$

if we take $M = w|\bar{u}|^2 + I_{max} + A_{max}$ such that satisfies $w|\bar{u}|^2 + I_max + A_max + \leq M$, which gives the integrand of functional J is bounded. Finally we have proved an existence an optimal control of the system. It means we can find the global minimum of optimal control that minimize the functional objective.

Optimally System. The boundedness and positivity of solutions, and an existence of the optimally system have been proved. Furthermore the problem of optimal control can be solved by applying the Minimum-Pontryagin Principle as necessary conditions for optimality system. We introduce the state variables S(t), I(t), A(t), T(t), and R(t); and define the adjoint variables that correspond to the state variables are $\lambda_1(t)$, $\lambda_2(t)$, $\lambda_3(t)$, $\lambda_4(t)$ and $\lambda_5(t)$. Furthermore, we introduce the Hamiltonian function as follows

$$(2.20) H = f + \sum_{i=1}^{5} \lambda_i g_i,$$

where λ_i and g_i are the co-state or we call adjoint variables and the right hand side of equation (2.1) respectively. Now, we have the Hamiltonian as follows

$$H = wu(t)^{2} + I + A + \lambda_{1} (\Lambda - \beta IS - \lambda_{1}S - dS)$$
(2.21)
$$+\lambda_{2} (\beta IS + \alpha_{1}T - dI - k_{1}I - u(t)I) + \lambda_{3} (k_{1}I - (\delta_{1} + d)A + \alpha_{2}T)$$

$$+\lambda_{4} (u(t)I - \alpha_{1}T - (d + \delta_{2} + \alpha_{2})T) + \lambda_{4} (\mu_{1}S - dR)$$

The optimally system is obtained when the Hamiltonian function satisfies the following conditions:

• State Equations

(2.22)
$$\frac{\partial H}{\partial \lambda_i} = g_i, \quad i = 1, 2, 3, \dots,$$

with the initial condition is $S(0) \ge 0$, $I(0) \ge 0$, $A(0) \ge 0$, $T(0) \ge 0$ and $R(0) \ge 0$. • Co-state Equations

(2.23)
$$\frac{d\lambda_i}{dt} = -\frac{\partial H}{\partial x_i}, \quad i = 1, 2, 3, \dots,$$

such that we have

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S} = (\lambda_1 - \lambda_2) \,\beta I + (\lambda_1 - \lambda_5) \,\mu_1 + \lambda_1 d,$$

$$\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial I} = -1 + (\lambda_1 - \lambda_2) \,\beta S + (\lambda_2 - \lambda_3) \,k_1 + (\lambda_2 - \lambda_4) \,u(t) + \lambda_2 d,$$

$$\frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial A} = -1 + \lambda_3 \left(\delta_1 + d\right),$$

$$\frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial T} = (\lambda_4 - \lambda_2) \,\alpha_1 + (\lambda_4 - \lambda_3) \,\alpha_2 + \lambda_4 \left(d + \delta_2\right)$$

$$\frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial R} = \lambda_5 d,$$

with transversal condition is $\lambda_1(t_f) = \lambda_2(t_f) = \lambda_3(t_f) = \lambda_4(t_f) = \lambda_5(t_f) = 0$ where t_f is the final time of the control.

• Stationer Condition

(2.25)
$$\frac{\partial H}{\partial u} = 0,$$

such that we obtain characteristic equation as following

(2.26)
$$u^*(t) = \begin{cases} 0 & \text{for } \frac{(\lambda_2 - \lambda_4)I}{2w} \le 0, \\ \frac{(\lambda_2 - \lambda_4)I}{2w} & \text{for } 0 \le \frac{(\lambda_2 - \lambda_4)I}{2w} \le 1, \\ 1 & \text{for } \frac{(\lambda_2 - \lambda_4)I}{2w} \ge 1, \end{cases}$$

or we can write the optimal control $u(t)^*$ as

(2.27)
$$u^*(t) = \min\left\{\max\left\{0, \frac{(\lambda_2 - \lambda_4)I}{2w}, 1\right\}\right\}.$$

3. NUMERICAL SIMULATION

Since our optimally system is in the form of the system of ordinary differential equation, it is difficult to solve analytically. Numerical approximation is a good choice to solve the problem. In [9] said the optimality system is a boundary value problem where we use the forward in time to solve the state equation (2.1) with initial conditions and backward in time to solve the co-state or adjoin system (2.22) and (2.23) with terminal or transversal conditions. Indeed, the state system moves forward with time and the co-states move backward with time and we coupled both situation in addition to controls which is a quite challenging problem. We solved the optimality system numerically by using an iterative process with the fourth order Runge-Kutta scheme. Following is the algorithm to obtain a control that optimally the system

- Step 1: We choose an initial guess for a control u^* .
- Step 2: We solved the state system (1) by using a forward sweep loop with initial conditions using an initial guess of the control.
- Step 3: After obtaining the solution for the state system, we use backward loop to solve the co-states or adjoins system using transversal or terminal conditions.
- Step 4: We update a control u^* in each iteration by using the values of the optimality system obtained in the previous iterations.
- Step 5: The procedure is continued iteratively till the convergence is achieved.

In order to obtain the entire procedure of what actually is occurring, the simulation of all-related populated is observed before we give the ARV treatment and after it. Numerical simulations will be illustrated by taking the set of parameter values from the article by [2] and we serve the data in Table 3.1.

Parameter	Value	Parameter	Value
Λ	0.55	δ_1	0.0909
d	0.0196	δ_2	0.0667
eta	0.03	k1	0.15
α_1	0.25	μ_1	0.03
$lpha_2$	0.01	c	0.0776

Table 3.1: Descriptions and parameters are from [2]

Figure 1 shows at initial period of a giving control strategy up to the sixth year, the maximum given optimal control is one. That at the seventh year, the given control strategy ARV decreases slowly reaches to zero at the final time. It means the control strategy ARV at initial time is given with the maximum control range because of the infected-HIV and full-blown HIV (AIDS) subpopulations have the highest level virus, then decreases to zero at the final time when the infected-HIV and full-blown HIV (AIDS) subpopulations show the good progress that the symptom of HIV-AIDS does not appear. It is suitable with our analytical solution that a set of optimal control is in equation (2.4) that is $U = \{u(t) : 0 \le u(t) \le 1, t \in [0, t_f]\}$. In the next subsection we will show the behavior and interpretation of the system when we give the ARV control strategy or not.

Furthermore when the control strategy in Figure 1 is given to the HIV-infection patient. The simulation result can be seen in the following figures. Figure 2 (A) shows the change of susceptible with and without control depend on time. At the beginning susceptible subpopulation without control decreases up to 0.63 at the fifth year. It is because of several factors for example natural death, the susceptible subpopulation changes their sex habit hence can avoid from HIV/AIDS risk, and susceptible subpopulation become infected subpopulation since they make



Figure 1: Numerical simulation of control strategy using parameters in Table 3.1.



Figure 2: Numerical simulation of susceptible and infected subpopulation with and without treatment using parameters in Table 3.1

a contact (sex, injection, etc.) with infected-HIV subpopulation. Furthermore the susceptible subpopulation without control increases after the fifth year until stable. It is because of the recruitment rate. When susceptible subpopulation is given the ARV control, the susceptible subpopulation decreases at the beginning. However that decreasing appear up to the fifteenth-year. Furthermore the susceptible subpopulation with control continuously increases up to 200 year.

When the susceptible subpopulation make a contact with HIV-infected subpopulation hence the HIV-infected subpopulation without the ARV control strategy increases. Moreover the successful of the treatment for the infected subpopulation increases the infected subpopulation. The treatment process is successful when the infected subpopulation make a treatment and the result is still infected subpopulation. And the other hand the process is fail when the infected subpopulation become full-blown HIV (AIDS). Furthermore the infected subpopulation without control decreases at the final time. It is because the infected subpopulation become full-blown



Figure 3: Numerical simulation of full-blown HIV (AIDS) and treatment subpopulations with and without treatment using parameters in Table 3.1.

HIV (AIDS) and there is a natural death. When there is a risk of the change of the infected subpopulation become full-blown HIV (AIDS), the ARV control will be given into the infected subpopulation until the infected subpopulation with control decreases started from the first year up to 200 year.

Figure 3 (A) explains the full-blown HIV (AIDS) subpopulation without control increases starting from the first year up to seventh year. It is because the infected subpopulation becomes full-blown HIV (AIDS) and there is the fail of the treatment on the HIV-infected subpopulation. After the seventh years the full-blown HIV (AIDS) decreases because of the death factor, such that full-blown HIV (AIDS) reaches 2.1582 at the final time. The consumption of ARV treatment for HIV-infected subpopulation can make full-blown HIV (AIDS) decreases faster than without giving treatment (control). It means the treatment for HIV-infected subpopulation effectively decreases full-blown HIV (AIDS) in Figure 3 (A) because of giving treatment as in Figure 1.

For the treatment subpopulation, we can analyze from Figure 3 (B). We see that the treatment subpopulation decreases and reaches zero value. It means there is no HIV-infected subpopulation doing the treatment process. If we give the treatment into HIV-infected subpopulation then the treatment subpopulation increases since the first day giving the ARV. Or we can say when the population of HIV-infection and full-blown HIV are treated with the ARV, it totally changes all population into the treatment population. It is because there are successful and fail of the treatment. Hence the treatment subpopulation decreases. The other hand death factor can decrease treatment subpopulation at final time.

Figure 4 (A) tells us that recovered subpopulation without giving control decreases since the first day of giving ARV. It means only a little the susceptible subpopulation have been changed their sexual habit. It is different when we give the control into recovered subpopulation. The control strategy on the recovered subpopulation increases since the 60th year up to 200th year. Even thought at the initial time the recovered subpopulation with control decreases, the giving control into HIV-infected subpopulation can increases recovered subpopulation.

The behavior of the solution in this research numerically similar as the solution given by [2]. The strength of our research is we can give the result the effectiveness of control strategy by giving the ARV treatment into HIV/AIDS populations such that the cost is minimum.



Figure 4: (A) Numerical simulation of recovered subpopulations with and without treatment. (B) Numerical simulation of the objective functional $J(u^*(t))$ in equation (2.3) as a cost function subject to the state system (2.1) when the combined ARV treatment is administered by using parameters in Table 3.1.

An optimal control purpose is to find the optimal control that minimize the functional. In the same way, we want to find the cost of the treatment that minimize the functional such that the effectiveness of the control strategy can be reached.

Figure 4 (B) tells us the functional objective decreases continuously from around 3600 at iteration 1-9 then stay stable around 1100 up to final time. It shows the cost function of the control strategy and the effectiveness of the ARV treatment applied for HIV-infected and full-blown HIV (AIDS) subpopulations. Finally we can give the result that giving the ARV treatment as control strategy for HIV-infected and full-blown HIV (AIDS) significantly increasing the recovered population. It show that the effectiveness and the successful of the ARV treatment can be reached as control strategy on HIV/AIDS epidemic model.

4. CONCLUSIONS

The epidemic model of HIV/AIDS has been derived. Optimal control analysis have been done by proving the boundedness and positivity of solutions. We have proved an existence an optimal control of the system. It means we can find the global minimum of optimal control that minimize the functional objective. The Minimum-Pontryagin principle has applied to get the optimally system such that the functional objective can reach the minimum of the individual with HIV infection, full-blown HIV (AIDS), and the cost of the treatment given to the individual with HIV/AIDS infection. The numerical simulation shows that the system with a given control ARV treatment can decrease the individual with HIV infection significantly. Our result coincides with that of [2] so that the effectiveness of an ARV treatment can be shown.

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