Application of optimal control strategies to HIVmalaria co-infection dynamics

by Fatmawati Fatmawati

PAPER · OPEN ACCESS

Application of optimal control strategies to HIV-malaria co-infection dynamics

To cite this article: Fatmawati *et al* 2018 *J. Phys.: Conf. Ser.* **974** 012057

Related content

Application of optimal control strategies to HIV-malaria co-infection dynamics

Fatmawati*, Windarto, Lathifah Hanif
Department of Mathematics, Faculty of Science and Technology, Universitas Airlangga, Surabaya 60115, Indonesia

E-mail: `fatmawati@fst.unair.ac.id`, `fatma47unair@gmail.com`

Abstract. This paper presents a mathematical model of HIV and malaria co-infection transmission dynamics. Optimal control strategies such as malaria preventive, anti-malaria and antiretroviral (ARV) treatments are considered into the model to reduce the co-infection. First, we studied the existence and stability of equilibria of the presented model without control variables. The model has four equilibria, namely the disease-free equilibrium, the HIV endemic equilibrium, the malaria endemic equilibrium, and the co-infection equilibrium. We also obtain two basic reproduction ratios corresponding to the diseases. It was found that the disease-free equilibrium is locally asymptotically stable whenever their respective basic reproduction numbers are less than one. We also conducted a sensitivity analysis to determine the dominant factor controlling the transmission. sic reproduction numbers are less than one. We also conducted a sensitivity analysis to determine the dominant factor controlling the transmission. Then, the optimal control theory for the model was derived analytically by using Pontryagin Maximum Principle. Numerical simulations of the optimal control strategies are also performed to illustrate the results. From the numerical results, we conclude that the best strategy is to combine the malaria prevention and ARV treatments in order to reduce malaria and HIV co-infection populations.

1. Introduction

HIV (Human Immunodeficiency Virus) is the infectious diseases that can develop into AIDS (Acquired Immune Deficiency Syndrome). HIV infects the immune system and weakens human defence system against infections and some types of cancer. A weakened immune in patients with HIV/AIDS will lead to a variety of bacteria/viruses are easy to infect the body (opportunistic infections). Until now, HIV/AIDS is untreatable disease, but the effective antiretroviral (ARV) drugs could control the disease. Moreover, a HIV patient with antiretroviral therapy could can enjoy healthy, long and productive lives [1].

Malaria is a contagious disease that is still a major health problem in the world. The disease is caused by parasites that are transmitted to people through the bites of infected female Anopheles mosquitoes. The female mosquito Anopheles require human blood for their reproductive process. In 2015, WHO reported that there are 91 countries and areas had ongoing malaria transmission. Malaria is preventable and curable, and increased efforts are dramatically reducing the malaria burden in many places [2].

Until now, malaria has not been regarded as an opportunistic infection of HIV disease. However, the weakening of the immune system due to HIV infection affects an increase in

malaria infections infected people. Malaria and HIV co-infection has caused more than 2 million deaths every year [3]. In areas highly endemic malaria, HIV-infected individuals more at risk of developing severe malaria. Some reports also recommend that antimalarial therapy failure might be more common in HIV-infected adults with low CD4-cell counts compared to those not infected with HIV. People who are stricken with acute malaria increases viral replication so that the increase in HIV viral load in patients with HIV [4].

Mathematical models are useful to analyze the transmission dynamics of HIV and malaria co-infection. The dynamics of HIV and malaria co-infection spread have been conducted in the literature [5, 6, 7]. For instance, the authors in [5] constructed and analyzed a simple mathematical model to study the co-infection of HIV and malaria. Mukandavire et al. [6] formulated and analyzed a realistic mathematical model for HIV-malaria co-infection, which combines the key epidemiological and biological features of each of the two diseases. Nyabadza et al. [7] developed a mathematical model to describe population dynamics of HIV/AIDS and malaria co-infections.

The optimal control strategies have been employed in the study of epidemiological models such as HIV, TB, Malaria, HCV, co-infection TB-HIV and Malaria-Cholera diseases dynamics [8, 9, 10, 11, 12, 13, 14]. Very little studies have been applied the optimal control to HIV and malaria co-infection model that conducted researchers. Recently, the authors in [15] have used optimal control strategies for a nonlinear dynamical system to describe the dynamics and effects of HIV-malaria co-infection in a workplace. In this paper, we developed a mathematical model of the HIV and malaria co-infection transmission dynamics of incorporate malaria preventive, anti-malaria treatment and ARV treatment for HIV as control optimal strategies.

The remainder of this paper is organized as follows. In Section 2, we propose a mathematical model of HIV and malaria co-infection transmission with controls on malaria prevention, anti-malaria and ARV treatments. In Section 3, we analyze the model without controls and perform sensitivity analysis of the basic reproduction numbers. In the Section 4, we present the optimal control analysis. In Section 5, we perform some numerical simulations to illustrate the purpose of the treatments. The conclusion of is presented in the last section.

2. Model formulation

In general, the population is classified into two classes namely human (host) population and the mosquito (vector) population. The human population was assumed to be homogeneous and closed. The total human population at time t, denoted by $N(t)$, is classified into five classes, namely, the class of susceptible population $(S(t))$, the class of the infected with malaria only $(I_m(t))$ and susceptible to HIV, the class of the infected with HIV only and susceptible to malaria $(I_h(t))$, the class of the infected with HIV and malaria both $(I_{hm}(t))$, and the class of the infected with AIDS population $(A(t))$. Hence, the total human population $N(t) = S(t) + I_m(t) + I_h(t) + I_{hm}(t) + A(t)$.

We also assume that the susceptible cannot get HIV and malaria infection simultaneously at the same time. The class of individuals with AIDS $(A(t))$ and dually infected individuals $(I_{hm}(t))$ are isolated, so that they cannot infect anyone.

The total vector population at time t, denoted by $N_v(t)$, is classified into two classes, namely, the class of susceptible vector population $(S_v(t))$ and the class of infected vector $(I_v(t))$. Thus, $N_v(t) = S_v(t) + I_v(t)$.

We suppose the malaria prevention $(u_1(t))$, anti-malaria treatment $(u_2(t))$ and the ARV treatment $(u_3(t))$ as the control efforts to reduce the HIV and malaria infection respectively. The control functions u_1, u_2 and u_3 are defined on interval $[0, t_f]$, where $0 \leq u_i(t) \leq 1$, $t \in [0, t_f], i = 1, 2, 3$ and t_f denotes the final time of the controls.

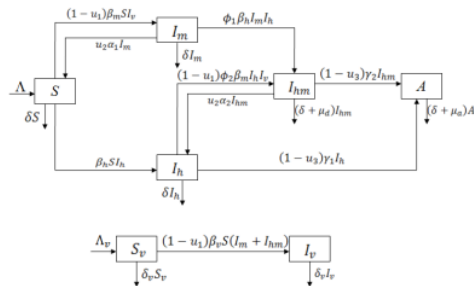the transmission diagram for deriving our model was shown in the Figure 1.

Figure 1. HIV and malaria co-infection transmission diagram.

The model is as follows.

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - (1-u_1)\beta_m S I_v - \beta_h S I_h + u_2\alpha_1 I_m - \delta S, \\
\frac{dI_m}{dt} &= (1-u_1)\beta_m S I_v - u_2\alpha_1 I_m - \phi_1\beta_h I_m I_h - \delta I_m, \\
\frac{dI_h}{dt} &= \beta_h S I_h + u_2\alpha_2 I_{hm} - (1-u_1)\phi_2\beta_m I_h I_v - (1-u_3)\gamma_1 I_h - \delta I_h, \\
\frac{dI_{hm}}{dt} &= \phi_1\beta_h I_m I_h + (1-u_1)\phi_2\beta_m I_h I_v - u_2\alpha_2 I_{hm} - (\delta+\mu_d)I_{hm} - (1-u_3)\gamma_2 I_{hm}, \\
\frac{dA}{dt} &= (1-u_3)\gamma_1 I_h + (1-u_3)\gamma_2 I_{hm} - (\delta+\mu_a)A, \\
\frac{dS_v}{dt} &= \Lambda_v - (1-u_1)\beta_v S_v(I_m + I_{hm}) - \delta_v S_v, \\
\frac{dI_v}{dt} &= (1-u_1)\beta_v S_v(I_m + I_{hm}) - \delta_v I_v.
\end{aligned}
\tag{1}
$$

Table 1. Parameters of model

Description	Parameter
Infection rate for HIV	β_h
Progression rate from malaria to HIV-malaria co-infection	ϕ_1
Progression rate from HIV to HIV-malaria co-infection	ϕ_2
Recovery rate from malaria	α_1
Recovery rate from malaria among HIV-malaria	α_2
Progression rate from HIV only to AIDS	γ_1
Progression rate from HIV-malaria co-infection to AIDS	γ_2
Disease AIDS induced death rate	μ_a
Disease HIV-malaria induced death rate	μ_d
Recruitment rate into the host population	Λ
Recruitment rate into the vector population	Λ_v
Infection rate for host	β_m
Infection rate for vector	β_v
Natural death rate for host	δ
Natural death rate for vector	δ_v

The region of biological interest of the model (1) is

$$\hbar = \hbar_h \times \hbar_v \subset \Re_+^5 \times \Re_+^2,$$

with

$$\hbar_h = \left\{ (S(t), I_m(t), I_h(t), I_{hm}(t), A(t)) \in \Re_+^5 : 0 \leq N_h(t) \leq \frac{\Lambda}{\delta} \right\},$$

and

$$\hbar_v = \left\{ (S_v(t), I_v(t)) \in \Re_+^2 : 0 \leq N_v(t) \leq \frac{\Lambda_v}{\delta_v} \right\}.$$

It is assumed that all parameters used in the model (1) are non-negative. The description of the parameters is given in Table 1. The region $\hbar$ is positively invariant. Hence, model (1) is well-posed in this region since any vector fields on the boundary will not move to the exterior region. So, if it was given any non-negative initial condition in $\Re_+^7$, then the solution was defined for any time $t \geq 0$ and the solution remain in the region. We desire to minimize the number of a HIV and malaria co-infection while keeping the costs of applying malaria preventive, anti-malaria and ARV treatment controls as low as possible. The cost function is defined as

$$J(u_1, u_2, u_3) = \int_0^{t_f} \left(I_m + I_{hm} + A + I_v + \frac{c_1}{2} u_1^2 + \frac{c_2}{2} u_2^2 + \frac{c_3}{2} u_3^2 \right) dt, \quad (2)$$

where c_1, c_2 and c_3 are the weighting constants for malaria preventive, anti-malaria and ARV treatment efforts, respectively. We take a quadratic form for measuring the control cost [8, 10]. The term $c_1 u_1^2, c_2 u_2^2$ and $c_3 u_3^2$ describe the cost associated with the malaria preventive, anti-malaria and ARV treatment controls respectively. The cost of malaria preventive is associated with the costs of vaccination, spraying of insecticide, personal protection and insecticide treated bed nets. Larger values of c_1, c_2 and c_3 will imply more expensive implementation cost for malaria preventive, anti-malaria and ARV treatment efforts. Our goal is to find an optimal control pair u_1^*, u_2^* and u_3^* such that

$$J(u_1^*, u_2^*, u_3^*) = \min_{\Gamma} J(u_1, u_2, u_3), \quad (3)$$

where $\Gamma = \{(u_1, u_2, u_3) | 0 \leq u_i \leq 1, i = 1, 2, 3\}$.

3. Model and sensitivity analysis

Consider the mathematical model in eq. (1) without the control functions u_1, u_2 and u_3. Let

$$
\begin{aligned}
R_m &= \frac{\sqrt{\beta_m \beta_v \Lambda \Lambda_v}}{\delta \delta_v} \\
R_h &= \frac{\beta_h \Lambda}{\delta(\delta + \gamma_1)}.
\end{aligned}
$$

Parameters R_m and R_h are basic reproduction ratio corresponding to the malaria infection, and HIV infection, respectively. These ratios define number of secondary cases of primary case throughout the infective period because of the type of infection [16, 17].

By setting $u_1 = u_2 = u_3 = 0$, the mathematical model in eq. (1) has four equilibria (to the coordinate $(S, I_m, I_h, I_{hm}, A, S_v, I_v)$, namely,

1. The disease-free equilibrium $E_0 = (\frac{\Lambda}{\delta}, 0, 0, 0, 0, \frac{\Lambda_v}{\delta_v}, 0)$.

2. The malaria endemic equilibrium $E_m = \left(\frac{\Lambda}{\beta_m I_v + \delta}, \frac{\beta_m \Lambda I_v}{\delta(\beta_m I_v + \delta)}, 0, 0, 0, \frac{\Lambda_v}{\beta_v I_m + \delta_v}, \frac{\beta_v \Lambda_v I_m}{\delta_v(\beta_v I_m + \delta_v)} \right)$.

3. The HIV endemic equilibrium $E_h = \left(\frac{\gamma_1 + \delta}{\beta_h}, 0, \delta(\gamma_1 + \delta)(R_h - 1), 0, \frac{\gamma_1 I_h}{\delta + \mu_a}, \frac{\Lambda_v}{\delta_v}, 0 \right)$. The equilibrium E_h exists if $R_h > 1$.

4. The HIV-malaria endemic equilibrium $E_{hm} = (S^*, I_m^*, I_h^*, I_{hm}^*, A^*, S_v^*, I_v^*)$, with

$$
\begin{aligned}
S^* &= \frac{\phi_2 \beta_m I_v + \gamma_1 + \delta}{\beta_h}, \\
I_m^* &= \frac{\beta_m S I_v}{\phi_1 \beta_h I_h + \delta}, \\
I_h^* &= \frac{\Lambda - \beta_m S I_v - \delta S}{\beta_h S}, \\
I_{hm}^* &= \frac{\phi_1 \beta_h I_m I_h + \phi_2 \beta_m I_h I_v}{\mu_d + \delta + \gamma_2}, \\
A^* &= \frac{\gamma_1 I_h + \gamma_2 I_{hm}}{\delta + \mu_a}, \\
S_v^* &= \frac{\Lambda_v}{\beta_v(I_m + I_{hm}) + \delta_v}, \\
I_v^* &= \frac{\beta_v S_v(I_m + I_{hm})}{\delta_v}.
\end{aligned}
$$

The equilibrium E_{hm} exists if $R_h > 1$ and $\delta(\delta + \gamma_1)(R_h - 1) > \phi_2 \beta_m^2 I_v^2 + \beta_m(\delta + \gamma_1)I_v + \delta \phi_2 \beta_m I_v$.

The following theorem give the stability criteria of the disease-free equilibrium.

Theorem 1 *The disease-free equilibrium E_0 is locally asymptotically stable whenever $R_m, R_h < 1$. Furthermore, the equilibrium E_0 is unstable if $R_m, R_h > 1$.*

Proof. Linearizing the mathematical model in eq. (1) near the equilibrium E_0 gives eigenvalues $-\delta, -\delta_v, -(\delta + \mu_a), -(\delta + \mu_d + \gamma_2), -(\delta + \gamma_1)(R_h - 1)$ and the roots of quadratic equation $x^2 + (\delta + \delta_v)x + \delta\delta_v(1 - T_m) = 0$, with $T_m = \frac{\beta_m \beta_v \Lambda \Lambda_v}{\delta^2 \delta_v^2}$. The quadratic equation have negative roots if $T_m < 1$ or equivalently $R_m < 1$. It is clear that all of the eigenvalues are negative if $R_h < 1$ and $R_m < 1$. So, if $R_m, R_h < 1$, then the equilibrium E_0 is locally asymptotic stable. Otherwise, it is unstable.

Next, we analyze the sensitivity of the basic reproduction numbers R_m and R_h to the parameters in the presented model. The purpose of this analysis was to find the parameters that have the greatest effects on the reproduction numbers. By using the method in [18], we derived the analytical expression for sensitivity index of the R_m and R_h to each parameters.

The sensitivity indices of a variable, R_0, that depends differentially on a parameter, l, is defined as

$$
\Upsilon_l^{R_0} := \frac{\partial R_0}{\partial l} \times \frac{l}{R_0}. \tag{4}
$$

Now, by using the parameter values in the Table 2, we have the following results in Table 3. For example, the sensitivity index of R_m with respect to β_m is

$$\Upsilon_{\beta_m}^{R_m} := \frac{\partial R_m}{\partial \beta_m} \times \frac{\beta_m}{R_m} = 0.5. \tag{5}$$

The sensitivity indices of R_m and R_h with respect to other parameters such as Λ, Λ_v, β_v, δ, δ_v, β_h, γ_1, can be derived in the same way as (5). The interpretation of the sensitivity index is as follow. Since $\Upsilon_{\beta_m}^{R_m} = 0.5$, that is to say, increasing (or decreasing) infection rate for malaria, β_m, by 10%, increases (or decreases) the reproduction number R_m by 5%. Thus, increasing (or decreasing) natural death rate δ by 10% decreases (increases) R_m by 10%.

Table 2. Parameter values.

Parameter	Value	Ref.
Λ	500/year	Assumed
δ	0.02/year	[13]
β_h	0.00031/year	Assumed
β_m	0.00045/year	Assumed
β_v	0.00035/year	Assumed
γ_1	0.01/year	Assumed
γ_2	0.05/year	Assumed
Λ_v	5000/year	Assumed
δ_v	0.1429/year	[18]
ϕ_1	1.1/year	Assumed
ϕ_2	1.15/year	Assumed
μ_a	0.02/year	Assumed
μ_d	0.03/year	Assumed
α_1	0.2/year	Assumed
α_2	0.2/year	Assumed

Table 3. Sensitivity indices to parameter for model (1).

Parameter	Sensitivity index (R_m)	Parameter	Sensitivity index (R_h)
Λ	0.5	Λ	1
Λ_v	0.5	β_h	1
β_m	0.5	δ	-1.67
β_v	0.5	γ_1	-0.33
δ	-1		
δ_v	-1		

4. Mathematical analysis of optimal control

In this section, we consider the mathematical model in eq. (1) with its control functions u_1, u_2 and u_3. We describe the cost function in eq. (2) for the model in eq. (1). The necessary conditions to find the optimal controls u_1^*, u_2^* and u_3^* such that condition (3) with constraint model (1) must satisfy come from the Pontriyagin Maximum Principle [19]. The principle converts the equations (1) - (3) into minimizing Hamiltonian function H problem with respect (u_1, u_2, u_3), that is

$$H(S, I_m, I_h, I_{hm}, A, S_v, I_v, u_1, u_2, u_3, \lambda_1, \lambda_2, \cdots, \lambda_7) =$$

$$I_m + I_{hm} + A + I_v + \frac{c_1}{2} u_1^2 + \frac{c_2}{2} u_2^2 + \frac{c_3}{2} u_3^2 + \sum_{i=1}^{7} \lambda_i g_i,$$

where g_i is the right hand side of the mathematical model in eq. (1) which is the i-th state variable equation. The variables $\lambda_i, \ i = 1, 2, \ldots, 7$, are called adjoint variables satisfying the following co-state equations

$$\frac{d\lambda_1}{dt} = (\lambda_1 - \lambda_2)(1 - u_1)\beta_m I_v + (\lambda_1 - \lambda_3)\beta_h I_h + \lambda_1 \delta,$$

$$\frac{d\lambda_2}{dt} = -1 + (\lambda_2 - \lambda_1)\alpha_1 u_2 + (\lambda_2 - \lambda_4)\phi_1 \beta_h I_h + (\lambda_6 - \lambda_7)(1 - u_1)\beta_v S_v + \lambda_2 \delta,$$

$$\frac{d\lambda_3}{dt} = (\lambda_1 - \lambda_3)\beta_h S + (\lambda_2 - \lambda_4)\phi_1 \beta_h I_h + (\lambda_3 - \lambda_4)(1 - u_1)\phi_2 \beta_m I_v$$
$$+ (\lambda_3 - \lambda_5)(1 - u_3)\gamma_1 + \lambda_3 \delta,$$

$$\frac{d\lambda_4}{dt} = -1 + (\lambda_4 - \lambda_3)u_2 \alpha_2 + (\lambda_4 - \lambda_5)(1 - u_3)\gamma_2 + (\lambda_6 - \lambda_7)(1 - u_1)\beta_v S_v +$$
$$\lambda_4(\delta + \mu_d), \qquad\qquad (6)$$

$$\frac{d\lambda_5}{dt} = -1 + \lambda_5(\delta + \mu_d),$$

$$\frac{d\lambda_6}{dt} = (\lambda_6 - \lambda_7)(1 - u_1)\beta_v(I_h + I_{hm}) + \lambda_6 \delta_v,$$

$$\frac{d\lambda_7}{dt} = -1 + (\lambda_1 - \lambda_2)(1 - u_1)\beta_m S + (\lambda_3 - \lambda_4)(1 - u_1)\phi_2 \beta_m I_h + \lambda_7 \delta_v,$$

where the transversality conditions $\lambda_i(t_f) = 0, i = 1, \ldots, 7$.

By using Pontryagin's Maximum Principle and the existence result for the optimal control pairs, the steps to obtain the optimal controls $u = (u_1^*, u_2^*, u_3^*)$ are as following [20, 21].

(i) Minimize the Hamiltonian function H with respect to u, that is $\frac{\partial H}{\partial u} = 0$ which is the stationary condition. Hence, we find

$$u_1^* = \begin{cases} 0 & \text{for} \quad u_1 \leq 0 \\ \frac{(\lambda_4 - \lambda_3)\phi_2 \beta_m I_v I_h + (\lambda_2 - \lambda_1)\beta_m S I_v + (\lambda_7 - \lambda_6)\beta_v S_v(I_h + I_{hm})}{c_1} & \text{for} \quad 0 < u_1 < 1 \\ 1 & \text{for} \quad u_1 \geq 1 \end{cases}$$

$$u_2^* = \begin{cases} 0 & \text{for} \quad u_2 \leq 0 \\ \frac{(\lambda_4 - \lambda_3)I_{hm}\alpha_2 + (\lambda_2 - \lambda_1)\alpha_1 I_h}{c_2} & \text{for} \quad 0 < u_2 < 1 \\ 1 & \text{for} \quad u_2 \geq 1 \end{cases}$$

$$u_3^* = \begin{cases} 0 & \text{for} \quad u_3 \leq 0 \\ \frac{(\lambda_5 - \lambda_3)\gamma_1 I_h + (\lambda_5 - \lambda_4)\gamma_2 I_{hm}}{c_3} & \text{for} \quad 0 < u_3 < 1 \\ 1 & \text{for} \quad u_3 \geq 1 \end{cases}$$

(ii) Solve the state system $\dot{x}(t) = \frac{\partial H}{\partial \lambda}$ which is the mathematical model in eq. (1), where $x = (S, I_m, I_h, I_{hm}, A, S_v, I_v)$, $\lambda = (\lambda_1, \lambda_2, ..., \lambda_7)$ and the initial condition $x(0)$.

(iii) Solve the co-state system $\dot{\lambda}(t) = -\frac{\partial H}{\partial x}$ which is the system in eq. (6) with the final condition $\lambda_i(t_f) = 0$, $i = 1, \ldots, 7$.

Henceforth, we find the following theorem.

Theorem 2 *The optimal controls (u_1^*, u_2^*, u_3^*) that minimizes the objective function $J(u_1, u_2, u_3)$ on Γ is given by*

$$u_1^* = \max\left\{0, \min\left(1, \frac{(\lambda_4 - \lambda_3)\phi_2\beta_m I_v I_h + (\lambda_2 - \lambda_1)\beta_m SI_v + (\lambda_7 - \lambda_6)\beta_v S_v(I_h + I_{hm})}{c_1}\right)\right\}$$

$$u_2^* = \max\left\{0, \min\left(1, \frac{(\lambda_4 - \lambda_3)I_{hm}\alpha_2 + (\lambda_2 - \lambda_1)\alpha_1 I_h}{c_2}\right)\right\},$$

$$u_3^* = \max\left\{0, \min\left(1, \frac{(\lambda_5 - \lambda_3)\gamma_1 I_h + (\lambda_5 - \lambda_4)\gamma_2 I_{hm}}{c_3}\right)\right\}$$

where λ_i, $i = 1, ..., 7$ is the solution of the co-state equations (6) with the transversality conditions $\lambda_i(t_f) = 0$, $i = 1, \ldots, 7$.

Substituting the optimal control (u_1^*, u_2^*, u_3^*) which is achieved from the state system in eq. (1) and the co-state system in eq. (6), we find an optimal system. The solutions of the optimality system will be solved numerically for some choices of the parameter. Because of lack of data, most of parameter values are assumed within realistic ranges for a typical scenario.

5. Numerical simulation

In this section, we perform some numerical simulations of the presented model in eq. (1) with and without optimal control. The optimal control strategy is found by the iterative method of the fourth order Runge-Kutta method. The state equations are initially solved by the forward Runge-Kutta method of the fourth order. Then, by using the backward Runge-Kutta method of the fourth order, we solved the co-state equations with the transversality conditions. The controls are updated by using a convex combination of the previous controls and the value from the characterizations of u_1^*, u_2^* and u_3^*. This process is reiterated and the iteration is ended if the current state, the adjoint, and the control values converge sufficiently [22].

We present four scenarios. In the first situations, we study combination of the malaria preventive and the anti-malaria treatment as control strategy. In the second scenario, we consider combination of the malaria preventive and ARV treatment controls. In the third scenario, we use the combination of the anti-malaria and ARV treatment controls. In the last one, we use the combination of the malaria preventive, anti-malaria and ARV treatment as control strategy. Parameters used in these simulations given in Table 2. In these simulations, we use initial condition $(S(0), I_m(0), I_h(0), I_{hm}(0), A(0), S_v(0), I_(0)) = (500, 100, 50, 30, 50, 5000, 100)$, weighting constants $c_1 = 20$, $c_2 = 50$, $c_3 = 50$.

5.1. First scenario

In this scenario, we apply the malaria prevention control u_1 and the anti-malaria treatment control u_2 to optimize the objective function J, while setting the ARV control u_3 to zero. For this scenario, we found in the Figure 2-3 that the population of malaria infected (I_m) and HIV-malaria co-infection (I_{hm}) decreases, while the population increases when there is no any controls. Similarly, the result in the Figure 4-5 show that the number of AIDS infected (A) and mosquito infected (I_v) a reduction in the number infected compared with the case without control. Hence, the malaria prevention and the anti-malaria treatment control gives a significant influence in controlling infected malaria, HIV-malaria co-infection and AIDS infected. The profile of the optimal treatment controls u_1^* and u_2^* for this scenario is presented in the Figure 6.
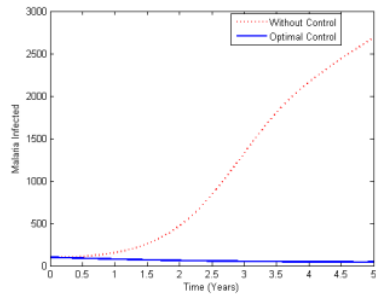
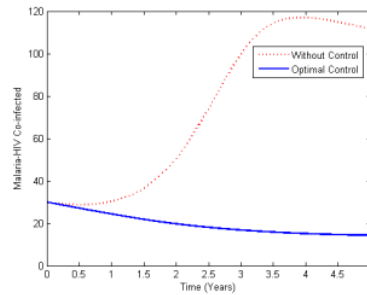**Figure 2.** The dynamics of I_m using the controls u_1^* and u_2^*.

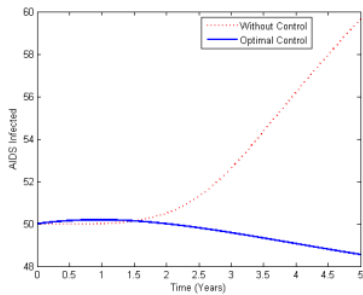**Figure 3.** The dynamics of I_{hm} using the controls u_1^* and u_2^*.

Figure 4. The dynamics of A using the controls u_1^* and u_2^*.
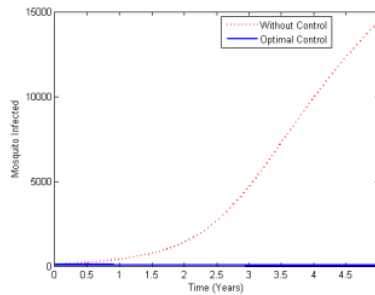

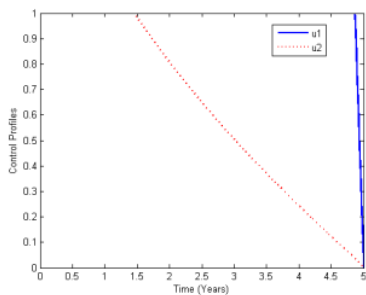**Figure 5.** The dynamics of I_v using the controls u_1^* and u_2^*.

Figure 6. The profile of the optimal controls u_1^* and u_2^*.

5.2. Second scenario

In the second scenario, we utilize the malaria prevention control u_1 and the ARV treatment control u_3 to optimize the objective function J, while set the anti-malaria treatment control u_2 to zero. The infected populations dynamics of this scenario are presented in Figure 7-10. We observe in Figure 7-8 that this control strategy results in a significant decrease in the number of malaria infected (I_m) and HIV-malaria co-infection (I_{hm}) compared with the case without control. Also in Figure 9-10, this control strategy results in a significant decrease in the number

of AIDS infected (A) and mosquito infected (I_v) as against an increase in the uncontrolled case. The result shown in the Figure 7-10 clearly suggests that this scenario is very effective in the control of the number of the infected. The control profiles of the malaria prevention and ARV treatment is shown in the Figure 11.
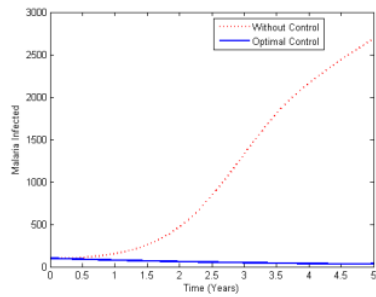

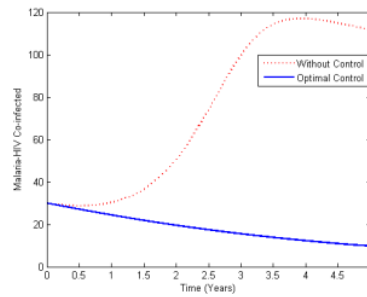**Figure 7.** The dynamics of I_m using the controls u_1^* and u_3^*.

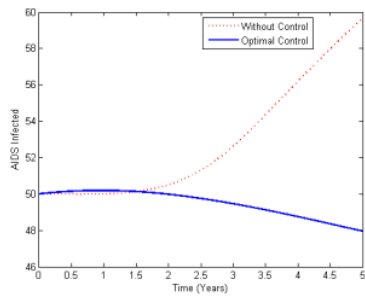**Figure 8.** The dynamics of I_{hm} using the controls u_1^* and u_3^*.

Figure 9. The dynamics of A using the controls u_1^* and u_3^*.
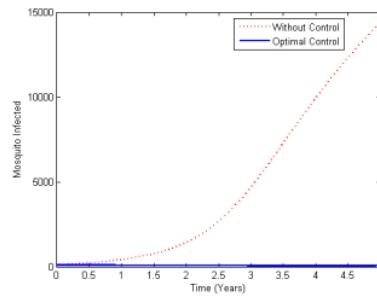

Figure 10. The dynamics of I_v using the controls u_1^* and u_3^*.
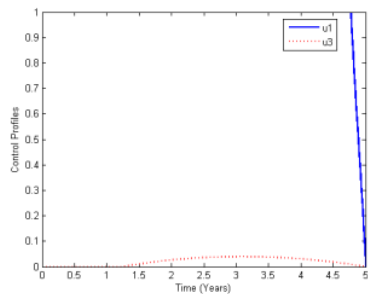

Figure 11. The profile of the optimal controls u_1^* and u_3^*.

5.3. Third scenario

In the third scenario, we active controls u_2 and u_3 on the anti-malaria and ARV treatment to optimize the objective function J whereas the malaria prevention control u_1 is set to zero. The dynamics of the infected populations of this scenario are given in Figure 12-15. We observe in Figure 12 that the malaria infected populations are lesser when the control strategy is used than when the control strategy is not implemented. It was also shown in Figure 13 that the number of HIV-malaria co-infection populations increases with this control strategy compared to the number without control. Figure 14-15 depict the number of AIDS infected and mosquito infected that the populations is higher with this control scenario than the cases without control. Figure 16 shows the control profiles of the anti-malaria (u_2) and ARV treatment (u_3) in which the control u_2 is given maximum in almost 5 years, while the the optimal control u_3 starts and remain at the lower bound in 5 years. The results show that the anti-malaria treatment give the positive impact to reduce the malaria infected, while the mosquito infected tend to increases using this strategy. Then, the HIV-malaria co-infection and AIDS infection populations also increase with this strategy due to there is no significant ARV treatment intervention.
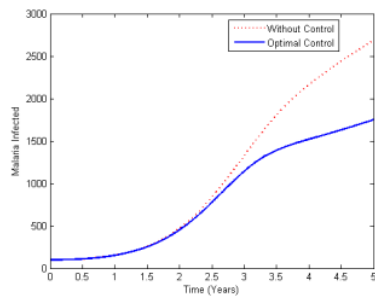

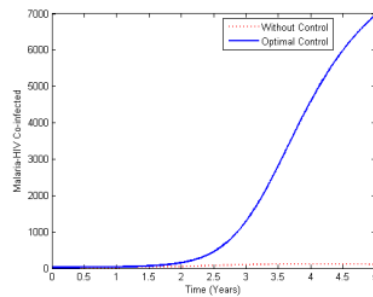**Figure 12.** The dynamics of I_m using the controls u_2^* and u_3^*.

Figure 13. The dynamics of I_{hm} using the controls u_2^* and u_3^*.
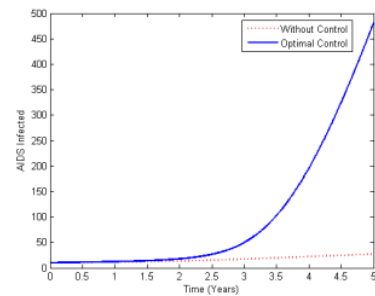

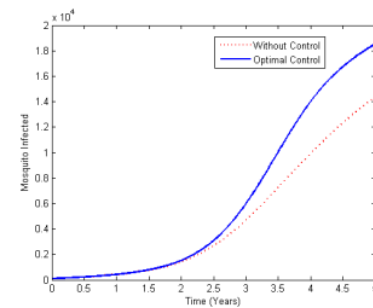**Figure 14.** The dynamics of A using the controls u_2^* and u_3^*.

Figure 15. The dynamics of I_v using the controls u_2^* and u_3^*.
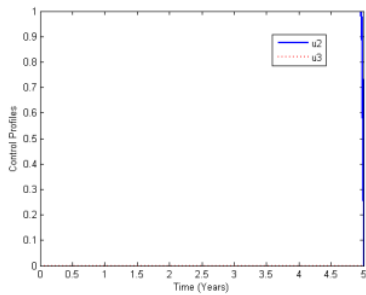
Figure 16. The profile of the optimal controls u_2^* and u_3^*.

5.4. Fourth scenario

In this scenario, all the controls (u_1, u_2 and u_3) are used to optimize the objective function J. The dynamics of the malaria infected, malaria-HIV co-infection, AIDS infection and mosquito infected are given in Figure 17-20. For this strategy, we observed in Figure 17-18 that the control strategies resulted in a decrease in the number of the malaria infected and HIV-malaria co-infection compared to the number without control. A similar reduction is observed in Figure 19-20 for AIDS infected and mosquito infected in the control strategy, while an increased number for the uncontrolled case resulted.
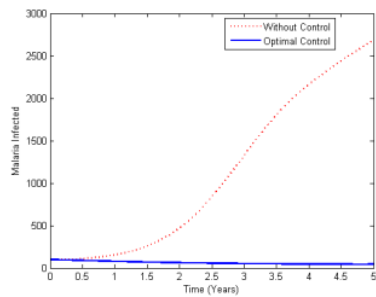

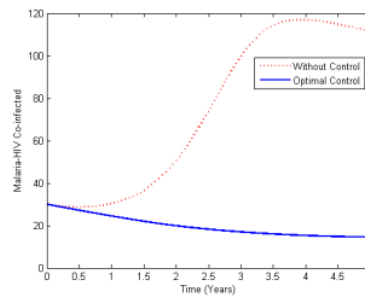**Figure 17.** The dynamics of I_m using the controls u_1^*, u_2^* and u_3^*.

Figure 18. The dynamics of I_{hm} using the controls u_1^*, u_2^* and u_3^*.

The profiles of the optimal malaria prevention u_1^*, anti-malaria treatment control u_2^* and ARV control u_3^* of this scenario is given in Figure 21. To reduce HIV and malaria co-infection in 5 years, the malaria prevention should be given intensively almost 5 years before dropping gradually until reaching the lower bound in the end 5th year. Meanwhile, anti-malaria treatment should be needed intensive effort during 1.5 years before finally dropping to its lower bound. While ARV treatment control decreases from 0.1 (10%) at the beginning time before finally dropping to its lower bound at the end of the intervention.

Based on the numerical results, the optimal control scenarios are arranged from the least to the costly based on the total cost function J. Table 4 shows the optimal values of the objective function J in the four scenarios. From Table 4, we conclude that the combination of the malaria
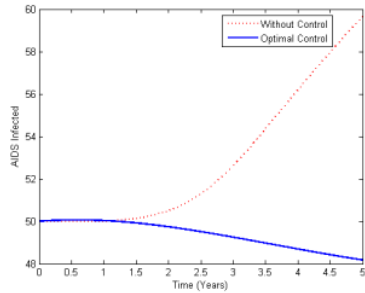
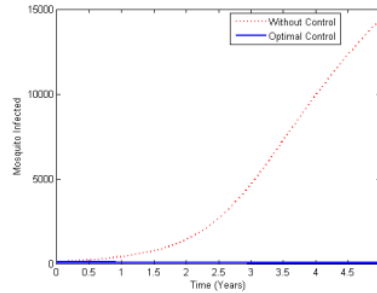**Figure 19.** The dynamics of A using the controls u_1^*, u_2^* and u_3^*

Figure 20. The dynamics of I_v using the controls u_1^*, u_2^* and u_3^*
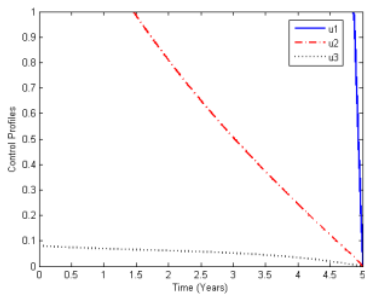

Figure 21. The profile of the optimal controls u_1^*, u_2^* and u_3^*

Table 4. Optimal values of the cost functional.

Scenario of the optimal control	Total cost functional J
u_1^*, and u_3^*	1.0359×10^3
u_1^*, u_2^*, and u_3^*	1.1234×10^3
u_1^*, and u_2^*	1.1237×10^3
u_2^*, and u_3^*	4.5127×10^4

preventive (u_1^*) and ARV treatment (u_3^*) have the least cost function followed by combination all controls $(u_1^*, u_2^*,$ and $u_3^*)$ to reduce the number of malaria infected, HIV-malaria co-infection, AIDS infected and mosquito infected.

6. Conclusion
In this paper, we have developed a deterministic mathematical model for the spread of malaria and HIV co-infection that incorporates malaria prevention, anti-malaria and ARV treatment as optimal control strategies. For the model without controls, we obtain two thresholds R_m and R_h which are basic reproduction ratios for the malaria and HIV diseases respectively. These ratios determine the existence and stability of the equilibria of the model. If the thresholds are less than unity then the diseases free equilibrium is locally asymptotically stable. Finally, the conditions for existence of optimal control is studied analytically using the Pontryagin Maximum

Principle. From our numerical analysis of the optimal control indicates that the best strategy is to combine the malaria prevention and ARV treatments followed by combination all controls in order to reduce malaria and HIV co-infection.

References

[1]   World Health Organization 2016 HIV/AIDS *Geneva: World Health Organization* [Online] Available from: http://www.who.int/mediacentre/factsheets/fs360/en/ [Accesed on 22nd Desember, 2016]

[2]   World Health Organization 2016 Malaria *Geneva: World Health Organization* [Online] Available from: http://www.who.int/mediacentre/factsheets/fs094/en/ [Accesed on 22nd Desember, 2016]

[3]   World Health Organization 2016 Malaria in HIV AIDS patients *Geneva: World Health Organization* [Online] Available from: http://www.who.int/malaria/areas/high_risk_groups/hiv_aids_patients/en/ [Accesed on 22nd Desember, 2016]

[4]   van Geertruyden J P 2014 Interaction between malaria and human immunodeciency virus onno *J. Vac. Sci. Technol.Clin Microbiol Infect* **20** 278

[5]   Barley K, Murillo D, Roudenko S, Tameru A M, and Tatum S 2012 A mathematical model of HIV and malaria co-infection in Sub-Saharan Africa *J. AIDS Clinic Res.* **3** 7

[6]   Mukandavire Z, Gumel A B, Garira W, Tchuenche J M 2009 Mathematical analysis of a model for HIV-malaria co-infection *Math. Biosci. Eng.* **6** 333

[7]   Nyabadza F, Bekele B T, Rua M A, Malonza D M, Chiduku N, and Kgosimore M 2015 The implication of HIV treatment on the HIV-malaria coinfection dynamic: a modeling perspective, *BioMed Res. Int.* **2015** article ID 659651.

[8]   Okosun K O, Makinde O D, Takaidza I 2013 Impact of optimal control on the treatment of HIV/AIDS and screening of unaware infectives *Appl. Math. Modelling* **37** 3802.

[9]   Ahmadin, Fatmawati 2014 Mathematical modeling of drug resistance in tuberculosis transmission and optimal control treatment *Appl. Math. Sci.* **8** 4547

[10] Makinde O D, Okosun K O 2011 Impact of chemo-therapy on optimal control of malaria disease with infected immigrants *Biosystems* **104** 32

[11] Fatmawati, Tasman H, 2015 An optimal control strategy to reduce the spread of malaria resistance *Math. Biosci.* **262** 73

[12] Mushayabasa S, 2017 Dynamics of HCV in the presence of optimal bleaching *Differ. Equ. Dyn. Syst.* **25** 101.

[13] Fatmawati, Tasman H, 2016 An optimal treatment control of TB-HIV coinfection *Int. J. Math. Math. Sci.* **2016** Article ID 8261208.

[14] Okosun K O, Makinde O D, 2014 A co-infection model of malaria and cholera diseases with optimal control *Math. Biosci.* **258** 19.

[15] Seidu B, Makinde O D, Seini I Y 2015 Mathematical analysis of the effects of HIV-malaria co-infection on workplace productivity, *Acta Biotheor.* **63** 151.

[16] Diekmann O, Heesterbeek J A P, Metz J A J 1990 On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogenous populations *J. Math. Biol.* **28** 362

[17] Diekmann O, Heesterbeek J A P 2000 *Mathematical Epidemiology of Infectious Diseases, Model Building, Analysis and Interpretation* (New York: John Wiley & Son)

[18] Chitnis N, Hyman J M, Cushing J M 2008 Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model *Bull. Math. Biol.* **70** 1272

[19] Pontryagin L S, Boltyanskii V G, Gamkrelidze R V, Mishchenko E F 1962 *The Mathematical Theory of Optimal Processes* (New York: Wiley)

[20] Lewis F L, Syrmos V L 1995 *Optimal Control* (New York: John Wiley & Sons)

[21] Naidu D S 2002 *Optimal Control Systems* (New York: CRC PRESS)

[22] Lenhart S, Workman J T 2007 *Optimal Control Applied to Biological Models* (London: John Chapman & Hall)

Application of optimal control strategies to HIVmalaria co-infection dynamics

20%	11%	18%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1   Marsudi, Noor Hidayat, Ratno Bagus Edy Wibowo. "Optimal control and sensitivity analysis of HIV model with public health education campaign and antiretroviral therapy", AIP Publishing, 2018
Publication   1%

2   Otieno, Gabriel, Joseph Koske, and John Mutiso. "Cost Effectiveness Analysis of Optimal Malaria Control Strategies in Kenya", Mathematics, 2016.
Publication   1%

3   Joshua Kiddy K. Asamoah, Farai Nyabadza, Baba Seidu, Mehar Chand, Hemen Dutta. "Mathematical Modelling of Bacterial Meningitis Transmission Dynamics with Control Measures", Computational and Mathematical Methods in Medicine, 2018
Publication   1%

4   Mudassar Imran, Muhammad Usman, Tufail Malik, Ali R. Ansari. "Mathematical analysis of   1%

the role of hospitalization/isolation in controlling the spread of Zika fever", Virus Research, 2018
Publication

5	files.ele-math.com Internet Source	1%
6	www.ncbi.nlm.nih.gov Internet Source	1%
7	www.who.int Internet Source	1%

8 Ana Carvalho, Carla M. A. Pinto. "A delay fractional order model for the co-infection of malaria and HIV/AIDS", International Journal of Dynamics and Control, 2016
Publication
1%

9 D. P. MOUALEU, J. MBANG, R. NDOUNDAM, S. BOWONG. "MODELING AND ANALYSIS OF HIV AND HEPATITIS C CO-INFECTIONS", Journal of Biological Systems, 2012
Publication
1%

10 theremustberocksinmyhead.blogspot.com
Internet Source
<1%

11 Yehuda Koren, L. Carmel, D. Harel. "ACE: a fast multiscale eigenvectors computation for drawing huge graphs", IEEE Symposium on Information Visualization, 2002. INFOVIS 2002., 2002
<1%

Publication

12 www.aimsciences.org
    Internet Source   <1 %

13 Roland Herzog, Karl Kunisch. "Algorithms for
    PDE-constrained optimization", GAMM-
    Mitteilungen, 2010   <1 %
    Publication

14 Alfred Hugo, Oluwole Daniel Makinde,
    Santosh Kumar, Fred F. Chibwana. "Optimal
    control and cost effectiveness analysis for   <1 %
    Newcastle disease eco-epidemiological model
    in Tanzania", Journal of Biological Dynamics,
    2016
    Publication

15 Ashrafi M. Niger. "Mathematical analysis of
    the role of repeated exposure on malaria
    transmission dynamics", Differential   <1 %
    Equations and Dynamical Systems, 07/2008
    Publication

16 Prabir Panja, Shyamal Kumar Mondal, Joydev
    Chattopadhyay. "Stability, Bifurcation and
    Optimal Control Analysis of a Malaria Model   <1 %
    in a Periodic Environment", International
    Journal of Nonlinear Sciences and Numerical
    Simulation, 2018
    Publication

17 Springer Proceedings in Mathematics & Statistics, 2014.
Publication
<1 %

18 www.scribd.com
Internet Source
<1 %

19 Hongda Shen, W. David Pan, Yuhang Dong, Mohammad Alim. "Lossless compression of curated erythrocyte images using deep autoencoders for malaria infection diagnosis", 2016 Picture Coding Symposium (PCS), 2016
Publication
<1 %

20 www.sdiarticle2.org
Internet Source
<1 %

21 Xueyan Bao, Xuefa Wen, Xiaomin Sun, Fenghua Zhao, Yuying Wang. "Interannual Variation in Carbon Sequestration Depends Mainly on the Carbon Uptake Period in Two Croplands on the North China Plain", PLoS ONE, 2014
Publication
<1 %

22 doi.org
Internet Source
<1 %

23 Maria Chiara D'Autilia, Ivonne Sgura, Benedetto Bozzini. "Parameter identification in ODE models with oscillatory dynamics: a Fourier regularization approach", Inverse Problems, 2017
<1 %

Publication

24 Leonardo Palombi, Stefania Moramarco. "Chapter 1 Health in Sub-Saharan Africa: HIV, TB and Malaria Epidemiology", Springer Science and Business Media LLC, 2018
Publication

<1%

25 Daozhou Gao, Shigui Ruan. "A Multipatch Malaria Model with Logistic Growth Populations", SIAM Journal on Applied Mathematics, 2012
Publication

<1%

26 Sulaiman Usman, Ibrahim Isa Adamu. "Modeling the Transmission Dynamics of the Monkeypox Virus Infection with Treatment and Vaccination Interventions", Journal of Applied Mathematics and Physics, 2017
Publication

<1%

27 T.K. Kar, Swapan Kumar Nandi, Soovoojeet Jana, Manotosh Mandal. "Stability and bifurcation analysis of an epidemic model with the effect of media", Chaos, Solitons & Fractals, 2019
Publication

<1%

28 www.rsisinternational.org
Internet Source

<1%

29 Augustino Isdory, Eunice W. Mureithi, David J. T. Sumpter. "The Impact of Human Mobility

<1%

on HIV Transmission in Kenya", PLOS ONE, 2015
Publication

30 Gumel, A.. "Effect of a preventive vaccine on the dynamics of HIV transmission", Communications in Nonlinear Science and Numerical Simulation, 200412
Publication
<1%

31 Ignacy Duleba, Wissem Khefifi. "Velocity space approach to motion planning of nonholonomic systems", Robotica, 2007
Publication
<1%

32 Omotayo S. Alaofin, Kantharuben Naidoo. "Prevalence of Human Immunodeficiency Virus and Malaria Co-Infection in Nigeria: A Review of Published Literature", Global Journal of Health Science, 2019
Publication
<1%

33 scottishjournal.co.uk
Internet Source
<1%

34 www.boffinaccess.com
Internet Source
<1%

35 www.lib.kobe-u.ac.jp
Internet Source
<1%

36 Anatoly B Schmidt. "Modeling the demand–price relations in a high-frequency foreign
<1%

exchange market", Physica A: Statistical Mechanics and its Applications, 1999
Publication

37 Dipo Aldila, Refqi Rifa Aprilliani, Maulana Malik. "Understanding HIV spread with vertical transmission through mathematical model", AIP Publishing, 2018
Publication
<1 %

38 S. Bowong, J. Kurths. "Modelling Tuberculosis and Hepatitis B Co-infections", Mathematical Modelling of Natural Phenomena, 2010
Publication
<1 %

39 Semu Mitiku Kassa, Senelani D. Hove-Musekwa. "Optimal control of allocation of resources and the economic growth in HIV-infected communities", Optimal Control Applications and Methods, 2014
Publication
<1 %

40 Soovoojeet Jana, Palash Haldar, T. K. Kar. "Mathematical analysis of an epidemic model with isolation and optimal controls", International Journal of Computer Mathematics, 2016
Publication
<1 %

41 repository.unair.ac.id
Internet Source
<1 %

42 scholar.ui.ac.id
Internet Source
<1 %

| 43 | 210.212.95.124
 Internet Source | <1% |

A. Ducrot. "A mathematical model for malaria involving differential susceptibility, exposedness and infectivity of human host", Journal of Biological Dynamics, 2009
Publication

| 44 | | <1% |

S. Athithan, Mini Ghosh, Xue-Zhi Li. "Mathematical modeling and optimal control of corruption dynamics", Asian-European Journal of Mathematics, 2018
Publication

| 45 | | <1% |

| 46 | advancesindifferenceequations.springeropen.com
 Internet Source | <1% |

| 47 | origem.info
 Internet Source | <1% |

| 48 | scholar.sun.ac.za
 Internet Source | <1% |

| 49 | unair.ac.id
 Internet Source | <1% |

| 50 | www.coursehero.com
 Internet Source | <1% |

| 51 | www.m-hikari.com
 Internet Source | <1% |

| 52 | www.omicsonline.org | |

Internet Source

<1%

53 "Intelligent Computing Technology", Springer Science and Business Media LLC, 2012
Publication

<1%

54 Calistus N. Ngonghala, Miranda I. Teboh-Ewungkem, Gideon A. Ngwa. "Persistent oscillations and backward bifurcation in a malaria model with varying human and mosquito populations: implications for control", Journal of Mathematical Biology, 2014
Publication

<1%

55 F. Nyabadza, B. T. Bekele, M. A. Rúa, D. M. Malonza, N. Chiduku, M. Kgosimore. "The Implications of HIV Treatment on the HIV-Malaria Coinfection Dynamics: A Modeling Perspective", BioMed Research International, 2015
Publication

<1%

56 Wang, G.. "Kalman-Bucy filtering equations of forward and backward stochastic systems and applications to recursive optimal control problems", Journal of Mathematical Analysis and Applications, 20080615
Publication

<1%

57 Yang, Ya Li, Jian Feng Cheng, Fang Chen, and Ya Yi Xu. "Optimal Control of a Tuberculosis Model with Chemoprophylaxis Treatment", Advanced Materials Research, 2013.
Publication

<1%

58 aip.scitation.org
Internet Source

<1%

59 export.arxiv.org
Internet Source

<1%

60 libeldoc.bsuir.by
Internet Source

<1%

61 link.springer.com
Internet Source

<1%

62 manuscript.sciknow.org
Internet Source

<1%

63 membership.sciencepublishinggroup.com
Internet Source

<1%

64 royalsocietypublishing.org
Internet Source

<1%

65 www.riksbank.se
Internet Source

<1%

66 www.tandfonline.com
Internet Source

<1%

67 Al-Tarazi, M.. "Precipitation of metal sulphides using gaseous hydrogen sulphide: mathematical modelling", Chemical Engineering Science, 200402
Publication

<1%

68 Rebecca C. Chukwuanukwu, Ernest O. Ukaejiofo, Prince U. Ele, Charles C. Onyenekwe et al. " Evaluation of some haemostatic parameters in malaria and HIV co-infection ", British Journal of Biomedical Science, 2016
Publication

<1%

69 Yang, W.W.. "A two-dimensional, two-phase mass transport model for liquid-feed DMFCs", Electrochimica Acta, 20070610
Publication

<1%

Exclude quotes   Off
Exclude bibliography   On

Exclude matches   Off

Application of optimal control strategies to HIVmalaria co-infection dynamics

FINAL GRADE

/0

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11

PAGE 12

PAGE 13

PAGE 14

PAGE 15