

IMPACT OF TREATMENT ON HIV-MALARIA CO- INFECTION BASED ON MATHEMATICAL MODELING

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ABSTRACT

The distribution of HIV and malaria overlap globally. So there is always a chance of co-infection. In this paper the impact of medication on HIV-Malaria co-infection has been analyzed and we have developed a mathematical model using the idea of the models of Mukandavire, et al. [13] and Barley, et al. [3] where treatment classes are included. The disease-free equilibrium (DFE) of the HIV-only model is globally-asymptotically stable (GAS) when the reproduction number is less than one. But it is shown that in the malaria-only model, there is a coexistence of stable disease-free equilibrium and stable endemic equilibrium, for a certain interval of the reproduction number less than unity. This indicates the existence of backward bifurcation. Numerical simulations of the full model are performed to determine the impact of treatment strategies. It is shown that malaria-only treatment strategy reduces more new cases of the mixed infection than the HIV-only treatment strategy. Moreover, mixed treatment strategy reduces the least number of new cases compared to single treatment strategies.

Keywords: HIV, Malaria, Co-infection, Treatment

1. Introduction

In the Sub-Saharan region of Africa, malaria and HIV are endemic. There are many factors behind the high incidence of HIV in Sub-Saharan Africa and one of the key factors is the dual infection with malaria and the geographic overlap between these two diseases [1, 14]. According to the World Health Organization (WHO), Malaria and HIV are responsible for more than two million deaths each year [23]. According to the Center for Disease Control and Prevention (CDC), about 5% increase occurs in malaria related deaths due to co-infection with HIV [7]. From these results we can guess that biological differences could alter the effect of co-infection. It is found that death rates due to malaria have almost doubled for co-infections with HIV [1].

After the discovery of human immune-deficiency virus (HIV), the intermediary of the acquired immune deficiency syndrome (AIDS) in 1981, it has become a new threat to global health and human development [17]. It has killed more than 25 million people worldwide but the HIV

prevalent in Bangladesh is still considerable [1, 15]. As a result of infection with the virus, the immune system deteriorates dynamically. HIV infection increases poverty, reduces the workforce and poses tremendous pressure on limited health and social services [19, 22]. On the other hand, malaria is a vector-borne disease. According to the World Malaria Report 2016, in 2015, almost 429000 people died from malaria globally. It is a threat to the unprivileged and it causes impoverishment [2]. If malaria is untreated, it attacks the liver and moves through the blood stream infecting every organ leading to death [3]. HIV promotes the chance of malaria infection and increases the development of symptoms of malaria in persons whose immune-system is very weak. The main purpose is to evaluate the consequence of treatment for HIV and malaria [4]. For this we shall formulate HIV-malaria co-infections model with treatment class [13, 17].

HIV infection is often associated with several comorbidities caused by the presence of malaria [21]. Studies show that co-infection fuels each other and information on co-infection effect on immune system is important for patient care [10, 18].

The paper is decorated as follows. In section 2, a basic HIV-Malaria co-infection model, with treatment as an intervention strategy, is formulated and analyzed. HIV-only and malaria-only sub models are explored in sections 3 and 4. Then the full model is explored in section 5. Simulation works are performed in details in section 6.

2. Model Formulation and Basic Properties

The whole human demography $N(t)$, at time t , is sub-divided into the following sub-populations: being susceptible to all pathogens $S(t)$, being infected with malaria only $I_M(t)$, being infected with HIV only $I_H(t)$, and being infected with both HIV and malaria $I_{HM}(t)$. Moreover, proportion of treated individuals infected with HIV only is represented by $W_H(t)$, proportion of treated individuals infected with malaria only is represented by $W_M(t)$, and proportion of treated individuals infected with both HIV and malaria is represented by $W_{HM}(t)$. So the total human populations are given by

$$N(t) = S(t) + I_H(t) + I_M(t) + I_{HM}(t) + W_H(t) + W_M(t) + W_{HM}(t).$$

Again the whole mosquito population $N_V(t)$, at time t , is subdivided into susceptible $S_V(t)$ and infectious $I_V(t)$. The total vector population is

$$N_V(t) = S_V(t) + I_V(t).$$

Assumptions

Here we consider some assumptions. These are followings:

A1: The newly sexually active susceptible individuals (S) are recruited into the human population at a constant rate Λ .

A2: The susceptible vector populations (S_V) are generated at a constant Λ_V .

A3: The natural death rate for human is α and for vector is μ_V . The disease induced death rate for HIV-infected individuals is μ_H , for malaria-infected individuals is μ_M and for mixed HIV-malaria infected individuals is μ_{HM} .

A4: The rate at which malaria infected individuals recover from malaria and return to the susceptible class is (ϑ) . Individuals with mixed HIV-malaria infection recover from malaria and may return to the HIV class at a reduced rate. Here the scaling parameter k is introduced for the recovery rate of malaria from mixed HIV-malaria infection and after recovery from malaria, individuals return to the HIV class at a rate $(k\vartheta)$.

A5: Susceptible vector populations acquire infection only from infected individuals and susceptible humans acquire infection only from infected mosquitoes.

A6: Individuals successfully treated for HIV are assumed to eventually succumb to the disease (due to the failure of treatment or resistance development) and progress to HIV at a reduced rate σ , where $0 < \sigma < 1$. Again, individuals in this class progress to malaria at a reduced rate σ_M , where $0 < \sigma_M < 1$. Individuals successfully treated for mixed HIV-malaria are assumed to eventually attack with the HIV disease (due to the failure of treatment or resistance development) and progress to HIV at a reduced rate σ_1 , where $0 < \sigma_1 < 1$.

Now we discuss about the transmission of the diseases.

Transmission by singly-infected individuals:

Susceptible individuals get infected with HIV at a rate λ_H , given by

$$\lambda_H = \frac{\beta_H(I_H + \eta_H W_H)}{N}. \quad (1)$$

Similarly, susceptible individuals get infected with malaria at a rate λ_M , which is given by

$$\lambda_M = \frac{\beta_M I_V b_M}{N}. \quad (2)$$

Transmission by Dually-Infected individuals:

Untreated Individuals:

Untreated dually-infected individuals (those in the I_{HM} class) transmit HIV at a rate

$$\lambda_{MH1} = \frac{\beta_H \rho_1 I_{HM}}{N}. \quad (3)$$

Treated Individuals:

Treated individuals with the mixed infection transmit HIV at a rate λ_{MH2} , where

$$\lambda_{MH2} = \frac{\beta_H \eta_H W_{HM}}{N}. \quad (4)$$

Adding all the three terms $(\lambda_H, \lambda_{MH1}, \lambda_{MH2})$ and expressing it as λ_{H1} , we get

$$\lambda_{H1} = \lambda_H + \lambda_{MH1} + \lambda_{MH2}.$$

Mosquitoes acquire malaria parasite at force of infection rate λ_V , where λ_V is given by

$$\lambda_V = \frac{\beta_{MV} b_M (I_M + \rho_2 I_{HM})}{N}. \quad (5)$$

Considering all suppositions we have the underlying system of differential equations:

$$\begin{aligned} S' &= \Lambda + vI_M + \rho W_M - \lambda_{H1}S - \lambda_M S - \alpha S, \\ I_M' &= \lambda_M S - \delta \lambda_{H1} I_M - k_1 I_M, \\ I_H' &= \lambda_{H1} S + v k I_{HM} + \sigma W_H + \sigma_1 W_{HM} - \theta \lambda_M I_H - k_2 I_H \\ I_{HM}' &= \delta \lambda_{H1} I_M + \theta \lambda_M I_H + \sigma_M W_H - k_3 I_{HM}, \\ W_M' &= \tau_1 I_M - k_4 W_M, \\ W_H' &= \tau_2 I_H - k_5 W_H, \\ W_{HM}' &= \tau I_{HM} - k_6 W_{HM}, \\ S_V' &= \Lambda_V - \lambda_V S_V - \mu_V S_V, \\ I_V' &= \lambda_V S_V - \mu_V I_V, \end{aligned} \quad (5)$$

where, prime denotes derivative and

$$\begin{aligned} k_1 &= v + \alpha + \tau_1 + \mu_M, k_2 = \alpha + \tau_2 + \mu_H, \\ k_3 &= \alpha + \tau + \mu_{HM} + v k, \\ k_4 &= \rho + \alpha, k_5 = \alpha + \sigma_M + \sigma, k_6 = \alpha + \sigma_1. \end{aligned}$$

The model flow diagram is delineated in Fig.1.and the parameters are described in Table 1.

Table 1. Description of parameters for the model (6).

Parameter	Description
Λ, Λ_V	Recruitment rate of humans and mosquitoes
β_H	Effective contact rate for HIV infection
β_M, β_{MV}	Transmission probability for malaria in humans and vectors
η_H, η_M	modification parameter
b_M	biting rate of mosquitoes
μ_H, μ_M, μ_{HM}	Disease induced mortality for HIV, malaria and mixed infection
α, μ_V	Natural death rate of humans and mosquitoes
ρ	Progression rate to susceptible class of individuals treated for malaria
ρ_1, ρ_2	Modifications parameters
τ_1, τ_2, τ	Treatment rates for I_H, I_M and I_{HM} classes
σ, σ_M	Progression rate to HIV or malaria by HIV infected treated individuals
σ_1	Progression rate to HIV by dually infected treated individuals
v	Recovery rate of humans from malaria
k	Reduction factor of the recovery rate for HIV-Malaria co-infection

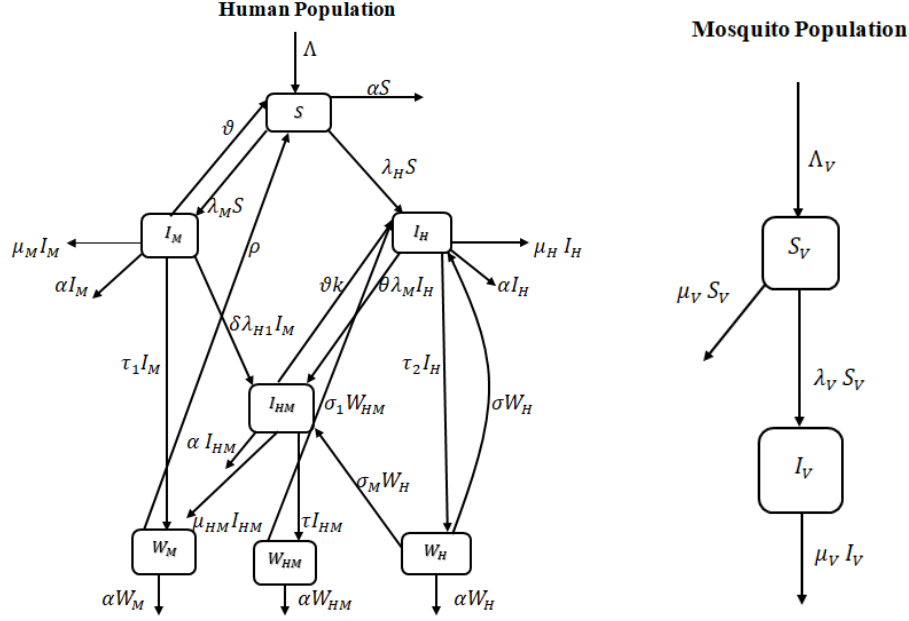


Fig. 1: Schematic diagram of the HIV-Malaria model (6)

3. HIV-only Model

The HIV-only model is

$$\begin{aligned} S' &= \Lambda - \lambda_H S - \alpha S, \\ I_H' &= \lambda_H S + \sigma W_H - k_2 I_H, \\ W_H' &= \tau_2 I_H - (\alpha + \sigma) W_H, \end{aligned} \quad (7)$$

where, $\lambda_H = \frac{\beta_H(I_H + \eta_H W_H)}{N}$, and $N = S + I_H + W_H$.

For this model, it can be shown that the region $\Omega_H = \{(S, I_H, W_H) \in \mathbb{R}_+^3 : N \leq \frac{\Lambda}{\alpha}\}$ is positively invariant and attracting with respect to the system (7) [13, 16, 17].

Local Stability of DFE

The DFE, ε_{H0} , of the HIV-only model (7), is

$$\varepsilon_{H0} = (S^*, I_H^*, W_H^*) = \left(\frac{\Lambda}{\alpha}, 0, 0 \right). \quad (8)$$

For the system (7), calculating the matrices F and V , for the new infection terms and the remaining transfer terms [20], it can be shown that the basic reproduction number [9], denoted by \mathcal{R}_H , is given by

$$\mathcal{R}_H = \rho(FV^{-1}) = \frac{\beta_H(\sigma + \alpha + \eta_H \tau_2)}{k_2(\sigma + \alpha) - \sigma \tau_2}, \quad (9)$$

where, ρ represents the spectral radius of FV^{-1} . The following result is established using Theorem 2 [20].

Lemma1. The DFE of the HIV-only model (7), given by (8), is locally-asymptotically stable (LAS) if $\mathcal{R}_H < 1$, and unstable if $\mathcal{R}_H > 1$.

The following results can be established (using the techniques in [11, 17])

Theorem 1. The DFE of the HIV-only model (7), given by ε_{H0} , is GAS whenever $\mathcal{R}_H < 1$.

Proof. The following Lyapunov function is considered:

$$\mathcal{F} = f_1 I_H + f_2 W_H,$$

where, $f_1 = \frac{\sigma + \alpha + \eta_H \tau_2}{\eta_H k_2 + \sigma}$, and $f_2 = 1$.

with Lyapunov derivative (where a dot denotes differentiation with respect to t).

$$\begin{aligned} \text{So } \dot{\mathcal{F}} &= f_1 \dot{I}_H + f_2 \dot{W}_H, \\ &= (\sigma + \alpha + \eta_H \tau_2) \dot{I}_H + (\eta_H k_2 + \sigma) \dot{W}_H, \\ &= (\sigma + \alpha + \eta_H \tau_2)(\lambda_H S + \sigma W_H - k_2 I_H) + (\eta_H k_2 + \sigma)(\tau_2 I_H - (\alpha + \sigma) W_H), \\ &= (\sigma + \alpha + \eta_H \tau_2) \lambda_H S - (I_H + \eta_H W_H)(\alpha k_2 + \sigma k_2 - \sigma \tau_2), \\ &= (\sigma + \alpha + \eta_H \tau_2) \lambda_H S - \frac{(\alpha k_2 + \sigma k_2 - \sigma \tau_2) N}{\beta_H} \lambda_H, \\ &= \frac{(\sigma k_2 + \alpha k_2 - \sigma \tau_2) \lambda_H N}{\beta_H} \left(\frac{\beta_H (\sigma + \alpha + \eta_H \tau_2) S}{(k_2 (\sigma + \alpha) - \sigma \tau_2) N} - 1 \right), \\ &\leq \frac{(\sigma k_2 + \alpha k_2 - \sigma \tau_2) \lambda_H N}{\beta_H} (\mathcal{R}_H - 1), \text{ (since } S \leq N), \\ &\leq 0 \text{ for } \mathcal{R}_H \leq 1. \end{aligned}$$

Since all the parameters are non-negative, $\dot{\mathcal{F}} \leq 0$ for $\mathcal{R}_H \leq 1$ with $\dot{\mathcal{F}} = 0$ if and only if $I_H = W_H = 0$. Hence \mathcal{F} is a Lyapunov function on Ω_H . Therefore, by the LaSalle's invariance principle [11], every solution to the equations of the model (7), with initial conditions in Ω_H , approaches ε_{H0} as $t \rightarrow \infty$, whenever $\mathcal{R}_H \leq 1$.

From the above results we can say that HIV will be eliminated if \mathcal{R}_H can be brought to a value less than unity.

Existence of Endemic Equilibrium (EE)

Let EE point be denoted by $\varepsilon_1 = (S^*, I_H^*, W_H^*)$,

$$\text{and } \lambda_H^* = \frac{\beta_H (I_H^* + \eta_H W_H^*)}{S^* + I_H^* + W_H^*}. \quad (10)$$

Setting the right hand sides of the model to zero (and noting that $\lambda_H^* = \lambda_H$ at equilibrium) gives

$$\begin{aligned}
S^* &= \frac{\Lambda}{\alpha + \lambda_H^*}, \\
I_H^* &= \frac{(\alpha + \sigma)\Lambda\lambda_H^*}{(\alpha + \lambda_H^*)(\alpha k_2 + \sigma(\alpha + \mu_H))}, \\
W_H^* &= \frac{\tau_2\Lambda\lambda_H^*}{(\alpha + \lambda_H^*)(\alpha k_2 + \sigma(\alpha + \mu_H))}.
\end{aligned} \tag{11}$$

Using (11) in the expression for λ_H^* in (10) shows that the nonzero (endemic) equilibria of the model satisfy

$$a_{11}\lambda_H^* - a_{12} = 0. \tag{12}$$

where, $a_{11} = \frac{\alpha + \sigma + \tau_2}{\alpha(k_2 + \sigma + \mu_H)}$, and $a_{12} = \mathcal{R}_H - 1$.

If $\mathcal{R}_H > 1$ then $a_{12} > 0$, and a_{11} is always positive. Thus, from the linear system (12) $\lambda_H^* = a_{12}/a_{11}$, which is unique and positive whenever $\mathcal{R}_H > 1$. Then substituting $\lambda_H^* = a_{12}/a_{11}$ into (11) we can determine the components of the endemic equilibrium ε_1 . Again, if $\mathcal{R}_H < 1$ then $a_{12} < 0$ and hence $\lambda_H^* < 0$ (which does not mean anything biologically). Hence there is no positive equilibria. These can be abbreviated below.

Lemma 2. The HIV-only model (7) has a unique EE if and only if $\mathcal{R}_H > 1$, and no EE otherwise.

Local Stability of Endemic Equilibrium

To study the local asymptotic stability of the endemic equilibrium the center manifold theory [5, 6] is used. To do this, the following simplification and change of variables are made. Let $S = x_1, I_H = x_2, W_H = x_3$ so that

$N = x_1 + x_2 + x_3$. Moreover, by using the vector notation $x = (x_1, x_2, x_3)^T$, the HIV-only model (7) can be written in the form $\frac{dx}{dt} = (f_1, f_2, f_3)^T$, as follows:

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda - \frac{\beta_H(x_2 + x_3\eta_H)x_1}{x_1 + x_2 + x_3} - \alpha x_1, \\
\frac{dx_2}{dt} &= f_2 = \frac{\beta_H(x_2 + x_3\eta_H)x_1}{x_1 + x_2 + x_3} - (\alpha + \mu_H + \tau_2)x_2 + \sigma x_3, \\
\frac{dx_3}{dt} &= f_3 = \tau_2 x_2 - \alpha x_3 - \sigma x_3.
\end{aligned} \tag{13}$$

The Jacobian of the system (13) at ε_{H0} , is given by

$$J(\varepsilon_{H0}) = \begin{pmatrix} -\alpha & -\beta_H & -\beta_H\eta_H \\ 0 & -(\alpha + \mu_H + \tau_2) + \beta_H & \sigma + \beta_H\eta_H \\ 0 & \tau_2 & -(\alpha + \sigma) \end{pmatrix}.$$

When $\mathcal{R}_H = 1$, let $\beta_H = \beta^*$ be a bifurcation parameter. From (9) using $\mathcal{R}_H = 1$ gives the expression for β_H as

$$\beta_H = \beta^* = \frac{(\alpha + \sigma)k_2 - \sigma\tau_2}{(\alpha + \sigma + \eta_H\tau_2)}. \quad (14)$$

Here the Jacobian ($J(\varepsilon_{H0})$) of (13) at the DFE has one eigenvalue of magnitude zero and the remaining eigenvalues have negative real part. So, the idea of center manifold theory [5, 6] can be applied to show the LAS of the EEP of (13) and hence of the original system (7), for β_H near β^* .

Eigenvectors of $J_{\beta^*} = J(\varepsilon_{H0})|_{\beta_H = \beta^*}$:

For $\mathcal{R}_H = 1$, the jacobian of (13) at $\beta_H = \beta^*$ denoted by (J_{β^*}) has a right eigenvector associated with the zero eigenvalue which is given by $= [w_1, w_2, w_3]^T$, where,

$$w_1 = -\frac{(\beta^*w_2 + \beta^*\eta_Hw_3)}{\alpha}, w_2 = w_2, w_3 = \frac{\tau_2w_2}{\alpha + \sigma}.$$

Moreover, J_{β^*} has a left eigenvector $v = [v_1, v_2, v_3]$, where,

$$v_1 = 0, v_2 = v_2, v_3 = \frac{(\sigma + \beta^*\eta_H)v_2}{\alpha + \sigma}.$$

Computations of a and b :

For the system (13), to determine the sign of a

$$\text{we have, } a = \sum_{k,i,j=1}^n v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0),$$

Using the associated non-zero partial derivatives of F (at the DFE) and after some algebraic manipulations it can be easily shown that the expression for a is

$$a = -\frac{2v_2\beta^*\alpha(w_2 + w_3)(w_2 + \eta_Hw_3)}{\Lambda} < 0.$$

For the sign of b we have

$$b = \sum_{k,i=1}^n v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0).$$

Using the associated non-zero partial derivatives of F (at the DFE) and after some algebraic manipulations it can be easily shown that the expression for b is

$$b = v_2(w_2 + w_3\eta_H) > 0.$$

Thus $a < 0$ and $b > 0$. So (by Center Manifold theorem [5, 6]) the following result can be established (the result holds for $\mathcal{R}_H > 1$ but close to 1).

Theorem 2. The unique endemic equilibrium confirmed by Center Manifold theory [5, 6] is LAS for \mathcal{R}_H near 1. In brief, the DFE of the HIV-only model (7) is GAS whenever $\mathcal{R}_H \leq 1$, and it has a unique endemic equilibrium point whenever $\mathcal{R}_H > 1$.

4. Malaria-only Model

The malaria-only model is given by:

$$\begin{aligned} S' &= \Lambda + vI_M + \rho W_M - \lambda_M S - \alpha S, \\ I_M' &= \lambda_M S - k_1 I_M, \\ W_M' &= \tau_1 I_M - k_4 W_M, \\ S_V' &= \Lambda_V - \lambda_V S_V - \mu_V S_V, \\ I_V' &= \lambda_V S_V - \mu_V I_V, \end{aligned} \tag{15}$$

where, $\lambda_M = \frac{\beta_M b_M I_V}{N}$, $\lambda_V = \frac{\beta_{MV} b_M I_M}{N}$, and $N = S + I_M + W_M$.

Local stability of the DFE

The DFE (ε_{M0}) of the malaria-only model (15) is given by

$$\varepsilon_{M0} = (S, I_M, W_M, S_V, I_V) = \left(\frac{\Lambda}{\alpha}, 0, 0, \frac{\Lambda_V}{\mu_V}, 0 \right).$$

The basic reproduction number, denoted by \mathcal{R}_M , is

$$\mathcal{R}_M = \frac{b_M \sqrt{\Lambda \Lambda_V \beta_M \beta_{MV} \alpha k_1}}{\Lambda \mu_V k_1}. \tag{16}$$

Thus, using Theorem 2 [20] the following result can be established.

Theorem3. The DFE of the malaria-only model (15) is LAS if $\mathcal{R}_M < 1$, and unstable if $\mathcal{R}_M > 1$.

The Endemic Equilibrium (EE):

Let the EEP of the system (15) be given by

$$\varepsilon_{M1} = (S^*, I_M^*, W_M^*, S_V^*, I_V^*), \text{ and } (\lambda_M^* = \lambda_M \text{ at equilibrium})$$

$$\text{So, } \lambda_M^* = \frac{\beta_M b_M I_V^*}{N^*}, \lambda_V^* = \frac{\beta_{MV} b_M I_M^*}{N^*}, \text{ and } N^* = S^* + I_M^* + W_M^*.$$

Setting the right hand sides of the model to zero we solve for S^* , I_M^* , W_M^* , S_V^* , I_V^* , and using these expressions along with λ_V^* in λ_M^* we get the following polynomial equation (in terms of λ_M^*)

$$\lambda_M^* [A(\lambda_M^*)^2 + B\lambda_M^* + C] = 0. \tag{17}$$

where, $A = \mu_V \Lambda (\tau_1 + k_4) (\beta_{MV} b_M k_4 \Lambda + \mu_V k_4 \Lambda + \mu_V \Lambda \tau_1)$,

$$\begin{aligned}
B &= (\beta_{MV} b_M k_4 \Lambda + \mu_V k_4 \Lambda + \mu_V \Lambda \tau_1 + \mu_V k_1 k_4 \Lambda^2 (\tau_1 + k_4)) \mu_V \\
&\quad - \beta_{MV} \beta_M b_M^2 k_4 \Lambda \Lambda_V (\alpha k_4 + \mu_M k_4 + \alpha \tau_1), \\
C &= \mu_V^2 k_1^2 k_4^2 \Lambda^2 (1 - \mathcal{R}_m^2).
\end{aligned}$$

Equation (17) says that the non-zero equilibria of the model satisfy

$$f(\lambda_M^*) = A(\lambda_M^*)^2 + B\lambda_M^* + C = 0. \quad (18)$$

Hence, we have the following result.

Theorem 4. The model (15) has

- (i) exactly an identical EE if $C < 0$ (i.e., $\mathcal{R}_M > 1$),
- (ii) exactly an identical EE if $B < 0$, and $C = 0$ or $B^2 - 4AC = 0$,
- (iii) exactly two EE if $B < 0, C > 0$ (i.e., $\mathcal{R}_M < 1$) and $B^2 - 4AC > 0$,
- (iv) no EE otherwise.

Existence of Backward Bifurcation

From the above Theorem 3 we see that the DFE of the malaria-only model is LAS if $\mathcal{R}_M < 1$. Still, it may not assure the global asymptotic stability of the equilibrium for $\mathcal{R}_M < 1$, which indicates the possibility of backward bifurcation [8, 9, 16]. This is investigated below, using the center manifold theorem [5, 6]. Let $S = x_1, I_M = x_2, W_M = x_3, S_V = x_4, I_V = x_5$.

The Jacobian of the system (15) at the DFE ε_{M0} is denoted by $J(\varepsilon_{M0})$ and is given by :

$$J(\varepsilon_{M0}) = \begin{pmatrix} -\alpha & v & \rho & 0 & -\beta_M b_M \\ 0 & -k_1 & 0 & 0 & \beta_M b_M \\ & \tau_1 & & & \\ 0 & \frac{-\beta_{MV} b_M \alpha \Lambda_V}{\Lambda \mu_V} & -k_4 & 0 & 0 \\ 0 & \Lambda \mu_V & 0 & -\mu_V & 0 \\ 0 & \frac{\beta_{MV} b_M \alpha \Lambda_V}{\Lambda \mu_V} & 0 & 0 & -\mu_V \end{pmatrix}.$$

When $\mathcal{R}_M = 1$, let $\beta_M = \beta^*$ be a bifurcation parameter. Solving (16) for b_M from $\mathcal{R}_M = 1$ gives

$$\beta_M = \beta^* = \frac{\mu_V^2 k_1^2 \alpha^2}{\alpha \beta_{MV} b_M^2 k_1 \Lambda \Lambda_V}. \quad (19)$$

Eigenvectors of $J_{\beta^*} = J(\varepsilon_{M0})|_{\beta_M = \beta^*}$:

When $\mathcal{R}_M = 1$, the Jacobian at $\beta_M = \beta^*$ expressed by (J_{β^*}) has a right eigenvector

$$w = [w_1, w_2, w_3, w_4, w_5]^T,$$

where, $w_1 = \frac{v w_2 + \rho w_3 - b_M \beta^* w_5}{\alpha}$, $w_2 = w_2$, $w_3 = \frac{\tau_1 w_2}{k_4}$, $w_4 = \frac{-\beta_{MV} b_M \alpha \Lambda_V w_2}{\Lambda \mu_V^2}$

$$\text{and } w_5 = \frac{\beta_{MV} b_M \alpha \Lambda v w_2}{\Lambda \mu_V^2}.$$

Moreover, J_{ρ^*} has a left eigenvector

$$\begin{aligned} v &= [v_1, v_2, v_3, v_4, v_5], \text{ where,} \\ v_1 &= 0, v_2 = v_2, v_3 = 0, \\ v_4 &= 0, v_5 = \frac{\beta^* b_M v_2}{\mu_V}. \end{aligned}$$

Computations of a and b:

After some calculation the expression for a is $a = -\frac{2b_M \alpha \beta_{MV} v_5 w_2 w_4 (\Delta - 1)}{\Lambda}$, where,

$$\Delta = \frac{\Lambda \beta^* \mu_V w_2 w_5 (w_2 + w_3) + \alpha \Lambda v \beta_{MV} v_5 w_2 (w_1 + w_2 + w_3)}{\Lambda \beta_{MV} \mu_V v_5 w_2 w_4},$$

and the expression for b is

$$b = v_2 w_5 b_M > 0.$$

The sign of a is not known. Hence, it follows (from Center Manifold Theorem [5, 6]) that model (15) experiences backward bifurcation at $\mathcal{R}_M = 1$ whenever

$$a = -\frac{2b_M \alpha \beta_{MV} v_5 w_2 w_4 (\Delta - 1)}{\Lambda} > 0. \quad (20)$$

This is abbreviated below.

Theorem 5. The malaria-only model (15) experiences backward bifurcation at $\mathcal{R}_M = 1$ whenever inequality (20) is satisfied.

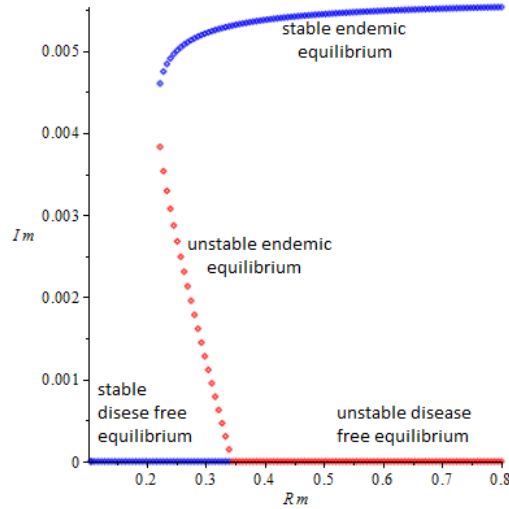


Figure 2. This figure demonstrates the occurrence of backward bifurcation for the malaria only model (15) using: $\Lambda = 0.001$, $\Lambda_V = 0.01$, $\alpha = 0.015$, $\mu_M = 0.15$, $\mu_V = 0.06$, $\rho = 0.06$, $\beta_{MV} = 0.08$, $v = 0.5$, $\tau_1 = 0.07$, $b_M = 0.8$ and different values of β_M , we have $a > 0$ and $b > 0$.

It is illustrated in (Figs. 2-3.). Using parameter values, we have $\mathcal{R}_M = 0.6737$ and $a = 0.00007681434774$ with $b = 0.03525$. The following figure (Fig. 2.) has been generated using Maple to illustrate the phenomenon of backward bifurcation for the malaria only model (15).

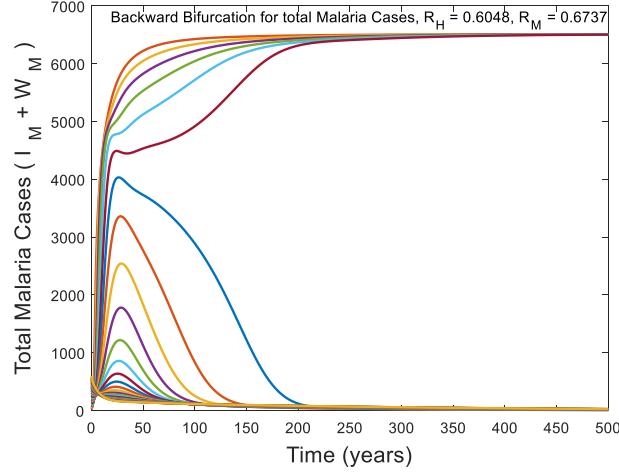


Figure 3. This figure demonstrates the occurrence of backward bifurcation for malaria-only with different initial conditions in the model (6). Parameter values used are as in Table 2 with $\mu_H = 0.01$, $\mu_V = 0.75$, $\rho = 0.1$, $\nu = 1.5$, $k = 1$, $\tau = 5$, $\tau_1 = 0.4$, $\tau_2 = 4$, $\sigma = 0.0303$, $\sigma_M = 0.02$, $\sigma_1 = 0.033$, $b_M = 1$.

5. Analysis of the HIV-Malaria Model

Local Stability of the DFE:

DFE of (6) is given by

$$\begin{aligned} \varepsilon_0 &= (S, I_M, I_H, I_{HM}, W_M, W_H, W_{HM}, S_V, I_V), \\ &= \left(\frac{\Lambda}{\alpha}, 0, 0, 0, 0, 0, \frac{\Lambda_V}{\mu_V}, 0 \right). \end{aligned} \quad (21)$$

The reproduction number for the full model (6) (denoted by \mathcal{R}_{HM}) is

$$\mathcal{R}_{HM} = \max\{\mathcal{R}_H, \mathcal{R}_M\}. \quad (22)$$

Using Theorem 2 [20], we have the following result.

Theorem 6. The DFE of the model (6) is LAS if $\mathcal{R}_{HM} < 1$, and unstable if $\mathcal{R}_{HM} > 1$.

Model (6) also experiences backward bifurcation as the malaria-only model (15). We claim the following.

Theorem 7. The full model (6) experiences backward bifurcation at $\mathcal{R}_{HM} = 1$ whenever inequality (23) is satisfied.

Proof. This can also be proved using the center manifold theorem [5, 6] on the model (6).

let $S = x_1, I_M = x_2, I_H = x_3, I_{HM} = x_4$ and $W_M = x_5, W_H = x_6, W_{HM} = x_7, S_V = x_8, I_V = x_9$.

The Jacobian of the system (6) at the DFE point ε_0 , is denoted by $J(\varepsilon_0)$ and is given by

$$J(\varepsilon_0) = \begin{pmatrix} -\alpha & \nu & -\beta_H & -J_1 & \rho & -J_2 & -J_2 & 0 & -J_3 \\ 0 & -k_1 & 0 & 0 & 0 & 0 & 0 & 0 & J_3 \\ 0 & 0 & J_4 & J_5 & 0 & J_6 & J_7 & 0 & 0 \\ 0 & 0 & 0 & -k_3 & 0 & \sigma_M & 0 & 0 & 0 \\ 0 & \tau_1 & 0 & 0 & -k_4 & 0 & 0 & 0 & 0 \\ 0 & 0 & \tau_2 & 0 & 0 & -k_5 & 0 & 0 & 0 \\ 0 & 0 & 0 & \tau & 0 & 0 & -k_6 & 0 & 0 \\ 0 & -J_8 & 0 & -J_9 & 0 & 0 & 0 & -\mu_V & 0 \\ 0 & J_8 & 0 & J_9 & 0 & 0 & 0 & 0 & -\mu_V \end{pmatrix}.$$

where, $J_1 = \beta_H \rho_1, J_2 = \beta_H \eta_H, J_3 = \beta_H b_M, J_4 = -k_2 + \beta_H, J_5 = \beta_H \rho_1 + \nu k, J_6 = \beta_H \eta_H + \sigma,$

$$J_7 = \beta_H \eta_H + \sigma_1, J_8 = \frac{\beta_M \nu b_M \alpha \Lambda_V}{\Lambda \mu_V}, J_9 = \frac{\beta_M \nu b_M \alpha \Lambda_V \rho_2}{\Lambda \mu_V}.$$

And $\mathcal{R}_{HM} = \max\{\mathcal{R}_H, \mathcal{R}_M\}$ as before,

$$\text{where, } \mathcal{R}_H = \frac{\beta_H(\sigma + \alpha + \eta_H \tau_2)}{k_2(\sigma + \alpha) - \sigma \tau_2}, \text{ and } \mathcal{R}_M = \frac{\sqrt{\Lambda \Lambda_V \beta_M \beta_{MV} \alpha k_1}}{\Lambda \mu_V k_1}.$$

When $\mathcal{R}_{HM} = 1$ (that is, $\mathcal{R}_H < \mathcal{R}_M = 1$), let $\beta_M = \beta^*$ be a bifurcation parameter.

$$\text{Then } \mathcal{R}_M = 1 \text{ gives the expression for } \beta_M \text{ as } \beta_M = \beta^* = \frac{k_1^2 \alpha^2 \mu_V^2}{\Lambda \Lambda_V \alpha k_1 \beta_{MV} b_M^2}.$$

Eigenvectors of $J_{\beta^*} = J(\varepsilon_0)|_{\beta_M = \beta^*}$:

when $\mathcal{R}_{HM} = 1$, the Jacobian of (6) at $\beta_M = \beta^*$ expressed by (J_{β^*}) has a right eigenvector

$$w = [w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9]^T, \text{ where,}$$

$$w_1 = \frac{\nu w_2 - \beta_H w_3 - J_1 w_4 + \rho w_5 - J_2 w_6 - J_2 w_7 - J_3 w_9}{\alpha},$$

$$w_2 = w_2, w_3 = \frac{k_5 w_6}{\tau_2}, w_4 = w_4, w_5 = \frac{\tau_1 w_2}{k_4},$$

$$w_6 = w_6, w_7 = \frac{\tau w_4}{k_6}, w_8 = -\frac{j_8 w_2 + J_9 w_4}{\mu_V}, w_9 = \frac{k_1 w_2}{J_3}.$$

Further, J_{β^*} has a left eigenvector $v = [v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9]$, where,

$$v_1 = 0, v_2 = v_2, v_3 = -\frac{\tau_2 w_6}{J_4}, v_4 = \frac{J_5 v_3 + \tau v_7 + J_9 v_9}{k_3}, v_5 = 0, v_6 = v_6, v_7 = \frac{J_7 v_3}{k_7}, v_8 = 0, v_9 = \frac{k_1 v_2}{J_8}.$$

Computations of a and b :

After some calculations, it can be shown that

$$b = b_M v_2 w_9 > 0,$$

Thus, it follows from Center Manifold Theorem [5, 6] that the model (6) experiences backward

bifurcation at $\mathcal{R}_{HM} = 1$ whenever

$$a > 0. \quad (23)$$

This is illustrated in Fig.4.

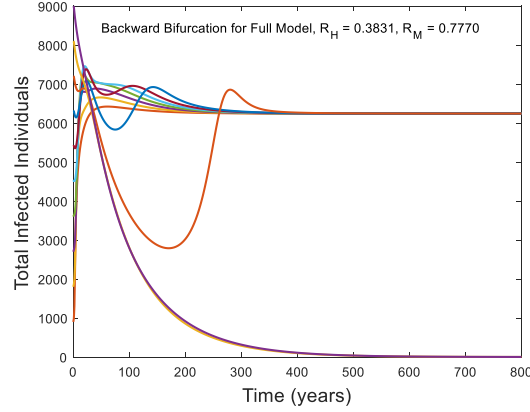


Fig. 4. This figure demonstrates the occurrence of backward bifurcation for the full model with different initial conditions in the model (6). Parameter values are obtained from Table 2 with $\alpha = 0.02, \mu_H = 0.01, \mu_V = 0.75, \mu_{HM} = 0.1, \beta_H = 0.6, v = 1.5, \tau = 5, \tau_1 = 0.4, \tau_2 = 5, \sigma = 0.04, \sigma_M = 0.04, \sigma_1 = 0.05, b_M = 1$.

Table 2. Description of parameters for the model (6).

Parameter	Nominal value	References
Λ, Λ_V	100, 100000	[12]
$\beta_H, \beta_M, \beta_{MV}$	0.75, 0.6, 0.6	[12]
$\eta_H, \sigma, \sigma_M, \sigma_1$	0.001, 0.003, 0.006, 0.001	assumed
b_M	(0.25, 1)	[12]
$\mu_H, \mu_M, \mu_{HM}, \mu_V$	0.02, 0.2, 0.01, 6	[12]
$\alpha, \rho, \rho_1, \rho_2$	0.015, 0.1, 1.02, 1.002	assumed
τ_1, τ_2, τ	Variable(treatment rate)	[17]
v, δ, θ, k	0.005, 1.002, 1.00, 0.5	[12]

6. Evaluation of treatment strategies

The full model (6) is now simulated to describe the treatment strategies as follows:

HIV-only treatment strategy

Here individuals in the I_H and I_{HM} class are treated at a rate τ_2 . In this case $\tau_1 = 0$ and $\tau = 0$. Using $\tau_2 = 0.02$, the results, illustrated in Fig.5a and Fig.5b, show that the number of new cases of HIV-infection and the mixed HIV-Malaria infection have reduced significantly. The result follows the similar trends for higher treatment rate (Fig.5.).

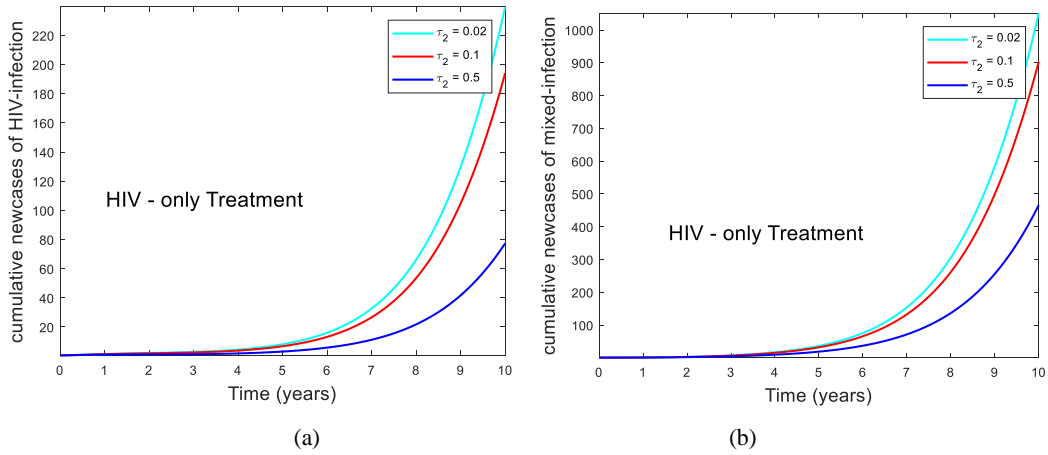


Fig. 5. The above figures (simulation of the model (6)) illustrate the cumulative number of new cases of HIV and the mixed infection showing the effect of HIV-only treatment (τ_2) to individuals transited with HIV-only and mixed infection. Parameter values are obtained from Table 2 with $\mu_H = 0.01$, $\beta_M = 2.6$, $\tau = 0$, $\tau_1 = 0$, $b_M = 1$ and different values of τ_2 .

Malaria-only Treatment Strategy

Here individuals in the I_M and I_{HM} class are treated at a rate τ_1 . Here $\tau_2 = 0$ and $\tau = 0$. Fig.6a and Fig.6b show that cumulative number of new cases of malaria-infection and mixed-infection have reduced remarkably. It is notable that the number of malaria cases prevented (Fig.6a) under the malaria-only treatment strategy is greater than the number of HIV cases prevented under the HIV-only treatment strategy (Fig.5a). The result follows the similar trends for higher treatment rate (Fig.6.).

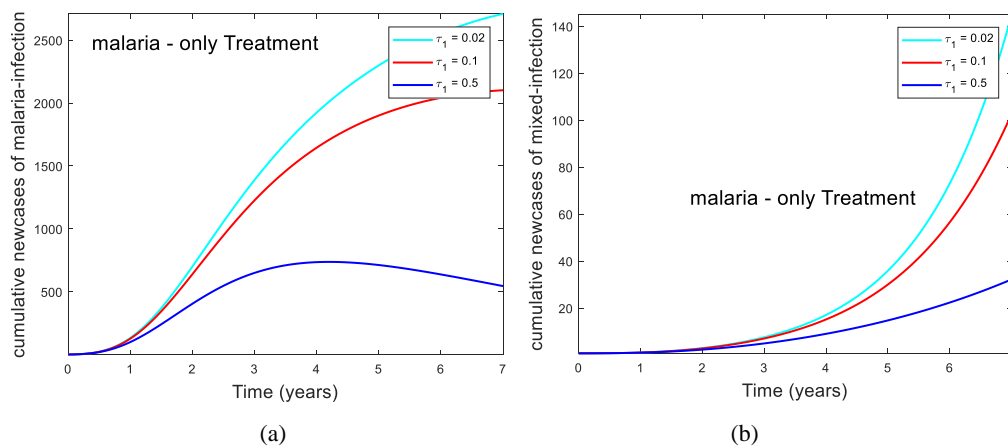


Fig. 6. The above figures (simulation of the model (6)) illustrate the cumulative number of new cases of malaria and the mixed infection showing the effect of malaria-only treatment (τ_1) to individuals transited with malaria-only and mixed infection. Parameter values are obtained from Table 2 with $\mu_H = 0.01$, $\beta_M = 2.6$, $\tau = 0$, $\tau_2 = 0$, $b_M = 1$ and different values of τ_1 .

Mixed Treatment strategy

Here individuals in the I_H , I_M and I_{HM} class are treated at a rate τ . In this case $\tau_1 = \tau_2 = 0$. The results obtained for mixed treatment using $\tau = 0.02$, depicted in Figs. 7a-7c show that this treatment strategy reduces more cumulative new cases of mixed infection than HIV and malaria infection. However, this strategy saves less number of new cases than the other two treatment strategies. The result follows the similar trends for higher treatment rate (Fig. 7.).

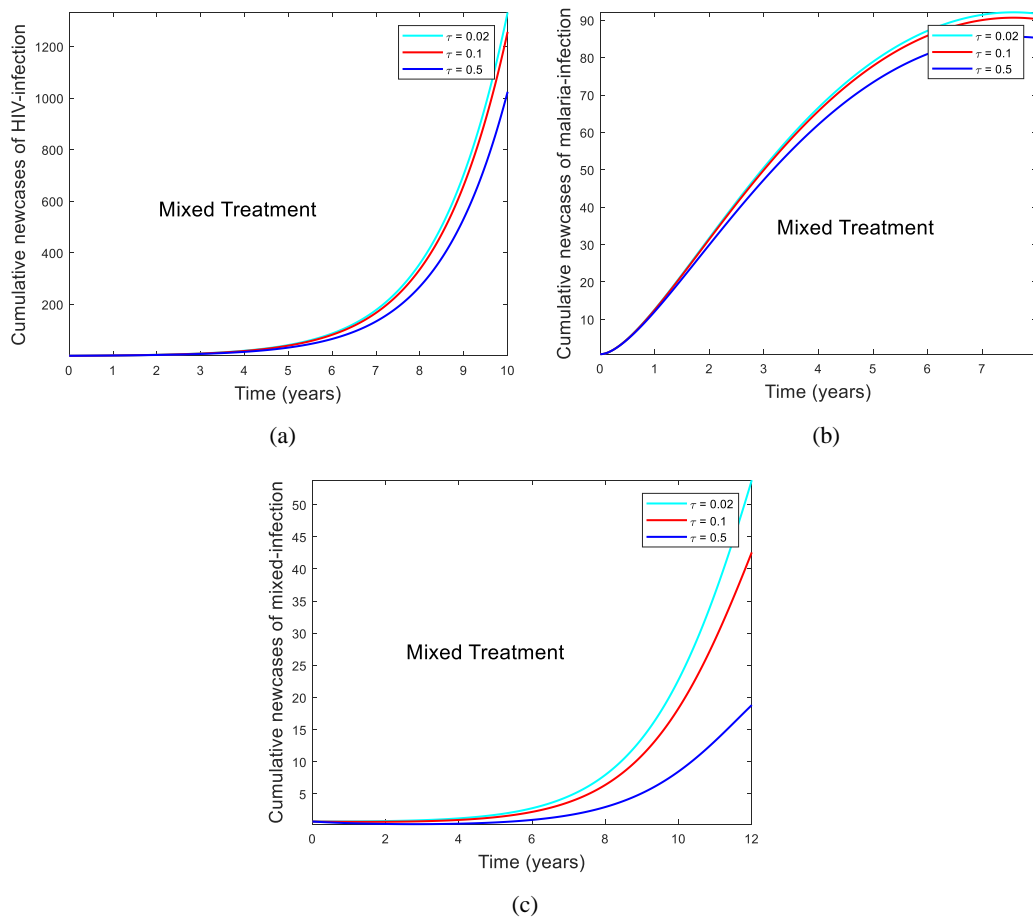


Fig. 7. The above figures (simulation of the model (6)) illustrate the cumulative number of new cases of HIV, malaria and the mixed infection showing the effect of mixed treatment (τ) to individuals transited with HIV-only, malaria-only and mixed infection. Parameter values are obtained from Table 2 with $\mu_H = 0.01$, $\beta_M = 1$, $\tau_1 = 0$, $\tau_2 = 0$, $b_M = 1$ and different values of τ .

7. Conclusions

The main theoretical results obtained are as follows:

1. The HIV-only model has a globally-asymptotically stable disease-free equilibrium when the reproduction number (\mathcal{R}_H) is less than one and unstable when \mathcal{R}_H is greater than one;

2. The HIV-only model has a unique endemic equilibrium whenever \mathcal{R}_H is greater than one.
3. The malaria-only model undergoes the phenomenon of backward bifurcation, where the stable disease-free equilibrium co-exists with a stable endemic equilibrium when the corresponding reproduction number (\mathcal{R}_M) is less than one.

Using numerical simulations the following results are found:

1. The full HIV-malaria model has a locally-asymptotically stable disease-free equilibrium when \mathcal{R}_{HM} is less than one, and unstable if \mathcal{R}_{HM} is greater than one. It also undergoes the phenomenon of backward bifurcation when we impose some conditions.
2. HIV-only and malaria-only treatment strategy resist more cumulative new cases of the respective diseases than the mixed infection;
3. The malaria-only treatment strategy saves more cumulative new cases than the HIV-only treatment strategy for the mixed infection;
4. The mixed treatment strategy is less effective than the other two treatment strategies as it saves the least number of cumulative new cases of HIV, malaria and the mixed infection.

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