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Predicting the effectiveness of drug interventions with 'HIV counseling & testing' (HCT) on the spread of HIV/AIDS: a theoretical study

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Abstract

In this paper, a dynamic compartmental model is constructed for the transmission of HIV/AIDS receiving drug treatment and knowledge from effective awareness programs through media. Using stability theory of differential equations the model is analyzed qualitatively. The equilibrium points in the local and global stability proof are found to be stable under certain conditions. Further, we use Pontryagin's Minimum Principle in the time-dependent constant control case to derive necessary conditions for the optimal control of the disease. Sensitivity analysis is also performed to check the robustness of the model with respect to small changes in parametric values of the system. In order to predict the long term dynamics of the disease, projections are made. These studies reveal that HIV incidence could be substantially reduced by improving the test-and-treat strategy and implication of media awareness.

Keywords: Epidemic model; HIV; Drug-dosing; Awareness programs; Basic reproductive number; Local & global stability; Numerical simulation; Sensitivity analysis

1 Introduction

According to the report from the US Centers for Disease Control and Prevention, acquired immune deficiency syndrome (AIDS) was first identified as a distinct infectious disease in the year 1981. Since then, more than 70 million people have been infected and about 35 million people have already died of this disease. World Health Organization (WHO) reported that globally, there were 36.9 million people who were living with HIV at the end of 2017 and 940,000 people died of HIV-related illnesses worldwide in the same year. Can you imagine what would happen if this number of deaths still happen for next few years?

Nevertheless, there is no room for complacency. Countries need to live up their commitment, adopted by the United Nations General Assembly in September 2015, to end the AIDS epidemic as a public health threat by 2030. The immediate challenge is to reach the Fast-Track targets for 2020, and a rational step should be immediately taken to make people aware about the disease, and its preventive measures, through the media, as HIV-related deaths are still unacceptably high.

Recent studies suggested that education and media have a great visitation in preventing the spread of HIV/AIDS among married couples in Bangladesh [1, 2]. Broadcast media, being the primary source of information, can not only increases the governmental health care involvement to control the spread of HIV but also makes people acquainted with the disease. Del Valle et al. (2004) studied the effects of education, temporary vaccination, and treatment on HIV transmission in a homosexually active population [3]. It was suggested by them that along with proper vaccination and treatment, awareness programs could be one of the effective solutions in reduction of such diseases. Gumel et al. (2004) worked on determining the optimal vaccine coverage and efficacy levels needed for community-wide eradication of HIV [4]. Baryarama et al. (2005) worked on a mathematical model and explained that there is a tendency for the epidemic to stabilize at higher numbers of infectives and AIDS cases than the minimum numbers attained during the first decline of the epidemic [5]. Hove-Musekwa et al. (2009) worked to determine the effects of carriers and randomly screened carriers, who are aware of their status, on the transmission of HIV [6]. Tripathi et al. (2007) also proposed a model presented without interventions, which considers infection leading to asymptomatic HIV infectives who are later screened and finally develop AIDS [7]. A similar approach was undertaken earlier by Hyman et al. (2003) with differential infectivity and staged progression models [8]. In our recent works, we have shown that the incidences can be controlled if people take obligatory precautions to make themselves protected [9, 10]. They can minimize the risk if they become well-informed and aware about the prevalence. Other research articles are also studied to improve this modeling process [11–14].

These studies have motivated us to formulate a mathematical model that incorporates both of these events: test-and-treat program and media awareness. In the modeling process, we assume that the growth rate of the cumulative density of awareness programs driven by the media is proportional to the number of untreated infectives present in the population. The whole population is divided into five separate classes; high-risk unaware susceptible class, class of non-diagnosed HIV infected individuals, diagnosed class of HIV-positive individuals who have not yet progressed to AIDS, class of those individuals with clinical AIDS, and aware susceptible class. We also discuss the equilibrium points and their stability. Finally, we solve the model numerically and then discuss the results from the biological aspect.

2 The model

We formulate a mathematical model which considers voluntary counseling and testing followed by immediate initiation of drug therapy, where HIV-positive individuals were identified and immediately received anti-retroviral treatment. Following this assumption, we consider a region with total population $N(t)$ at any instant of time t. The whole population is subdivided into five classes, that are: unaware susceptibles, $S(t)$; aware susceptibles, $S_+(t)$; unaware and untreated infected individuals, $I(t)$; diagnosed and treated infected individuals who have not yet developed to AIDS, $I_D(t)$; and diagnosed infected individuals with clinical AIDS, $I_{DA}(t)$. Therefore, $N = S + S_+ + I + I_D + I_{DA}$. As mentioned earlier, the number of awareness campaigns is considered explicitly and is represented by $M(t)$ at time t. The growth rate of awareness campaigns is assumed to be proportional to the number of diagnosed infected people, with and without AIDS developed, present in the population. Moreover, the diminution of awareness campaigns due to societal and psychological barriers is also incorporated in the model. Further, it is also assumed that people

with possession of awareness may lose it with the passage of time, due to memory fading or other reasons. On the basis of the assumptions above, the dynamics of model are governed by the following system of nonlinear ordinary differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \beta(I + \lambda_1 I_D + \lambda_2 I_{DA})S - dS - cSM + \omega S_+, \\
\frac{dI}{dt} &= \beta(I + \lambda_1 I_D + \lambda_2 I_{DA})S - (\delta + d + d_I)I, \\
\frac{dI_D}{dt} &= \rho\delta I - \big(\xi' + d + \alpha_I\big)I_D, \\
\frac{dI_{DA}}{dt} &= (1-\rho)\delta I + \xi' I_D - (d + \alpha_A)I_{DA}, \\
\frac{dS_+}{dt} &= cSM - (d + \omega)S_+, \\
\frac{dM}{dt} &= \mu(I_D + I_{DA}) - \mu_0 M,
\end{aligned} \tag{1}$$

with initial values $S(0) = S_0$, $I(0) = I_0$, $I_D(0) = I_{D_0}$, $I_{DA}(0) = I_{DA_0}$, $S_+(0) = S_{+_0}$ and $M(0) = M_0$ at $t = 0$, and $\xi' = \xi(1 - \eta)$, where η is effectiveness of the drug input and ξ represents the rate of progression from HIV diagnosis to the AIDS class.

Here, the constant recruitment rate in the susceptible population is Π either by birth or immigration. There is a constant natural death rate d. β is the product of the effective contact rate between susceptible and infected individuals to result in HIV infection and the transmission probability of HIV per contact. λ_1, λ_2 are the modification factors accounting for varying levels of the activity and infectiousness of the diagnosed HIV-positive individuals and the AIDS patients, respectively. The dissemination rate of awareness among susceptible, at which they form the *aware class*, is represented by c. The transfer rate from aware susceptible to unaware susceptible class is denoted as ω. δ is the diagnosis rate and d_I is the natural death rate of infected individuals. ρ is the proportion of diagnosed individuals who have not yet developed to AIDS ($0 \le \rho \le 1$). Here, α_I and α_D are additional death rates for the diagnosed HIV-positive individuals and for those who are AIDS infected, respectively. The parameter μ is the proportionality constant which governs the implementation of awareness programs and μ_0 denotes the depletion rate of these programs due to ineffectiveness, public interests, social problems, etc.

Throughout this paper, to shorten the notation, we use the following notations: $\mu_1 = \delta + d + d_I$, $\mu_2 = \xi' + d + \alpha_I$, $\mu_3 = d + \alpha_A$, $\mu_4 = d + \omega$.

2.1 Model properties:

System (1) will be analyzed in a domain $\mathcal{D} \subset \mathbb{R}^6_+$, where all feasible solutions enter the region

$$\mathcal{D} = \left\{(S, I, I_D, I_{DA}, S_+, M) \in \mathbb{R}^6_+ : 0 \le N \le \frac{\Pi}{d}, 0 \le M \le \frac{\mu\Pi}{\mu_0 d}\right\}. \tag{2}$$

Theorem 2.1 *The solutions of system* (1) *with initial conditions satisfy* $S(t) > 0$, $I(t) > 0$, $I_D(t) > 0$, $I_{DA}(t) > 0$, $S_+(t) > 0$, $M(t) > 0$ *for all* $t > 0$. *The region* $\mathcal{D} \in \mathbb{R}^6_+$ *is positively invariant and attracting with respect to system* (1).

Proof From the first equation of (1) we have

$$\dot{S} \geq -\big[\beta(I + \lambda_1 I_D + \lambda_2 I_{DA}) + d + cM\big]S,$$

giving

$$S(t) \geq S(0)\exp\left[-\int_0^t \big\{\beta(I + \lambda_1 I_D + \lambda_2 I_{DA}) + d + cM\big\}\,ds\right] > 0.$$

In a similar fashion we can show that $I(t)$, $I_D(t)$, $I_{DA}(t)$, and $S_+(t)$ are all strictly positive. Thus we can conclude that all solutions of system (1) remain positive for all $t > 0$. Now, we will show that all feasible solutions are uniformly bounded in $\mathcal{D}$. Using the fact that $N = S + I + I_D + I_{DA} + S_+$, we get

$$\dot{N} = \Pi - dN - d_I I - \alpha_I I_D - \alpha_A I_{DA} \leq \Pi - dN.$$

Solving this differential equation, we have

$$0 \leq N(t) \leq \frac{\Pi}{d} + N(0)e^{-dt},$$

where $N(0)$ represents the initial value of the total population at time $t = 0$. Thus, $0 \leq N(t) \leq \frac{\Pi}{d}$ hold, as $t \to \infty$. Therefore, it is clear from the above that Π/d is an upper bound of N, provided $N(0) \leq \Pi/d$. If $N(0) > \frac{\Pi}{d}$, then N will decrease to this level. Hence, all feasible solutions of the system attracted or remain in the region $\mathcal{D}$. Further, the usual existence, uniqueness, and continuation results hold for the system in this region. □

3 Analysis of equilibria

In this section, we focus on the existence and stability of equilibria for system (1). The equilibrium points are obtained by equating the right-hand side of each equation in (1) to zero and it is found that system (1) has two non-negative equilibria.

Let $(S^*, I^*, I_D^*, I_{DA}^*, S_+^*, M^*)$ denote an equilibrium point. Clearly, from the third equation we have $I_D^* = \frac{\rho\delta}{\mu_2} I^*$, then from the fourth equation $I_{DA}^* = \frac{\delta}{\mu_2\mu_3}[\rho\xi' + (1-\rho)\mu_2]I^*$. Next, from the second equation we obtain two possibilities: either $I^* = 0$ or $\beta S^*[1 + \lambda_1\frac{\rho\delta}{\mu_2} + \lambda_2\frac{\delta}{\mu_2\mu_3}(\rho\xi' + (1-\rho)\mu_2)] = \mu_1$. In the first case we subsequently obtain $M^* = 0$ from the sixth equation, $S_+^* = 0$ from the fifth equation, and $S^* = \frac{\Pi}{d} =: S_0$ from the first one, which gives us disease-free equilibrium (DFE). In the latter case we easily see that $S^* = \frac{\mu_1}{\beta[1+\lambda_1\frac{\rho\delta}{\mu_2}+\lambda_2\frac{\delta}{\mu_2\mu_3}(\rho\xi'+(1-\rho)\mu_2)]} > 0$ and all other coordinates of this equilibrium point are dependent on the value of I^*, namely $S_+^* = \frac{c}{\mu_4}S^*M^*$ and $M^* = \frac{\mu\delta}{\mu_0\mu_2\mu_3}[\rho(\mu_3+\xi') + (1-\rho)\mu_2]I^*$, which allows to calculate I^* from the first equation. We obtain

$$\begin{aligned}
&\Pi - \mu_1 I^* - dS^* - d\frac{c}{\mu_4}S^*\frac{\mu\delta}{\mu_0\mu_2\mu_3}\big[\rho\big(\mu_3 + \xi'\big) + (1-\rho)\mu_2\big]I^* = 0,\\
&\implies \quad I^* = \frac{\Pi - dS^*}{\mu_1 + \frac{cdS^*\mu\delta}{\mu_0\mu_2\mu_3\mu_4}[\rho(\mu_3+\xi') + (1-\rho)\mu_2]}.
\end{aligned}$$

It is obvious that $I^* > 0$ implies positivity of all other coordinates, and therefore $S^* < S_0$ is the condition guaranteeing the existence of positive (endemic) equilibrium (EE).

3.1 Disease-free equilibrium (DFE) and basic reproduction number $\mathcal{R}_0$

The model has always a disease-free equilibrium $E_0 = (S_0, 0, 0, 0, 0, 0) = (\frac{\Pi}{d}, 0, 0, 0, 0, 0)$. Local stability of E_0 is governed by basic reproduction number $\mathcal{R}_0$; cf. [15]. Biologically speaking, $\mathcal{R}_0$ is an average number of new secondary infections generated by a single HIV infected individual, introduced into a susceptible population. The basic reproduction number $\mathcal{R}_0$ could be determined using the next generation approach [15]. Using this approach we need to renumber the model variables in such a way that compartments reflecting infected individuals are at the beginning, so we have $x = (I, I_D, I_{DA}, S, S_+, M)^T$, with the number of infected compartments equal to 3. Now, by $\mathcal{X}_S$ we denote the set of all disease-free states, $\mathcal{X}_S = \{x \geq 0 : x_i = 0 \text{ for } i = 1, 2, 3\}$. System (1) shall be written in the form

$$\dot{x}_i = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), \quad i = 1, 2, \ldots, 6,$$

where $\mathcal{F}_i$ describes a rate of appearance of new infections in compartment i, while $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$ and $\mathcal{V}_i^+$ is a rate of transfer into the compartment i, $\mathcal{V}_i^-$ is a rate of transfer out of the compartment i. The following assumptions are to be posed:

- (A1) $\mathcal{F}_i(x) \geq 0$, $\mathcal{V}_i^+(x) \geq 0$, $\mathcal{V}_i^-(x) \geq 0$ for any $x \geq 0$;
- (A2) if $x_i = 0$, then $\mathcal{V}_i^- = 0$;
- (A3) $\mathcal{F}_i = 0$ for $i > 3$;
- (A4) if $x \in \mathcal{X}_S$, then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+(x) = 0$ for $i = 1, 2, 3$;
- (A5) if x_0 is DFE, then eigenvalues of the Jacobi matrix $Df(x_0)$ restricted to the subspace $\mathcal{F} = 0$ have all eigenvalues with negative real parts.

According to Lemma 1 in [15]

$$\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \qquad \mathcal{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

where F and V are squared matrices of dimension m and $\mathcal{R}_0 = \varrho(FV^{-1})$ (ϱ denotes a spectral radius). Eventually, according to Theorem 2 in [15], we know that x_0 is locally asymptotically stable for $\mathcal{R}_0 < 1$ and unstable for reverse inequality.

In the case of system (1),

$$\mathcal{F} = \begin{pmatrix} \beta(I + \lambda_1 I_D + \lambda_2 I_{DA})S \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

and

$$\mathcal{V}^+ = \begin{pmatrix} 0 \\ \rho\delta I \\ (1-\rho)\delta I + \xi' I_D \\ \Pi + \omega S_+ \\ cSM \\ \mu(I_D + I_{DA}) \end{pmatrix}, \qquad \mathcal{V}^- = \begin{pmatrix} \mu_1 I \\ \mu_2 I_D \\ \mu_3 I_{DA} \\ \beta(I + \lambda_1 I_D + \lambda_2 I_{DA})S + dS + cSM \\ \mu_4 S_+ \\ \mu_0 M \end{pmatrix}.$$

It is obvious that $\mathcal{F}$, $\mathcal{V}^+$, $\mathcal{V}^-$ satisfy Assumptions (A1)–(A4). Moreover,

$$Df(x)|_{\mathcal{F}=0} = \begin{pmatrix} -\mu_1 & 0 & 0 & 0 & 0 & 0 \\ \rho\delta & -\mu_2 & 0 & 0 & 0 & 0 \\ (1-\rho)\delta & \xi' & -\mu_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & -d-cM & \omega & -cS \\ 0 & 0 & 0 & cM & -\mu_4 & cS \\ 0 & \mu & \mu & 0 & 0 & -\mu_0 \end{pmatrix},$$

and all eigenvalues z of $Df(E_0)|_{\mathcal{F}=0}$ are real negative. Namely, $z_1 = -\mu_1$, $z_2 = -\mu_2$, $z_3 = -\mu_3$, $z_4 = -d$, $z_5 = -\mu_4$, $z_6 = -\mu_0$. Therefore, all assumptions posed in [15] are satisfied and E_0 is locally stable if $\mathcal{R}_0 < 1$.

Let us calculate $\mathcal{R}_0$. The matrices F and V for new infection terms and remaining transfer terms are respectively given by

$$F = \begin{pmatrix} \frac{\beta\Pi}{d} & \lambda_1\frac{\beta\Pi}{d} & \lambda_2\frac{\beta\Pi}{d} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} \mu_1 & 0 & 0 \\ -\rho\delta & \mu_2 & 0 \\ -(1-\rho)\delta & -\xi' & \mu_3 \end{pmatrix}.$$

The basic reproduction number $\mathcal{R}_0$ is thus given by $\mathcal{R}_0 = \varrho(FV^{-1}) = \frac{\beta\Pi}{d\mu_1}(1 + \lambda_1\frac{\rho\delta}{\mu_2} + \lambda_2\frac{\delta[\rho\xi'+(1-\rho)\mu_2]}{\mu_2\mu_3})$.

Corollary 3.1 *If* $\frac{\beta\Pi}{d\mu_1}(1 + \lambda_1\frac{\rho\delta}{\mu_2} + \lambda_2\frac{\delta[\rho\xi'+(1-\rho)\mu_2]}{\mu_2\mu_3}) < 1$, *then the disease-free equilibrium* E_0 *is locally asymptotically stable.*

Notice that, the inequality $\mathcal{R}_0 < 1$ is equivalent to $S^* > S_0$ which means that the positive equilibrium EE does not exist. On the other hand, if EE exists, then DFE is unstable.

3.2 Endemic equilibrium (EE) and its stability

System (1) has an endemic equilibrium $E^* = (S^*, I^*, I_D^*, I_{DA}^*, S_+^*, M^*)$ with positive coordinates provided that $\mathcal{R}_0 > 1$. From the analysis presented at the beginning of this section we have

$$S^* = \frac{\Pi}{d\mathcal{R}_0},$$

$$I^* = \frac{\Pi(\mathcal{R}_0 - 1)\mu_0\mu_2\mu_3\mu_4}{\mu_0\mu_1\mu_2\mu_3\mu_4\mathcal{R}_0 + \Pi c\mu\delta[\rho(\mu_3 + \xi') + (1-\rho)\mu_2]},$$

$$I_D^* = \frac{\rho\delta}{\mu_2}I^*,$$

$$I_{DA}^* = \frac{\delta}{\mu_2\mu_3}\big[\rho\xi' + (1-\rho)\mu_2\big]I^*,$$

$$S_+^* = \frac{\Pi c\mu}{d\mathcal{R}_0\mu_0\mu_1\mu_4}\left[\rho\delta + \frac{\delta[\xi' + (1-\rho)(d+\alpha_I)]}{\mu_3}\right]I^*,$$

$$M^* = \frac{\mu}{\mu_0\mu_1}\left[\rho\delta + \frac{\delta[\xi' + (1-\rho)(d+\alpha_I)]}{\mu_3}\right]I^*.$$

Remark Observe from the expression of I^* that when $\mathcal{R}_0 > 1$, the endemic equilibrium exists. We thus have the existence condition of the endemic equilibria. It is also important to note that $\frac{\partial I^*}{\partial c}$ and $\frac{\partial I^*}{\partial \delta}$ are negative. This means, as long as infected individuals become aware and go under treatment, the equilibrium level of unaware and untreated infectives starts to decrease. This shows that the dissemination rate and the treatment rate really have significant input in HIV control.

In order to attain full characterization of the endemic equilibrium E^*, we study the asymptotic stability behavior using Lyapunov's stability theory. If this function has only a single minimum, i.e., an equilibrium point, and it is strictly decreasing along all non-equilibrium solutions, then all solutions tend to the equilibrium point where the scalar function (Lyapunov function) is minimum. The results obtained by performing local and global stability analysis of the obtained equilibria are stated in the following theorems.

Theorem 3.2 *The endemic equilibrium E^* is locally asymptotically stable (LAS) in $\mathcal{D}$, provided the inequalities hold*:

$$\psi_3 \xi'^2 < \frac{4}{25}\psi_2\mu_2\mu_3, \tag{3}$$

$$\psi_5 \mu^2 < \frac{1}{5}\psi_2\mu_0\mu_2, \tag{4}$$

$$\psi_5 \mu^2 < \frac{1}{5}\psi_3\mu_0\mu_3, \tag{5}$$

$$\psi_4 c^2 S^{*2} < \frac{1}{3}\psi_5\mu_0\mu_4, \tag{6}$$

where ψ_i $(i = 2, 3, 4, 5)$ are chosen so that conditions (35), (36), (37), and (38) are satisfied.

In the next theorem, we show that the endemic equilibrium point $E^*(S^*, I^*, I_D^*, I_{DA}^*, S_+^*, M^*)$ is globally asymptotically stable.

Theorem 3.3 *The endemic equilibrium E^* is globally asymptotically stable (GAS) in $\mathcal{D}$, provided the following inequalities hold*:

1 $(d + \mu_3)^2 < \frac{2}{3}\frac{d^2\mu_4}{cM^*}$;

2 $$\max\left\{\frac{1}{11}\left[\left(\frac{(2d+\alpha_I)^2}{d} + \frac{c\alpha_I^2 M^*}{d\mu_4}\right)\frac{c\alpha_A^2 M^*}{\mu_4} + \left((\alpha_I+\alpha_A)^2 + \frac{(d_I+\alpha_A)^2\xi'^2}{(1-\rho)^2\delta^2}\right)\right]W,\right.$$
$$\frac{1}{8}\frac{\lambda_1^2(2d+d_I)^2\Pi^2}{d^2(I^*+\lambda_1 I_D^*+\lambda_2 I_{DA}^*)^2}\left[\alpha_A + \frac{(d_I+\alpha_A)\mu_3}{(1-\rho)\delta}\right], \frac{1}{8}\frac{\lambda_2^2(2d+d_I)^2\Pi^2}{d^2(I^*+\lambda_1 I_D^*+\lambda_2 I_{DA}^*)^2}\left[\alpha_I\right.$$
$$\left.+\frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\right], \frac{1}{12}\left[\alpha_I + \frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\right]\left[\alpha_A + \frac{(d_I+\alpha_A)\mu_3}{(1-\rho)\delta}\right]\Bigg\}$$
$$< \frac{1}{36}\left[\alpha_I + \frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\right]\left[\alpha_A + \frac{(d_I+\alpha_A)\mu_3}{(1-\rho)\delta}\right]W;$$

3 $$\frac{dc\Pi^2}{\mu_0 d^2\mu_4 M^*} < \frac{1}{27}\min\left\{\frac{\mu_0}{\mu^2}\left[\alpha_I + \frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\right], \frac{\mu_0}{\mu^2}\left[\alpha_A + \frac{(d_I+\alpha_A)\mu_3}{(1-\rho)\delta}\right]\right\},$$

where $W = [d_I\beta(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA}^*) + (2d + d_I)(\mu_1 - \frac{\Pi\beta}{d})]$.

For the proof of Theorems 3.2 and 3.3 see Appendices 1 and 2, respectively.

4 Optimal control strategy

In this section, we formulate an optimal control problem using Pontryagin minimum principle [16] in order to obtain an optimal strategy for our epidemiological system (1). Generally we solve these types of problems by finding the time-dependent profiles of the control variable to optimize a particular performance. It is apparent from our previous discussion that to control the spread of HIV/AIDS, it is obligatory to propagate awareness amongst individuals. In this section, we consider a control problem together with the mathematical model described by equation (1) with the objective function given by

$$J\big[u_1(t), u_2(t)\big] = \int_{t_0}^{t_f} \big[Pu_1^2(t) + Qu_2^2(t) - S_+^2(t)\big]\,dt, \tag{7}$$

where $u_1(t)$ and $u_2(t)$ are the control variables representing efficacy of drug-dosing and implementation rate of awareness campaigns, respectively. The parameters P and Q are weight constants for control inputs. The first term in (7) represents systemic cost of the drug treatments and second term represents cost associated with the implementation of awareness campaign. The objective function (7) expresses our goal to minimize costs for both drug-dosing and successful media campaigns, while maximizing aware susceptible individuals. Therefore, we seek an optimal control pair (u_1, u_2) such that

$$J\big(u_1^*, u_2^*\big) = \min\big\{J(u_1, u_2) : (u_1, u_2) \in \mathcal{U}\big\}, \tag{8}$$

subject to the system of ODEs

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \beta(I + \lambda_1 I_D + \lambda_2 I_{DA})S - dS - cSM + \omega S_+,\\
\frac{dI}{dt} &= \beta(I + \lambda_1 I_D + \lambda_2 I_{DA})S - \mu_1 I,\\
\frac{dI_D}{dt} &= \rho\delta I - \xi\big[1 - \eta u_1(t)\big]I_D - (d + \alpha_I)I_D,\\
\frac{dI_{DA}}{dt} &= (1 - \rho)\delta I + \xi\big\{1 - \eta u_1(t)\big\}I_D - \mu_3 I_{DA},\\
\frac{dS_+}{dt} &= cSM - \mu_4 S_+,\\
\frac{dM}{dt} &= u_2(t)(I_D + I_{DA}) - \mu_0 M,
\end{aligned} \tag{9}$$

where $\mathcal{U} = \{(u_1, u_2) : u_i \text{ measurable}, 0 \le u_i(t) \le 1, t \in [t_0, t_f], \text{for } i = 1, 2\}$.

4.1 The optimality system

We begin this section by noting that the existence of an optimal control pair that can be obtained using a result from Fleming et al. (2012) [17]. It is rather straightforward to show that the right-hand sides of system (1) are bounded by a linear function of the state and control variables, and the integrand of the objective function (7) is concave on $\mathcal{U}$ and is bounded below. These bounds give one the compactness needed to establish the existence of optimal controls using standard arguments (see [17]).

The Pontryagin minimum principle [16] converts the problem of minimizing the cost functional (8) subject to state variables into minimizing the Hamiltonian [18, 19] with respect to the controls at each time t. From Hamiltonian H we have

$$\begin{aligned}
&H(S, I, I_D, I_{DA}, M, S_+, u_1, u_2, \xi_1, \xi_2, \xi_3, \xi_4, \xi_5, \xi_6)\\
&\quad = Pu_1^2(t) + Qu_2^2(t) - S_+^2\\
&\qquad + \xi_1\big\{\Pi - \beta(I + \lambda_1 I_D + \lambda_2 I_{DA})S - dS - cSM + \omega S_+\big\}\\
&\qquad + \xi_2\big\{\beta(I + \lambda_1 I_D + \lambda_2 I_{DA})S - \mu_1 I\big\}\\
&\qquad + \xi_3\big\{\rho\delta I - \xi\big[1 - \eta u_1(t)\big]I_D - (d + \alpha_I)I_D\big\}\\
&\qquad + \xi_4\big\{(1-\rho)\delta I + \xi\big[1 - \eta u_1(t)\big]I_D - \mu_3 I_{DA}\big\}\\
&\qquad + \xi_5\{cSM - \mu_4 S_+\} + \xi_6\big\{u_2(t)(I_D + I_{DA}) - \mu_0 M\big\},
\end{aligned}$$

where ξ_i $(i = 1, 2, \ldots, 6)$ are the adjoint variables.

Given an optimal control and corresponding states, there exists adjoint variable ξ_i satisfying the following equations:

$$\begin{aligned}
\frac{d\xi_1}{dt} &= -\frac{\partial H}{\partial S} = \xi_1\big[\beta(I + \lambda_1 I_D + \lambda_2 I_{DA}) + d - cM\big] - \xi_2\beta(I + \lambda_1 I_D + \lambda_2 I_{DA}) - \xi_5 cM,\\
\frac{d\xi_2}{dt} &= -\frac{\partial H}{\partial I} = (\xi_1 - \xi_2)\beta S + \mu_1 - \xi_3\rho\delta - \xi_4(1-\rho)\delta,\\
\frac{d\xi_3}{dt} &= -\frac{\partial H}{\partial I_D} = \lambda_1\beta(\xi_1 - \xi_2)S + \xi_3\big(\xi\big[1 - \eta u_1(t)\big] + d + \alpha_I\big) - \xi_4\xi\big[1 - \eta u_1(t)\big] - \xi_6 u_2(t),\\
\frac{d\xi_4}{dt} &= -\frac{\partial H}{\partial I_{DA}} = \lambda_2\beta(\xi_1 - \xi_2)S + \xi_4\mu_3 - \xi_6 u_2(t),\\
\frac{d\xi_5}{dt} &= -\frac{\partial H}{\partial S_+} = 2S_+ - \xi_1\omega + \xi_5\mu_4,\\
\frac{d\xi_6}{dt} &= -\frac{\partial H}{\partial M} = \xi_1 cS - \xi_5 cS + \xi_6\mu_0,
\end{aligned} \tag{10}$$

with transversality conditions $\xi_i(t_f) = 0$ for $i = 1, 2, \ldots, 6$.

The Hamiltonian is minimized with respect to u_1 and u_2 at the optimal value (u_1^*, u_2^*), so the derivative of the H with respect to u_1 and u_2 at (u_1^*, u_2^*) must be zero. Now, using the fact that

$$\begin{aligned}
H &= Pu_1^2(t) + Qu_2^2(t) + \xi_3\xi\eta u_1(t)I_D - \xi_4\xi\eta u_1(t)I_D + \xi_6 u_2 I\\
&\quad + \text{other terms without } u_1 \text{ and } u_2,
\end{aligned} \tag{11}$$

and differentiating the expression for H with respect to u_1 and u_2 give

$$\frac{\partial H}{\partial u_1^*} = 2Pu_1^*(t) + \xi\eta(\xi_3 - \xi_4)I_D = 0, \tag{12}$$

$$\frac{\partial H}{\partial u_2^*} = 2Qu_2^*(t) + \xi_6(I_D + I_{DA}) = 0. \tag{13}$$

According to *Pontryagin's Minimum Principle*, the unrestricted optimal control u_1^* and u_2^* satisfies $\frac{\partial H}{\partial u} = 0$ at (u_1^*, u_2^*). So we have

$$u_1^*(t) = \frac{\xi\eta(\xi_4 - \xi_3)I_D}{2P}, \tag{14}$$

$$u_2^*(t) = -\frac{\xi_6(I_D + I_{DA})}{2Q}. \tag{15}$$

Since the standard control is bounded, we conclude for the control u_1 that

$$u_1^*(t) = \begin{cases} 0, & \text{if } \frac{\xi\eta(\xi_4-\xi_3)I_D}{2P} \leq 0; \\ \frac{\xi\eta(\xi_4-\xi_3)I_D}{2P}, & \text{if } 0 < \frac{\xi\eta(\xi_4-\xi_3)I_D}{2P} < 1; \\ 1, & \text{if } \frac{\xi\eta(\xi_4-\xi_3)I_D}{2P} \geq 1. \end{cases} \tag{16}$$

Hence the compact form of u_1^* is

$$u_1^* = \max\left[\min\left[1, \frac{\xi\eta(\xi_4 - \xi_3)I_D}{2P}\right], 0\right]. \tag{17}$$

In a similar manner we can get the compact form of u_2^*

$$u_2^* = \max\left[\min\left[1, -\frac{\xi_6(I_D + I_{DA})}{2Q}\right], 0\right]. \tag{18}$$

Therefore, we have the following theorem.

Theorem 4.1 *If the objective cost function $J(u_1, u_2)$ over $\mathcal{U}$ attains its minimum for the optimal control $u^* = (u_1^*, u_2^*)$ corresponding to the endemic equilibrium $(S^*, I^*, I_D^*, I_{DA}^*, S_+^*, M^*)$, then there exist adjoint functions ξ_1, ξ_2, ξ_3, ξ_4, ξ_5, ξ_6 satisfying equations (10) along with the transversality condition $\xi_i(t_f) = 0$ $(i = 1, 2, \ldots, 6)$.*

5 Numerical simulation

To study the dynamical behavior of our model (1), we perform numerical computations with initial values $S(0) = 200$, $I(0) = 15$, $I_D(0) = 10$, $I_{DA} = 5$, $S_+(0) = 50$, and $M(0) = 5$. The set of parameter values is given in Table 1. These values are cumulated from different journals and the rest are hypothetical parameters relevant to HIV/AIDS. Numerical simulations are done using MATLAB (version 7.6.0).

Initially, to confirm the feasibility of our analysis regarding existence and its stability conditions for system (1), we have carried out some numerical simulations by selecting the following parametric set as described in Table 1. For the set of parameter values given in Table 1, it may be checked that the condition of existence of an endemic equilibrium E^* and the stability conditions are satisfied. The eigenvalues of the Jacobian matrix corresponding to the equilibrium E^* of the model system (1) are obtained as -0.8689, -0.7432, $-0.3938 \pm 0.1232i$, and $-0.07094 \pm 0.0383i$. We note that all eigenvalues of the Jacobian matrix are either negative or have negative real parts. Hence, the endemic equilibrium E^* is locally asymptotically stable for the above set of parameter values.

From our analytical results, it is observed that when $\beta = 0.002$, $\mathcal{R}_0$ becomes $0.85 < 1$ and when $\beta = 0.005$, $\mathcal{R}_0 = 2.125 > 1$. We have plotted the observed population trajectories

Table 1 List of parameters used for system (1)

Parameter	Definition	Value/year	References
Π	Constant recruitment rate in the susceptible population	15	[6]
β	Contact rate between susceptible and infected individuals	0.002–0.2	[6]
λ_1	Modification factor	0.01	Estimated
λ_2	Modification factor	0.01–0.8	Estimated
μ	The proportionality constant which governs the implementation of awareness programs	0.025	[9]
d	Natural death rate of susceptible	0.01–0.025	[6, 9]
d_I	Natural death rate of infected individuals	0.005–0.01	[9]
c	Transfer rate of susceptible from unaware to aware class	0.00002–0.02	[9]
ω	Transfer rate from aware susceptible to unaware susceptible class	0.4	[6, 9]
ρ	The proportion of diagnosed individuals who have not yet developed to AIDS	0.75	Estimated
δ	Diagnosis rate	0.304	[9]
α_I	Additional death rates for the diagnosed HIV-positive individuals	0.0172	[6]
α_A	Additional death rates for those who are AIDS infected	0.0138	[6]
μ_0	Depletion rate of ineffective media programs	0.06	[9]
ξ	Rate of progression from HIV diagnosis to the AIDS class	0.4	Estimated
η	Effectiveness of the drug input	0.6	Estimated
u_1, u_2	Control variables	0.0–1.0	Estimated

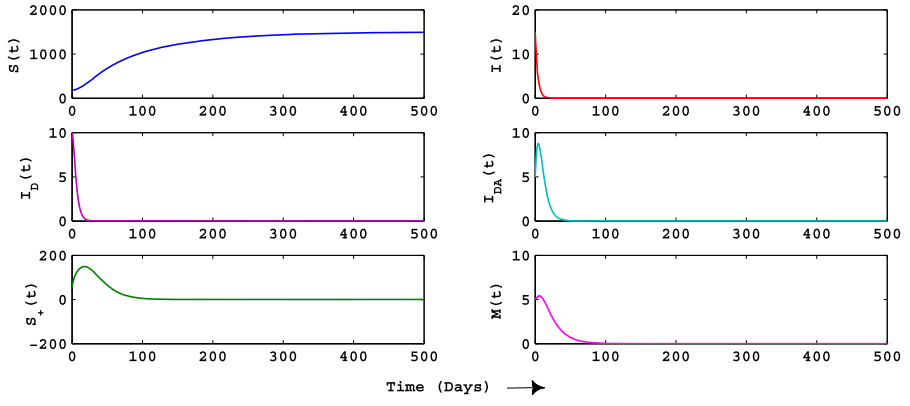

Figure 1 Trajectories showing the time-dependent changes in concentration of the model variables when $\mathcal{R}_0 < 1$

in the graphs depicting their respective individual trends for $\beta = 0.002$ and $\beta = 0.005$ in Figs. 1 and 2, respectively. These figures clearly illustrate the change in equilibrium level from disease-free state to endemic state. Hence, it is clear that the state of the system depends on the disease progression rate and for high transmission rate, the system attains its endemic state. In Figs. 3 and 4 respectively, we show the nonlinear stability behaviors of (S^*, I^*) and (I_D^*, I_{DA}^*) in $S-I$ and $I_D - I_{DA}$ spaces. These two figures convey that both the trajectories are initiating inside the region of attraction approach towards the equilibrium values (S^*, I^*) and (I_D^*, I_{DA}^*), respectively.

The variations of human population and awareness programs with respect to time t for different values of u_1 and u_2 are shown in Fig. 5. For this we took initial values $S(0) = 35{,}000$, $I(0) = 20{,}000$, $I_D(0) = 500$, $I_{DA} = 200$, $S_+(0) = 500$, $M(0) = 25$, constant recruitment rate as $\Pi = 10{,}000$/year and other parameters are fixed as in Table 1. It can be concluded from this figure that with proper inputs in control parameters u_1 and u_2, it yields more trustworthy results in increasing the awareness within susceptible populations ($S(t)$ and

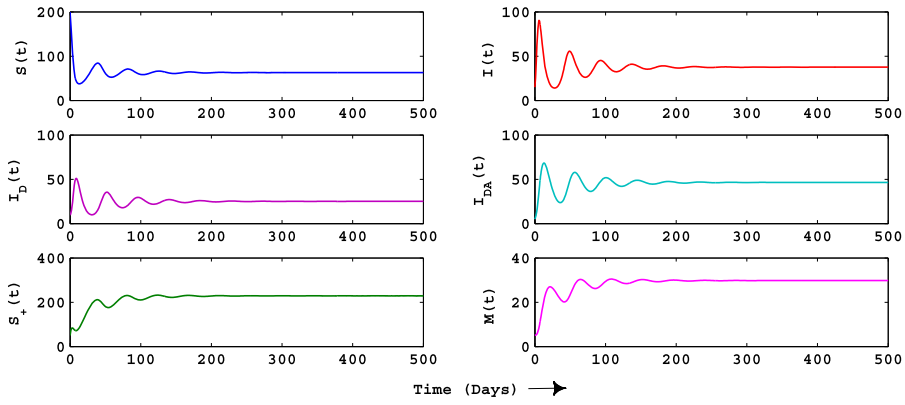

Figure 2 Trajectories showing the time-dependent changes in concentration of the model variables when $\mathcal{R}_0 > 1$

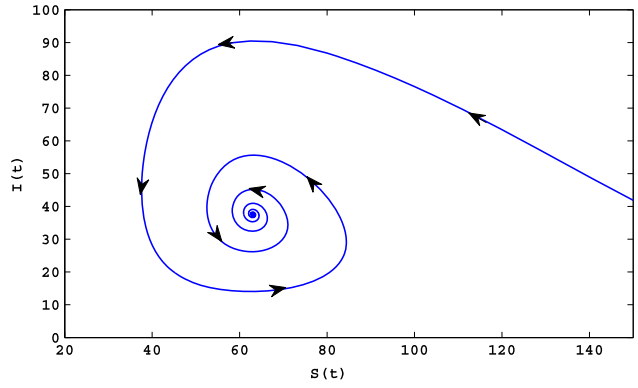

Figure 3 Nonlinear stability of (S^*, I^*) in S–I plane

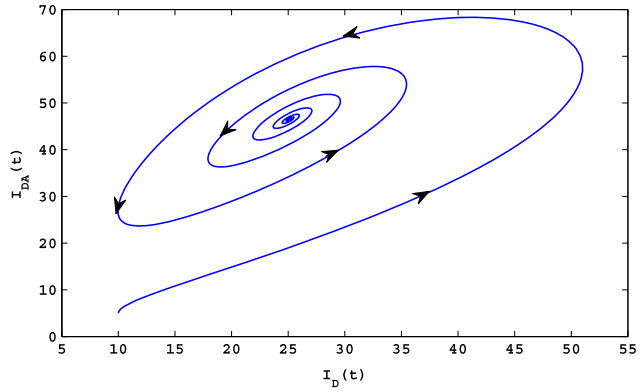

Figure 4 Nonlinear stability of (I_D^*, I_{DA}^*) in I_D–I_{DA} plane

$S_+(t)$) and decreasing infection incidences among the infected populations ($I(t)$, $I_D(t)$, and $I_{DA}(t)$). Here, red trajectories indicate the graphs for control inputs $(u_1, u_2) = (0.0, 0.2)$, whereas black and blue trajectories indicate the graphs for $(u_1, u_2) = (0.5, 0.4)$ and $(u_1, u_2) =$

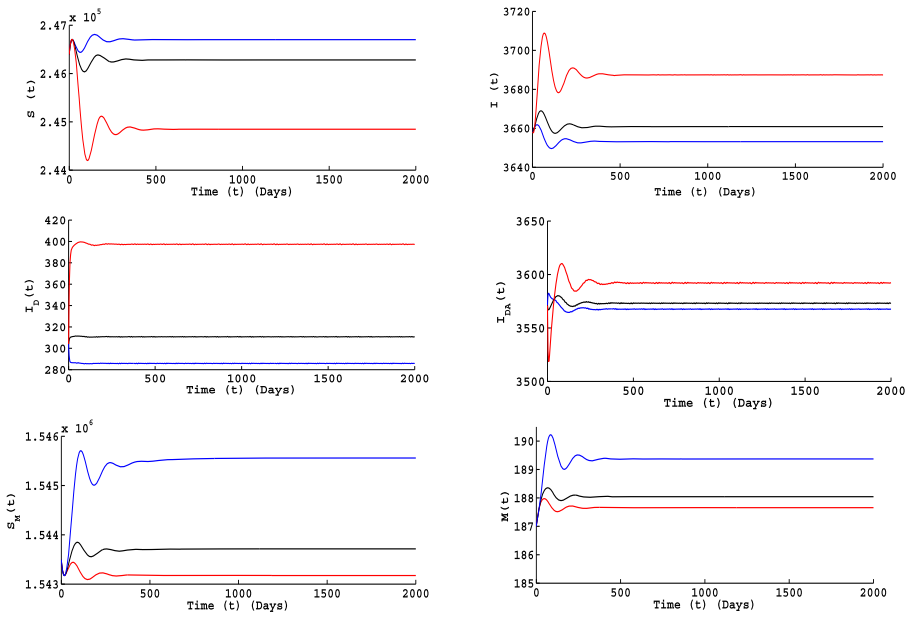

Figure 5 Population graphs are plotted here for different values of (u_1, u_2). Red trajectories are drawn for the pair of control input values $(u_1, u_2 = (0.0, 0.2))$, whereas black and blue trajectories indicate the graphs for $(u_1, u_2) = (0.5, 0.4)$ and $(u_1, u_2) = (0.5, 0.6)$, respectively

$(0.5, 0.6)$, respectively. Noteworthily, when u_2 has greater value than u_1 (blue lines), the graph reflects more significant results rather than the case when $u_1 > u_2$ (black lines). This indicates that people need to be more vigilant and aware about their personal health behavior, instead of being reluctant during therapeutic regime or engaging in sexual acts.

Lastly, we use sensitivity analysis method to investigate the impact of various intervention measures on HIV transmission. We hope that these results obtained here could improve the knowledge of the effect of different interventions. Here we derive sensitivity index by using partial rank correlation coefficients (PRCC) of the basic reproductive ratio with respect to the parameters. The normalized forward sensitivity index of $\mathcal{R}_0$ with respect to a parameter 'a' is defined as follows Abiodun et al. (2013) [20]:

$$\Pi_a^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial a} \times \frac{a}{\mathcal{R}_0}. \tag{19}$$

It follows from Fig. 6 that the basic reproductive ratio $\mathcal{R}_0$ for system (1) is most negatively correlated with δ and ξ', which implies that increasing the values of factors can lead to a decrease in disease prevalence. Thus, disease prevalence is sensitive to diagnosis rate and drug efficacy. Increasing the drug efficacy and diagnosis rate can greatly reduce new cases and prevalence. We also considered how the values of δ and ξ' jointly influence the reproduction number $\mathcal{R}_0$. Figure 7 shows a three-dimensional contour plot of δ, ξ', and $\mathcal{R}_0$. We simultaneously plot the $\mathcal{R}_0 = 1$ plane and show the intersections of the two planes. The points where these two planes intersect are the threshold values of diagnosis rate δ and drug efficacy ξ' at necessary for the control of the epidemic. The contour shows that δ does not play a significant role in mitigating the disease when compared to ξ'. This can be interpreted in the context of the epidemic to mean that regular treatment

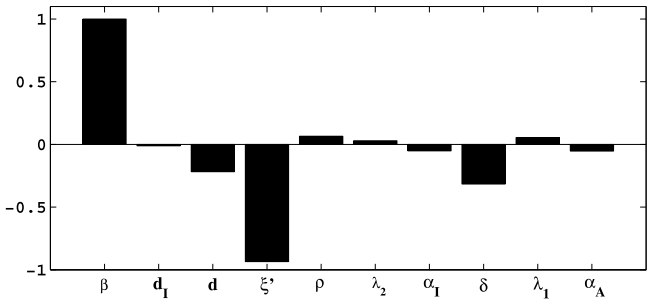

Figure 6 Tornado plots of sensitivity of $\mathcal{R}_0$ for each of the parameters

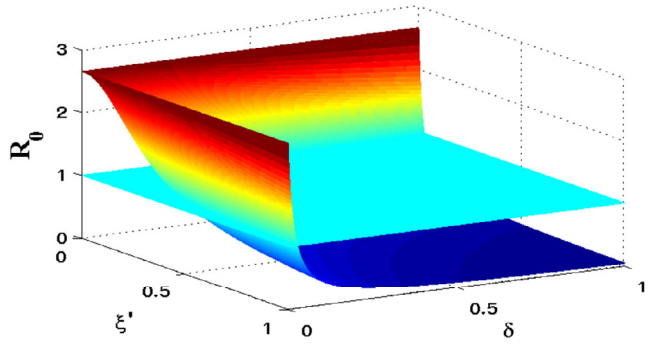

Figure 7 A three-dimensional plot

and drug effectiveness are highly prevailing to make a meaningful impact on the current HIV epidemic.

6 Conclusion

In this paper, we have established an epidemic model to investigate the likely impact of awareness campaigning driven by media along with screening and treatment on the dynamics of HIV/AIDS. This model looks at the recently launched HIV counseling and testing (HCT) campaign followed by awareness campaigning, to model its feasible impact on the dynamics of the disease. HIV awareness and prevalence of the disease are inversely correlated with each other and depend upon human behavior. The model analysis shows how the inclusion of awareness modifies the contact structure and thereby affects the disease states. The model exhibits two equilibria, namely disease-free equilibrium and endemic equilibrium. We have studied the existence and stability of the disease-free and endemic equilibria. We obtain the basic reproduction number ($\mathcal{R}_0$) which determines the persistence of the disease. For $\mathcal{R}_0$ below the unity, disease cannot persist in the system, whereas for $\mathcal{R}_0$ above the unity, disease coexists in the system. We have also observed that the basic reproduction number $\mathcal{R}_0$ contains terms like δ, ξ' etc., but does not contain any awareness related terms. However, HCT itself has very little impact on reducing the prevalence of HIV unless the efficacy of the campaigns exceeds an evaluated threshold. We prove the local and global asymptotic stability of the disease-free equilibrium. Also, for $\mathcal{R}_0 > 1$, the global stability of the endemic equilibrium is also derived by constructing a Lyapunov function.

Developing an optimal strategy that minimizes the total number of infected individuals and the costs associated, drug-dosing and the implementation of awareness campaigns, we have extended our proposed model, where we consider that drug-dosing and implementation of awareness campaigns are not constants but vary with time. The obtained optimality system (8) subject to (9) measures a cost effective way of controlling the disease by expanding the number of effective awareness campaigning. Also, drug-dosing through antiviral therapy is equally important, which decelerates the AIDS progression significantly due to reduction in viral load. However, we should keep in mind that we should always run awareness campaigning in a cabalistic way so that people always keep receiving the latest information about the disease. Since it is observed that if the awareness of the local prevalence of a disease is not addressed by the media or local health authorities, it is more likely to be raised by the acts of informal information spread. If the information about infectious disease is disseminated in the population, people regulate their behavior according to their awareness level.

Appendix 1: Proof of Theorem 3.2

We consider the following positive definite function:

$$\mathcal{L} = \frac{1}{2}s^2 + \frac{\psi_1}{2}i^2 + \frac{\psi_2}{2}i_d^2 + \frac{\psi_3}{2}i_{da}^2 + \frac{\psi_4}{2}s_+^2 + \frac{\psi_5}{2}m^2, \tag{20}$$

where ψ_j $(j = 1, 2, \ldots, 5)$ are some positive constants and will be defined later. Here s, i, i_d, i_{da}, s_+, and m are small perturbations in S, I, I_D, I_{DA}, S_+, and M around equilibrium E^*, respectively, i.e., $S = S^* + s$, $I = I^* + i$, $I_D = I_D^* + i_d$, $I_{DA} = I_{DA}^* + i_{da}$, $S_+ = S_+^* + s_+$, and $M = M^* + m$. Now, differentiating $\mathcal{L}$ with respect to 't' and using the linearized system of (1) around E^*, we get

$$\begin{aligned}\mathcal{L}' = {} & -\left(\frac{\Pi + \omega S_+^*}{S^*}\right)s^2 - \psi_1\left[\mu_1 - \beta S^*\right]i^2 - \psi_2\mu_2 i_d^2 - \psi_3\mu_3 i_{da}^2 - \psi_4\mu_4 s_+^2 - \psi_5\mu_0 m^2 \\ & - \left[\beta S^* - \psi_1\left(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA}^*\right)\right]is + \left[\psi_1\beta\lambda_1 S^* + \psi_2\rho\delta\right]ii_d + \left[\psi_1\beta\lambda_2 S^*\right. \\ & \left. + \psi_3(1-\rho)\delta\right]ii_{da} + \psi_3\xi' i_d i_{da} + \psi_5\mu i_d m + \psi_5\mu i_{da} m + \psi_4 c S^* s_+ m - \beta\lambda_1 S^* s i_d \\ & + \left(\omega + \psi_4 c M^*\right)ss_+ - cS^* sm - \beta\lambda_2 S^* s i_{da}.\end{aligned}$$

Now, we choose $\psi_1 = \frac{\beta S^*}{(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA}^*)}$, so that we get

$$\begin{aligned}\mathcal{L}' = {} & -\left(\frac{\Pi + \omega S_+^*}{S^*}\right)s^2 - \frac{\beta S^*[\mu_1 - \beta S^*]}{(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA}^*)}i^2 - \psi_2\mu_2 i_d^2 - \psi_3\mu_3 i_{da}^2 - \psi_4\mu_4 s_+^2 - \psi_5\mu_0 m^2 \\ & + \left[\frac{\beta^2\lambda_1 S^{*2}}{(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA}^*)} + \psi_2\rho\delta\right]ii_d + \left[\frac{\beta^2\lambda_2 S^{*2}}{(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA}^*)} + \psi_3(1-\rho)\delta\right]ii_{da} \\ & + \psi_3\xi' i_d i_{da} + \psi_5\mu i_d m + \psi_5\mu i_{da} m + \psi_4 c S^* s_+ m - \beta\lambda_1 S^* s i_d + \left(\omega + \psi_4 c M^*\right)ss_+ \\ & - \beta\lambda_2 S^* sm - \beta\lambda_2 S^* s i_{da}.\end{aligned} \tag{21}$$

It is evident from equation (21) that $\mathcal{L}'$ will be negative definite if the following inequalities are satisfied:

$$\beta^2\lambda_1^2 S^{*2} < \frac{4}{25}\psi_2\left(\frac{\Pi + \omega S_+^*}{S^*}\right)\mu_2, \tag{22}$$

$$\beta^2\lambda_2^2 S^{*2} < \frac{4}{25}\psi_3\left(\frac{\Pi + \omega S_+^*}{S^*}\right)\mu_3, \tag{23}$$

$$\omega^2 < \frac{4}{15}\psi_4\left(\frac{\Pi + \omega S_+^*}{S^*}\right)\mu_4, \tag{24}$$

$$\psi_4 c^2 M^{*2} < \frac{4}{15}\left(\frac{\Pi + \omega S_+^*}{S^*}\right)\mu_4, \tag{25}$$

$$c^2 S^{*2} < \frac{1}{5}\psi_5\mu_0\left(\frac{\Pi + \omega S_+^*}{S^*}\right), \tag{26}$$

$$\frac{\beta^3\lambda_1^2 S^{*3}}{(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA}^*)} < \frac{1}{5}\psi_2\left[\mu_1 - \beta S^*\right]\mu_2, \tag{27}$$

$$\psi_2\rho^2\delta^2 < \frac{1}{5}\frac{\beta S^*[\mu_1 - \beta S^*]}{(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA}^*)}\mu_2, \tag{28}$$

$$\frac{\beta^3\lambda_2^2 S^{*3}}{(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA}^*)} < \frac{1}{5}\psi_3\left[\mu_1 - \beta S^*\right]\mu_3, \tag{29}$$

$$\psi_3(1-\rho)^2\delta^2 < \frac{1}{5}\frac{\beta S^*[\mu_1 - \beta S^*]}{(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA}^*)}\mu_3, \tag{30}$$

$$\psi_3\xi'^2 < \frac{4}{25}\psi_2\mu_2\mu_3, \tag{31}$$

$$\psi_5\mu^2 < \frac{1}{5}\psi_2\mu_0\mu_2, \tag{32}$$

$$\psi_5\mu^2 < \frac{1}{5}\psi_3\mu_0\mu_3, \tag{33}$$

$$\psi_4 c^2 S^{*2} < \frac{1}{3}\psi_5\mu_0\mu_4. \tag{34}$$

Now, from inequalities (22)–(30), we can choose positive values of ψ_2, ψ_3, ψ_4, and ψ_5, provided the following conditions hold properly:

$$\text{Condition 1:}\quad \max\left\{\frac{5\beta^3 S^{*3}\lambda_1^2}{(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA^*})[\mu_1 - \beta S^*]\mu_2}, \frac{25\beta^2\lambda_1^2 S^{*3}}{4(\Pi + \omega S_+^*)\mu_2}\right\} < \psi_2 < \frac{1}{5}\frac{\beta S^*[\mu_1 - \beta S^*]\mu_2}{\rho^2\delta^2(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA^*})}, \tag{35}$$

$$\text{Condition 2:}\quad \max\left\{\frac{5\beta^3\lambda_1^2 S^{*3}}{(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA^*})[\mu_1 - \beta S^*]\mu_3}, \frac{25\beta^2\lambda_2^2 S^{*3}}{4(\Pi + \omega S_+^*)\mu_3}\right\} < \psi_3 < \frac{1}{5}\frac{\beta S^*[\mu_1 - \beta S^*]\mu_3}{(1-\rho)^2\delta^2(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA^*})}, \tag{36}$$

$$\text{Condition 3:}\quad \frac{15 S^*\omega^2}{4\mu_4(\Pi + \omega S_+^*)} < \psi_4 < \frac{4(\Pi + \omega S_+^*)\mu_4}{15c^2 S^* M^{*2}}, \tag{37}$$

$$\text{Condition 4:}\quad \psi_5 > \frac{5c^2 S^{*3}}{\mu_0(\Pi + \omega S_+^*)}. \tag{38}$$

We can assert from inequalities (31)–(38) that $\mathcal{L}'$ is negative definite, and hence the theorem follows.

Appendix 2: Proof of Theorem 3.3

To study the global stability of the endemic equilibrium, we construct the following positive definite Lyapunov function:

$$\begin{aligned}\mathcal{V} = {}& \frac{1}{2}\left[\left(S-S^*\right)+\left(I-I^*\right)+\left(I_D-I_D^*\right)+\left(I_{DA}-I_{DA}^*\right)+\left(S_+-S_+^*\right)\right]^2+\frac{\phi_1}{2}\left(I-I^*\right)^2 \\ &+\frac{\phi_2}{2}\left(I_D-I_D^*\right)^2+\frac{\phi_3}{2}\left(I_{DA}-I_{DA}^*\right)^2+\frac{\phi_4}{2}\left(S_+-S_+^*\right)^2+\frac{\phi_5}{2}\left(M-M^*\right)^2, \end{aligned} \tag{39}$$

where the coefficients ϕ_j $(j = 1, 2, \ldots, 5)$ are positive constants to be chosen suitably later. The corresponding derivative of the Lyapunov function is given as

$$\begin{aligned}\mathcal{V}' = {}& \left[\left(S-S^*\right)+\left(I-I^*\right)+\left(I_D-I_D^*\right)+\left(I_{DA}-I_{DA}^*\right)+\left(S_+-S_+^*\right)\right]\times\left(\frac{dS}{dt}+\frac{dI}{dt}+\frac{dI_D}{dt}\right. \\ &\left.+\frac{dI_{DA}}{dt}+\frac{dS_+}{dt}\right)+\phi_1\left(I-I^*\right)\frac{dI}{dt}+\phi_2\left(I_D-I_D^*\right)\frac{dI_D}{dt}+\phi_3\left(I_{DA}-I_{DA}^*\right)\frac{dI_{DA}}{dt} \\ &+\phi_4\left(S_+-S_+^*\right)\frac{dS_+}{dt}+\phi_5\left(M-M^*\right)\frac{dM}{dt}. \end{aligned} \tag{40}$$

Using equation (1) and doing some algebraic manipulations, we get the above equation as follows:

$$\begin{aligned}\mathcal{V}' = {}& -d\left[\left(I-I^*\right)+\left(I_D-I_D^*\right)+\left(I_{DA}-I_{DA}^*\right)+\left(S_+-S_+^*\right)\right]^2-d\left(S-S^*\right)^2-\left[d_I+\phi_1\mu_1\right. \\ &\left.-\phi_1\beta S\right]\left(I-I^*\right)^2-\left[\alpha_I+\phi_2\mu_2\right]\left(I_D-I_D^*\right)^2-\left[\alpha_A+\phi_3\mu_3\right]\left(I_{DA}-I_{DA}^*\right)^2-\phi_4\mu_4\left(S_+\right. \\ &\left.-S_+^*\right)^2-\phi_5\mu_0\left(M-M^*\right)^2-\left[2d+d_I-\phi_1\beta\left(I^*+\lambda_1I_D^*+\lambda_2I_{DA}^*\right)\right]\left(S-S^*\right) \\ &\times\left(I-I^*\right)-\left[2d+\alpha_I\right]\left(S-S^*\right)\left(I_D-I_D^*\right)-\left(d+\mu_3\right)\left(S-S^*\right)\left(I_{DA}-I_{DA}^*\right) \\ &-\left[2d-\phi_4cM^*\right]\left(S-S^*\right)\left(S_+-S_+^*\right)-d_I\left(I-I^*\right)\left(S_+-S_+^*\right)-\left[\left(d_I+\alpha_I\right)-\phi_1\lambda_1\beta S\right. \\ &\left.-\phi_2\rho\delta\right]\left(I-I^*\right)\left(I_D-I_D^*\right)-\alpha_A\left(I_{DA}-I_{DA}^*\right)\left(S_+-S_+^*\right)-\left[\left(d_I+\alpha_A\right)-\phi_1\lambda_\beta S\right. \\ &\left.-\phi_3(1-\rho)\delta\right]\left(I-I^*\right)\left(I_{DA}-I_{DA}^*\right)-\left[\left(\alpha_A+\alpha_I\right)-\phi_3\xi'\right]\left(I_D-I_D^*\right)\left(I_{DA}-I_{DA}^*\right) \\ &-\alpha_I\left(I_D-I_D^*\right)\left(S_+-S_+^*\right)+\phi_5\mu\left(I_D-I_D^*\right)\left(M-M^*\right)+\phi_5\mu\left(I_{DA}-I_{DA}^*\right)\left(M-M^*\right) \\ &+\phi_4cS\left(S_+-S_+^*\right)\left(M-M^*\right). \end{aligned} \tag{41}$$

Now we pick $\phi_1 = \frac{(2d+d_I)}{\beta(I^*+\lambda_1I_D^*+\lambda_2I_{DA}^*)}$, $\phi_2 = \frac{(d_I+\alpha_I)}{\rho\delta}$, $\phi_3 = \frac{(d_I+\alpha_A)}{(1-\rho)\delta}$, $\phi_4 = \frac{2d}{cM^*}$ so that some nonlinear terms become vanished. Note that, the coefficient of $(I-I^*)^2$ is

$$d_I+\phi_1\mu_1-\phi_1\beta S \geq d_I+\phi_1\mu_1-\phi_1\beta\frac{\Pi}{d}>0$$

in presence of infection. Hence, we have

$$d_I+\frac{(2d+d_I)}{\beta(I^*+\lambda_1I_D^*+\lambda_2I_{DA}^*)}\left[\mu_1-\frac{\beta\Pi}{d}\right]>0 \tag{42}$$

and $\mathcal{V}'$ turns to this form

$$\begin{aligned}\mathcal{V}' <{}& -d\big[\big(I-I^*\big)+\big(I_D-I_D^*\big)+\big(I_{DA}-I_{DA}^*\big)+\big(S_+-S_+^*\big)\big]^2-d\big(S-S^*\big)^2-\bigg[d_I\\&+\frac{(2d+d_I)}{\beta(I^*+\lambda_1I_D^*+\lambda_2I_{DA}^*)}\bigg(\mu_1-\frac{\beta\Pi}{d}\bigg)\bigg]\big(I-I^*\big)^2-\bigg[\alpha_I+\frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\bigg]\big(I_D-I_D^*\big)^2\\&-\bigg[\alpha_A+\frac{(d_I+\alpha_A)\mu_3}{(1-\rho)\delta}\bigg]\big(I_{DA}-I_{DA}^*\big)^2-\frac{2d\mu_4}{cM^*}\big(S_+-S_+^*\big)^2-\phi_5\mu_0\big(M-M^*\big)^2\\&-[2d+\alpha_I]\big(S-S^*\big)\big(I_D-I_D^*\big)-[d+\mu_3]\big(S-S^*\big)\big(I_{DA}-I_{DA}^*\big)\\&+\frac{\lambda_1(2d+d_I)S}{(I^*+\lambda_1I_D^*+\lambda_2I_{DA}^*)}\big(I-I^*\big)\big(I_D-I_D^*\big)+\frac{\lambda_2(2d+d_I)S}{(I^*+\lambda_1I_D^*+\lambda_2I_{DA}^*)}\big(I-I^*\big)\big(I_{DA}-I_{DA}^*\big)\\&-d_I\big(I-I^*\big)\big(S_+-S_+^*\big)-\bigg[(\alpha_I+\alpha_A)-\frac{(d_I+\alpha_A)\xi'}{(1-\rho)\delta}\bigg]\big(I_D-I_D^*\big)\big(I_{DA}-I_{DA}^*\big)\\&-\alpha_I\big(I_D-I_D^*\big)\big(S_+-S_+^*\big)+\phi_5\mu\big(I_D-I_D^*\big)\big(M-M^*\big)-\alpha_A\big(I_{DA}-I_{DA}^*\big)\big(S_+-S_+^*\big)\\&+\phi_5\mu\big(I_{DA}-I_{DA}^*\big)\big(M-M^*\big)+\frac{2dS}{M^*}\big(S_+-S_+^*\big)\big(M-M^*\big).\end{aligned}\tag{43}$$

Now $\mathcal{V}'$ will be negative definite if the following conditions hold:

$$(2d+\alpha_I)^2<\frac{1}{3}d\bigg[\alpha_I+\frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\bigg],\tag{44}$$

$$(d+\mu_3)^2<\frac{2}{3}\frac{d^2\mu_4}{cM^*},\tag{45}$$

$$\begin{aligned}\frac{\lambda_1^2(2d+d_I)^2S_R^2}{(I^*+\lambda_1I_D^*+\lambda_2I_{DA}^*)^2}<{}&\frac{2}{9}\big[d_I\beta\big(I^*+\lambda_1I_D^*+\lambda_2I_{DA}^*\big)+(2d+d_I)(\mu_1-\beta S_R)\big]\\&\times\bigg[\alpha_I+\frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\bigg],\end{aligned}\tag{46}$$

$$d_I^2<\frac{1}{3}\frac{d\mu_4}{cM^*}\big[d_I\beta\big(I^*+\lambda_1I_D^*+\lambda_2I_{DA}^*\big)+(2d+d_I)(\mu_1-\beta S_R)\big],\tag{47}$$

$$\begin{aligned}\frac{\lambda_2^2(2d+d_I)^2S_R^2}{(I^*+\lambda_1I_D^*+\lambda_2I_{DA}^*)^2}<{}&\frac{2}{9}\big[d_I\beta\big(I^*+\lambda_1I_D^*+\lambda_2I_{DA}^*\big)+(2d+d_I)(\mu_1-\beta S_R)\big]\\&\times\bigg[\alpha_A+\frac{(d_I+\alpha_A)\mu_3}{(1-\rho)\delta}\bigg],\end{aligned}\tag{48}$$

$$(\alpha_I+\alpha_A)^2<\frac{1}{9}\bigg[\alpha_I+\frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\bigg]\bigg[\alpha_A+\frac{(d_I+\alpha_A)\mu_3}{(1-\rho)\delta}\bigg],\tag{49}$$

$$\frac{(d_I+\alpha_A)^2\xi'^2}{(1-\rho)^2\delta^2}<\frac{1}{9}\bigg[\alpha_I+\frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\bigg]\bigg[\alpha_A+\frac{(d_I+\alpha_A)\mu_3}{(1-\rho)\delta}\bigg],\tag{50}$$

$$\alpha_I^2<\frac{1}{6}\frac{d\mu_4}{cM^*}\bigg[\alpha_I+\frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\bigg],\tag{51}$$

$$\phi_5\mu^2<\frac{2}{9}\mu_0\bigg[\alpha_I+\frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\bigg],\tag{52}$$

$$\alpha_A^2<\frac{1}{6}\frac{\mu_4}{cM^*}\bigg[\alpha_A+\frac{(d_I+\alpha_A)\mu_3}{(1-\rho)\delta}\bigg],\tag{53}$$

$$\phi_5\mu^2 < \frac{2}{9}\mu_0\left[\alpha_A + \frac{(d_I+\alpha_A)\mu_3}{(1-\rho)\delta}\right], \tag{54}$$

$$\frac{dcS_R^2}{M^*} < \frac{1}{6}\phi_5\mu_0\mu_4. \tag{55}$$

Now, from inequalities (52), (54), and (55), we may choose a positive value of ϕ_5 if

$$\frac{dcS_R^2}{\mu_0\mu_4 M^*} < \frac{1}{27}\min\left\{\frac{\mu_0}{\mu^2}\left[\alpha_I + \frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\right], \frac{\mu_0}{\mu^2}\left[\alpha_A + \frac{(d_I+\alpha_A)\mu_3}{(1-\rho)\delta}\right]\right\}, \tag{56}$$

and from the rest of inequalities (except (45)), we get

$$\begin{aligned}
&\max\left\{\frac{1}{11}\left[\left(\frac{(2d+\alpha_I)^2}{d} + \frac{c\alpha_I^2 M^*}{d\mu_4}\right)\frac{c\alpha_A^2 M^*}{\mu_4} + \left((\alpha_I+\alpha_A)^2 + \frac{(d_I+\alpha_A)^2\xi'^2}{(1-\rho)^2\delta^2}\right)\right]W,\right.\\
&\quad\frac{1}{8}\frac{\lambda_1^2(2d+d_I)^2S_R^2}{(I^*+\lambda_1 I_D^*+\lambda_2 I_{DA}^*)^2}\left[\alpha_A + \frac{(d_I+\alpha_A)\mu_3}{(1-\rho)\delta}\right], \frac{1}{8}\frac{\lambda_2^2(2d+d_I)^2S_R^2}{(I^*+\lambda_1 I_D^*+\lambda_2 I_{DA}^*)^2}\left[\alpha_I\right.\\
&\quad\left.+\frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\right], \frac{1}{12}\left[\alpha_I + \frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\right]\left[\alpha_A + \frac{(d_I+\alpha_A)\mu_3}{(1-\rho)\delta}\right]\Bigg\}\\
&< \frac{1}{36}\left[\alpha_I + \frac{(d_I+\alpha_I)\mu_2}{\rho\delta}\right]\left[\alpha_A + \frac{(d_I+\alpha_A)\mu_3}{(1-\rho)\delta}\right]W,
\end{aligned} \tag{57}$$

where $W = [d_I\beta(I^* + \lambda_1 I_D^* + \lambda_2 I_{DA}^*) + (2d+d_I)(\mu_1 - \beta S_R)]$.

Finally, using the region of attraction $\mathcal{D}$, the above inequalities (56) and (57) reduce to the third and second conditions, respectively, in Theorem (3.3), which gives sufficient conditions for the stability of the endemic equilibrium point E^*, and hence the theorem follows.

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