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Modelling and optimal control of HIV/AIDS prevention through PrEP and limited treatment

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HIGHLIGHTS

- A model for transmission of HIV/AIDS with treatment and PrEP is introduced.
- Dynamical behaviour of the model is discussed.
- An optimal control problem to minimize the cost and disease fatality is set up.
- Important observations of the control problem have been obtained.
- Numerical simulations have been performed to support the analytical results.

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ABSTRACT

Epidemic outbreak is one of the primary issue that induce behavioural changes in healthy individuals to avoid contracting infection. We here propose a compartmental model for the transmission of HIV/AIDS including treatment and Pre-exposure prophylaxis (PrEP). It accounts for the effect of individual's behavioural response due to information of PrEP also. Taking PrEP by uninfected individuals actually can prevent the acquisition of HIV infection. Model analysis has been performed as well as the local and global stability of equilibrium points is established. Further, an optimal control problem has been formulated to minimize the cost and disease fatality by choosing the treatment and the effect of information regarding PrEP as control variables. Numerical analysis gives that if only control via information regarding PrEP is used, then it will be economical for early phase of the time period whereas treatment works well for long term control. Moreover, simultaneous use of both the control interventions is more useful than any single applied control policy and it reduces the number of infective individuals and also minimizes the economic cost generated from disease burden and controls. In the model it can be observed how uptake of PrEP can effect in the population by reducing the number of HIV infections. Moreover the combined effect of both the control policies is found to be more economical during the entire epidemic period whereas the implementation of a single policy is comparatively found less economical viable.

1. Introduction

There are new scientific advancement and serious health interventions these days but HIV/AIDS epidemic is till now one of the devastating disease in human history. UNAIDS data [1] claims that there already been a indicative decline and stabilization in new HIV infectives since 2012, but there are still many countries severely affected. In fact there are some

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regions where women fill up more than half of population living with HIV. Statistical data of South Africa reveals that in 2016, the country had almost 7.03 million of people who is HIV infected [2] with incidence rate 4 in 100 women per year [3,4]. HIV spread throughout the world in various ways such as (i) sexual intercourse, (ii) sharing contaminated blood products or needles and (iii) by vertical transmission from infected mothers to their newborn babies during pregnancy, delivery or breastfeeding. HIV infection is a slow progressive disease where the disease stages can be indicated by virus number in the body. Normally in a healthy individual's blood, the amount of CD4+ T-cells is in between 800 and 1200/mm^3 but once this number decline and reaches to 200 or below in a HIV infected patient, the person is classified as having AIDS. There are mainly three main stages of HIV infection as described in [5]: (i) the initial stage of infection, which occurs within weeks of acquiring the virus and often is characterized by influenza or mono like illness that generally resolves within weeks, (ii) chronic asymptomatic infection that lasts an average of 8–10 years and (iii) symptomatic infection in which the body's immune system has been suppressed and complications have occurred, is called the AIDS. Without any treatment, HIV infection become fatal within 5–10 years and the average survival time after developing AIDS is only 9.2 months, while with drug therapies treated individuals can live longer free of HIV related symptoms [6,5]. Medical management of HIV infection recommends two therapies as most significant advancement [7]. Firstly, antiretroviral therapy (ART) has to be initiated among everyone who lives with HIV at any CD4+ cell count. This HIV treatment reduces the viral load below the level of detection of most sensitive medical assessment and it reconstitutes the immune system [8]. The Global AIDS Update 2016 of Joint United Nations Programme on HIV/AIDS gives that the global coverage of ART reached a peak of 46% at the end of 2015. The treatment helps to decline the AIDS-relate death globally to 26% since 2010. This data is collected from an estimation 1.5 million in 2010 to 1.1 million in 2015. But it is also true that in 2015, almost 2 million new infections has been reported [9]. The second recommendation is the use of daily pre-exposure prophylaxis (PrEP) which is a preventive choice for people who are at substantial risk to be infected with HIV infection. Substantial gaps remain in understanding the trade-offs between costs and benefits of choosing HIV prevention strategies like taking PrEP as a precaution by the uninfected individuals [10]. The authorities in WHO are now trying to use PrEP as a safe, effective prevention outside the medical trial setting. But it is also important to note that PrEP cannot be used by anyone; the people who are HIV negative but have a risk to get infected can take PrEP [11]. Report says that South Africa is the first country where Medicines Control Council approved PrEP in its national HIV programme. These days there are many countries with regulatory approval for PrEP. Statistical report shows that globally female sex workers (FSW) got more affected with HIV than general population. FSW are 13.5 times more likely to be living with HIV than general women population [12]. The European Medicine Agency has also allowed PrEP to be marketed across the European Unions 28 countries by giving the authorization [13].

Medical facilities have improved significantly these days but for the complex nature of diseases, the policy makers find a bit difficult to choose the proper detection and prevention. There are different tools and techniques available to predict the system dynamics and also to suggest the suitable control intervention. Mathematical modelling is one of the most useful tools in this case [14–17]. Some research works are based on the pharmaceutical as well as non-pharmaceutical control interventions like vaccination, quarantine, treatment etc. [15,17,18].

Another important thing that can be observed during the epidemic outbreak is the behavioural change due to information of disease and its prevention. Often these changes are found to be useful as it reduces the transmission of disease [19–22]. The information can be spread through various ways such as educational campaigns, social media etc. People's response to the risk of disease mainly depends on their perception and it is influenced by public and media. So it is an interesting topic for the researchers to study the influence of information on spread of HIV [20–25]. There are mainly two ways to incorporate the behavioural change in a model. Firstly, a rectification in incidence rate in order to reduce the contact rate due to awareness of disease [21,26–28]. Secondly by introducing a subclass of individuals with awareness [20,22–24,29,30]. Besides of it, some researchers have incorporated the impact of behavioural response on control interventions like vaccination etc. [31,32].

In most of the cases, there are various tools like mass media, which are used to control and eradicate the epidemic [27]. The media coverage can effect the disease transmission rate which is accounted by considering a rectified incidence rate with saturated function of infected population [21]. But it is also true that media effect cannot wash out a disease completely but it only can reduce the disease prevalence. It is learnt from the work of Xiao et al. [33] that impact of media coverage can reduce the severity of outbreak. Their findings suggested that the media impact cannot be always effective to reduce transmission rather a switching pattern that was found in early stage of outbreak.

Joshi et al. [20] divided the susceptible population into three subclasses in an HIV epidemic model in Uganda on the basis of information level generated from social and educational awareness campaigns. They compared the statistical data with their results and reached at a conclusion that information (regarding awareness) reduces the infection level. Mishra et al. (2011) in their paper considered a separate compartment for awareness which consists of those susceptible who become aware due to the awareness programs on the media [22]. They have observed that awareness cannot eradicate the disease but can only control the disease burden. Alberto d'Onofrio and his co-workers considered the effect of information related change as vaccination process as well as contact pattern. Also, they have analysed the global stability and bifurcations around stationary states of the epidemic models [34,35]. Again in some works, Samanta (2010, 2011) has analysed some nonautonomous HIV/AIDS epidemic models with distributed time delay [36–38]. Sharma and Samanta (2014) have developed a five compartmental HIV/AIDS epidemic model with two infectious stages before full-blown AIDS defined [39]. They have proved that the delay parameter can turn a stable system into an unstable one by crossing a threshold value. Bera et al. (2015), in their paper, described internal HIV dynamics between $CD4+T$ cells and the immune response cells (i.e. *CTLs*) of an untreated individual by introducing discrete time-delay in their proposed model [40].

Several epidemic models have already been considered where the effect of information have been incorporated either in disease transmission or have taken a new compartment of aware individuals. We express the awareness caused by the effect of information of disease as 'behavioural response of susceptible individuals'. If the susceptible individuals get proper information regarding the disease, they try to adopt protective measures like vaccination, isolation etc. These susceptible individuals can protect themselves by changing their behaviour. But as time passes if they stop to take preventive measures, they will lose their protectiveness and move back to susceptible class further [41].

Modelling of a population dynamics of an infectious disease is quite useful for the public health sector as they can plan optimally about the prevention. There are few research articles [42–45] based on the mathematical modelling of HIV epidemic with use of PrEP. For example, Silva and Torres have considered a HIV/AIDS transmission model using PrEP and then considered an optimal control problem where determination of PrEP strategy (that minimizes the pre-infected individuals and cost associated with PrEP) is the main objective [43]. Again, Mukandavire et al. in their work mainly compare the impact of condom use and the use of PrEP among sex workers [42]. They have found that promoting the condom use should be the mainstay of HIV prevention strategy for female sex workers. PrEP can only be used if the population is at high risk level of getting infected and it can also be implemented to fill prevention gaps where condoms cannot be used. Grant and his co-workers have proposed a static model of HIV/AIDS epidemic where they have compared HIV-risk estimates before and after applying PrEP and determined the maximum tolerated reductions in condom use for HIV risk not to change [44]. Based on one of the case studies in South Africa, it can be stated that PrEP has a positive impact to reduce HIV risk even if reductions in condom use do occur.

Now diseases exhibit a lot of economic burden including productivity loss, health care related expenses, losses due to disease related death and loss of employment etc. Again control policies implementation costs includes treatment, vaccination etc. So, policy makers have to implement such a policy that can control the spread of disease as well as can minimize the overall cost incurred during a certain time period. Depending on the availability of resources, a single control intervention or multiple control interventions can be chosen. Multiple control intervention optimal control theory can be used to address how long the controls should be applied. A lot of works have already been done in epidemiology for various control interventions including both pharmaceutical and non-pharmaceutical interventions [19,46–49,29,17].

Behncke (2000) took pharmaceutical treatment and health-promotional campaigns as control measure and showed their effect together with importance of financial support for an SIR model [47]. Qualitative analysis shows that control policies can reduce the disease level while financial support promotes the campaigns which help in suppressing the disease transmission rate. In HIV epidemic models also, the effect of information or eradication has been used as control policies [29,48]. For example, Kassa et al. incorporated an optimal control problem for HIV in Botswana considering the effects of educational campaigns and treatment as controls [29]. They observed that the combination of these controls can minimize the economic load and minimize HIV burden also. Joshi et al. considered an optimal control problem where the level of information has been taken as control intervention [48]. From the numerical simulations it has been proved here that in presence of optimal information the disease transmission is lower and the infective population is minimized.

In the present work it is tried to demonstrate the extent to which PrEP (pre-exposure prophylaxis) can possibly reduce the prevalence of the HIV in certain population, in presence of treatment. We have introduced a compartmental model with two stages of infection (asymptomatic and symptomatic) and assumed that susceptible individuals can take PrEP to prevent themselves from HIV but they become exposed to HIV if they stop to take oral PrEP. The proposed model takes into consideration that the individuals in the symptomatic phase can move back to the asymptomatic phase after successful treatment. Rest of the paper has been organized as follows: in the following section, we have formulated a mathematical model which accounts for the information regarding PrEP induced behavioural response. Section 3 shows that the proposed model is well-posed. In Section 4, equilibrium analysis is performed while Section 5 analyzes the sensitivity of various parameters in R_0. Section 6 deals with the local as well as global stability conditions of the equilibrium points. In Section 7, it has been shown that the system performs a forward bifurcation for $R_0 > 1$. In the later part, we have formulated corresponding optimal control problem in Section 9. In the subsequent sections (including Section 8) we have performed numerical simulations for the proposed model systems and the last part includes a general discussion and some concluding remarks.

2. Mathematical model: Basic equations

A seven compartmental HIV epidemic model has been formulated that includes the effect of information induced behaviour response against the disease prevalence. A population of size $N(t)$ at time t has been considered which is subdivided into the classes of susceptible $S(t)$, the asymptomatic phase $I_1(t)$, the symptomatic phase $I_2(t)$, the AIDS patients $A(t)$, infective population in treatment $T(t)$ and the individuals under PrEP (pre-exposure prophylaxis): $E(t)$. Now, heterogeneity in sexual behaviour (either in sex acts per partner, the number of sexual partners or the pattern of mixing between potential partners (i.e., non-random mixing)) leads to a complicated mathematical calculations and, in general, acts to reduce the endemic prevalence [50–53]. However, the simplest conceptual framework based on homogeneous behaviour gives us clear understandings on epidemiological pattern and transmission success [53]. Here the mixing of susceptible with both the infective is considered to be homogeneous and accordingly the incidence rate is assumed to be βSI.

When a disease outbreaks in population, information regarding disease mainly spreads through various media such as TV, newspaper etc. and as well as active social and educational campaigns from the government. This information density is proportional to the infective population density (considering only the symptomatic phase) and will change as infective population changes. Let $Z(t)$ be the density of information spreads in the population such that $Z(t) = 0$ when $I_2(t) = 0$. This information increases the awareness in the behavioural change in susceptible individuals to protect themselves from contracting infection. An example regarding spread of information has been observed in the case of Ebola in Senegal [54]. Even though the people are informed, everyone does not respond to it equally due to lack of resources, financial condition and heedless nature etc. So, only a fraction of susceptible population with information, is responding to the information of disease and changing their behaviour by taking PrEP (moves to $E(t)$ class). Here, we have considered that, PrEP is so effective that all susceptible individuals under PrEP treatment will be transferred to class E. Also, the individuals who will stop PrEP become susceptible again. This rate of behavioural response via information interaction will be a function of both the densities of susceptible individuals and information, i.e., $f(S(t), Z(t))$. Also, the growth of information is a function of $I_2(t)$, i.e., $g(I_2(t))$, as the growth of information depends only on the density of symptomatic infected individuals. The corresponding schematic diagram of the model dynamics has been depicted in Fig. 1. We shall use $S(t) = S$, $I_1(t) = I_1$, $I_2(t) = I_2$, $T(t) = T$, $A(t) = A$, $E(t) = E$ and $Z(t) = Z$ for the sake of calculations. The corresponding model dynamics is presented by the following system of nonlinear ODE's:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - c(\beta_1 I_1 + \beta_2 I_2)S - \mu S + \theta E - f(S, Z), \qquad S(0) = S_0 > 0,\\
\frac{dI_1}{dt} &= c(\beta_1 I_1 + \beta_2 I_2)S - (\mu + k_1)I_1 + \eta(I_1 + I_2) + \alpha I_2, \qquad I_1(0) = I_{1,0} > 0,\\
\frac{dI_2}{dt} &= k_1 I_1 - (\alpha + \mu + k_2)I_2 - \rho I_2, \qquad I_2(0) = I_{2,0} > 0,\\
\frac{dT}{dt} &= k_2 I_2 - (\mu + \gamma)T, \qquad T(0) = T_0 > 0,\\
\frac{dA}{dt} &= \rho I_2 - (\mu + \delta)A + \gamma T, \qquad A(0) = A_0 > 0,\\
\frac{dE}{dt} &= f(S, Z) - (\mu + \theta)E, \qquad E(0) = E_0 > 0,\\
\frac{dZ}{dt} &= g(I_2) - a_0 Z, \qquad Z(0) = Z_0 > 0,
\end{aligned} \tag{1}$$

All the model parameters are assumed to be non-negative with the following interpretations.

Λ: Recruitment rate.

μ: Natural death rate.

δ: Disease related death rate.

β_1, β_2: Probabilities of disease transmission per contact by an infective in asymptomatic and symptomatic phase respectively.

c: Average number of sexual contacts of one individual with others per unit time.

k_1, k_2, γ: Progression rate from I_1 to I_2, I_2 to T and T to A respectively.

ρ: Proportion of infective population in symptomatic phase who enter into A due to lack of treatment and awareness.

θ: Rate of individuals (defaulters) who stop to take PrEP and return back to susceptible stage.

a_0: Natural degradation rate of information which is caused due to natural fading of memory about information with time as well as the complacent behaviour.

α: Rate of transfer from I_2 to I_1 due to treatment.

η: Vertical transmission rate co-efficient.

$f(S, Z)$: Rate of behavioural response of susceptible individuals, caused by the information of the disease prevalence, by taking available protective measures such as PrEP protection to become protective. Now, the response is not 100% effective due to financial obstacle, heedless nature of individuals etc. So, we consider the information interaction term as $f(S, Z) = (u_1 d)ZS$, where $u_1 d$ indicates corresponding response rate and d is the information interaction rate parameter by which individuals change their behaviour and $0 \leq u_1 \leq 1$ is response intensity.

$g(I_2)$: Rate of growth of information. It depends on the symptomatic infective population only. Whenever disease outbreaks, several health agencies and government become more active to spread the information or awareness regarding the prevalence of disease among the population. Here it is assumed that initial growth of information is proportional to the density of symptomatic infective population but for large infective population, growth of information will be saturated. So, we consider $g(I_2) = \frac{aI_2}{1+bI_2}$ as saturated functional form, where a indicates the growth rate of information and b is the saturation constant [34].

The model involves the following assumptions:

(1) $S(t)$ is composed of individuals who have not been yet infected but may be infected through sexual intercourse or other ways with two types of infective.

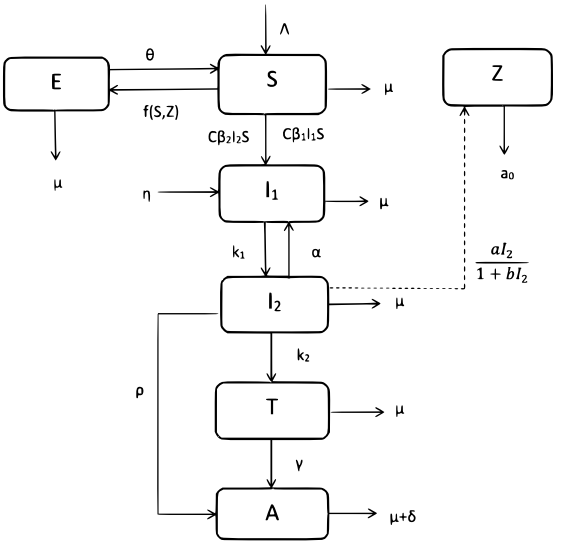

Fig. 1. Schematic diagram for the HIV model.

(2) I_1 is composed of such individuals who have HIV without symptoms.
(3) I_2 is composed of such individuals who have developed HIV infection with complications and different symptoms.
(4) T is composed of infective who are in symptomatic phase but become aware of their infection and enter into drug therapy.
(5) A is composed of such individuals whose body's immune system has been totally suppressed by HIV infection and they are in the final stage of AIDS.
(6) Only two clinical stages (I_1 and I_2) have been considered for the sake of simplifications.
(7) $S(t)$ become infected by adequate contact with infective individuals (both I_1 and I_2).
(8) Vertical transmission is considered only in asymptomatic (I_1) stage, transmitted by both type of infected individuals.
(9) Infected population who are in treatment do not have any contribution in viral transmission.
(10) Class A is too ill to reproduce and so they are incapable to contribute viral transmission both horizontally and vertically.
(11) It is assumed that $\mu > \eta$ and $\eta < \frac{\alpha\mu+(\mu+k_1)(\mu+\rho+k_2)}{k_1+k_2+\alpha+\rho+\mu}$.

3. Positivity & boundedness

Let us discuss the positivity and boundedness of the model system (1) to ensure that the model is well-posed.

Theorem 3.1. *All solutions of system (1) that start in $\mathbb{R}^7_+$ remain positive for all the time.*

Proof. Since the right hand side of system (1) is continuous and locally Lipschitzian on C (space of continuous functions), the solution $(S(t), I_1(t), I_2(t), T(t), A(t), E(t), Z(t))$ of (1) exists and is unique on $[0, \xi)$, where $0 < \xi \leq +\infty$. First we show that, $S(t) > 0,\ \forall\, t \in [0, \xi)$. If it does not hold, then $\exists t_1 \in [0, \xi)$ such that $S(t_1) = 0,\ \dot{S}(t_1) \leq 0$ and $S(t) > 0,\ \forall\, t \in [0, t_1)$. So there must have $I_1(t) > 0,\ \forall\, t \in [0, t_1)$. Suppose the statement is not true. Then $\exists t_2 \in (0, t_1)$ such that $I_1(t_2) = 0,\ \dot{I_1}(t_2) \leq 0$ and $I_1(t) > 0,\ \forall\, t \in [0, t_2)$. Our claim is $\dot{I_2}(t) > 0,\ \forall\, t \in [0, t_2)$. If it is not true then $\exists t_3 \in (0, t_2)$ such that $I_2(t_3) = 0,\ \dot{I_2}(t_3) \leq 0$ and $I_2(t) > 0,\ \forall\, t \in [0, t_3)$. From 3rd equation of (1):

$$\frac{dI_2(t_3)}{dt} = k_1 I_1(t_3) - (\alpha + \mu + k_2 + \rho) I_2(t_3) = k_1 I_1(t_3) > 0,$$

which is a contradiction to $\dot{I_2}(t_3) \leq 0$. So, $I_2(t) > 0,\ \forall\, t \in [0, t_2)$.

So, 2nd equation of (1) gives

$$\begin{aligned}\frac{dI_1(t_2)}{dt} &= c(\beta_1 I_1(t_2) + \beta_2 I_2(t_2))S(t_2) - (\mu - \eta) I_1(t_2) - k_1 I_1(t_2) + (\eta + \alpha) I_2(t_2) \\ &= c\beta_2 I_2(t_2) S(t_2) + (\eta + \alpha) I_2(t_2) > 0,\end{aligned}$$

which is a contradiction to $\dot{I_1}(t_2) \leq 0$. So, $I_1(t) > 0,\ \forall\, t \in [0, t_1)$.

Similarly we have, $I_2(t) > 0,\ \forall\, t \in [0, t_1)$.

Now we claim $T(t) > 0,\ \forall t \in [0, t_1)$. Suppose it is not true. Then $\exists t_4 \in (0, t_1)$ such that $T(t_4) = 0,\ \dot{T}(t_4) \leq 0$ and $T(t) > 0,\ \forall t \in [0, t_4)$. Now from the 4th equation of (1):

$$\frac{dT(t_4)}{dt} = k_2 I_2(t_4) - (\mu + \gamma)T(t_4) = k_2 I_2(t_4) > 0,$$

which is a contradiction to $\dot{T}(t_4) \leq 0$. So, $T(t) > 0,\ \forall t \in [0, t_1)$.

Next, we claim $A(t) > 0,\ \forall t \in [0, t_1)$. If it is not true, then $\exists t_5 \in (0, t_1)$ such that $A(t_5) = 0,\ \dot{A}(t_5) \leq 0$ and $A(t) > 0,\ \forall t \in [0, t_5)$. The 5th equation of (1) gives that

$$\frac{dA(t_5)}{dt} = \rho I_2(t_5) + \gamma T(t_5) - (\mu + \delta)A(t_5) = \rho I_2(t_5) + \gamma T(t_5) > 0,$$

which is a contradiction to $\dot{A}(t_5) \leq 0$. So, $A(t) > 0,\ \forall t \in [0, t_1)$.

Now we claim $Z(t) > 0,\ \forall t \in [0, t_1)$. If it is not true, then $\exists t_6 \in (0, t_1)$ such that $Z(t_6) = 0,\ \dot{Z}(t_6) \leq 0$ and $Z(t) > 0,\ \forall t \in [0, t_6)$. From 7th equation of (1) we get

$$\frac{dZ(t_6)}{dt} = \frac{aI_2(t_6)}{1 + bI_2(t_6)} - a_0 Z(t_6) = \frac{aI_2(t_6)}{1 + bI_2(t_6)} > 0,$$

which is a contradiction to $\dot{Z}(t_6) \leq 0$. So, $Z(t) > 0,\ \forall t \in [0, t_1)$.

Next, we claim $E(t) > 0,\ \forall t \in [0, t_1)$. Suppose it is not true. Then $\exists t_7 \in (0, t_1)$ such that $E(t_7) = 0,\ \dot{E}(t_7) \leq 0$ and $E(t) > 0,\ \forall t \in [0, t_7)$. From 6th equation of (1) we get,

$$\frac{dE(t_7)}{dt} = u_1 dS(t_7)Z(t_7) - (\mu + \theta)E(t_7) = u_1 dS(t_7)Z(t_7) > 0,$$

which is a contradiction to $\dot{E}(t_7) \leq 0$. So, $E(t) > 0,\ \forall t \in [0, t_1)$.

It follows from the 1st equation of (1):

$$\begin{aligned}\frac{dS(t_1)}{dt} &= \Lambda - c(\beta_1 I_1(t_1) + \beta_2 I_2(t_1))S(t_1) - \mu S(t_1) + \theta E(t_1) - u_1 dS(t_1)Z(t_1)\\ &= \Lambda + \theta E(t_1) > 0,\end{aligned}$$

which is a contradiction to $\dot{S}(t_1) \leq 0$. It shows that $S(t) > 0,\ \forall t \in [0, \xi)$. By the steps discussed previously, it follows that $I_1(t) > 0,\ I_2(t) > 0,\ T(t) > 0,\ A(t) > 0,\ E(t) > 0$ and $Z(t) > 0$, for all $t \in [0, \xi)$, where $0 < \xi \leq +\infty$. Hence the theorem. □

Theorem 3.2. *All solutions of system (1) that start in $\mathbb{R}^7_+$ are uniformly bounded.*

Proof.

$$\text{Consider, } N(t) = S(t) + I_1(t) + I_2(t) + T(t) + A(t) + E(t).$$
$$\therefore \frac{dN}{dt} = \Lambda - \mu N + \eta(I_1 + I_2) - \delta A \leq \Lambda - (\mu - \eta)N.$$

The solution $N(t)$ of the above differential equation has the following property:

$$0 < N(t) \leq N(0)e^{-(\mu-\eta)t} + \frac{\Lambda}{\mu - \eta}\left(1 - e^{-(\mu-\eta)t}\right),$$

where $N(0)$ represents the sum of the initial values of the variables (S, I_1, I_2, T, A, E).

As $t \to \infty,\ 0 < N(t) \leq \frac{\Lambda}{\mu-\eta}$.

$$\text{Now, } \frac{dZ}{dt} = \frac{aI_2}{1 + bI_2} - a_0 Z \leq aI_2 - a_0 Z$$

$$\Rightarrow \frac{dZ}{dt} + a_0 Z \leq \frac{a\Lambda}{\mu - \eta} \text{ (for large time } t).$$

The solution $Z(t)$ will be of the form:

$$0 < Z(t) \leq Z(0)e^{-a_0 t} + \frac{a\Lambda}{a_0(\mu - \eta)}\left(1 - e^{-a_0 t}\right),$$

where $Z(0)$ represents the initial value of Z.

As $t \to \infty,\ 0 < Z(t) \leq \frac{a\Lambda}{a_0(\mu-\eta)}$.

Therefore, all solutions of system (1) will enter into the region:

$$\Xi = \left\{(S, I_1, I_2, T, A, E, Z) \in \mathbb{R}^7_+ : 0 \le N(t) \le \frac{\Lambda}{\mu - \eta}; 0 < Z(t) \le \frac{a\Lambda}{a_0(\mu - \eta)}\right\}. \quad \square$$

Since the variables T and A of system (1) do not appear in the rest of the equations, in the subsequent analysis we only consider the following subsystem:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - c(\beta_1 I_1 + \beta_2 I_2)S - \mu S + \theta E - u_1 dSZ, \qquad S(0) = S_0 > 0,\\
\frac{dI_1}{dt} &= c(\beta_1 I_1 + \beta_2 I_2)S - (\mu + k_1)I_1 + \eta(I_1 + I_2) + \alpha I_2, \qquad I_1(0) = I_{1,0} > 0,\\
\frac{dI_2}{dt} &= k_1 I_1 - (\alpha + \mu + k_2)I_2 - \rho I_2, \qquad I_2(0) = I_{2,0} > 0,\\
\frac{dE}{dt} &= u_1 dSZ - (\mu + \theta)E, \qquad E(0) = E_0 > 0,\\
\frac{dZ}{dt} &= \frac{aI_2}{1 + bI_2} - a_0 Z, \qquad Z(0) = Z_0 > 0,
\end{aligned} \tag{2}$$

4. Equilibrium analysis

In this section, the stability analysis of system (2) will be performed. The stability of the equilibrium points can be determined by a threshold basic reproduction number R_0.

4.1. Basic reproduction number

R_0 is defined as the number of new infective individuals generated from a single infective individual when introduced to susceptible population. Here the method developed by van den Driessche and Watmough [55] has been used to calculate the basic reproduction number R_0 of system (2).

Let $x = (I_1, I_2, S, E, Z)$. The system (2) can be written as

$$\frac{dx}{dt} = \mathfrak{F}(x) - \nu(x) = \begin{pmatrix} c(\beta_1 I_1 + \beta_2 I_2)S \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} - \begin{pmatrix} (\mu + k_1)I_1 - \eta(I_1 + I_2) - \alpha I_2 \\ -k_1 I_1 + (\alpha + \mu + k_2)I_2 + \rho I_2 \\ -\Lambda + c(\beta_1 I_1 + \beta_2 I_2)S + \mu S - \theta E + u_1 dSZ \\ -u_1 dSZ + (\mu + \theta)E \\ -\frac{aI_2}{1+bI_2} + a_0 Z \end{pmatrix},$$

where $\mathfrak{F}(x)$ consists of the new infection term only and $\nu(x)$ contains the other terms. So, the corresponding linearized matrices of $\mathfrak{F}(x)$ and $\nu(x)$ evaluated at disease-free equilibrium $E_0(\frac{\Lambda}{\mu}, 0, 0, 0, 0)$ are respectively

$$(D\mathfrak{F}(x))(E_0) = \begin{pmatrix} \frac{c\beta_1\Lambda}{\mu} & \frac{c\beta_2\Lambda}{\mu} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$(D\nu(x))(E_0) = \begin{pmatrix} \mu + k_1 - \eta & -(\eta + \alpha) & 0 & 0 & 0 \\ -k_1 & \alpha + \mu + \rho + k_2 & 0 & 0 & 0 \\ \frac{c\beta_1\Lambda}{\mu} & \frac{c\beta_2\Lambda}{\mu} & \mu & -\theta & \frac{u_1 d\Lambda}{\mu} \\ 0 & 0 & 0 & \mu + \theta & -\frac{u_1 d\Lambda}{\mu} \\ 0 & -a & 0 & 0 & a_0 \end{pmatrix}$$

Here Infected components are I_1, I_2 and Z. So, we shall consider only these three components of $D\mathfrak{F}(x)$ and $D\nu(x)$ to obtain R_0. Therefore, F and V should be considered as:

$$F = \begin{pmatrix} \frac{c\beta_1\Lambda}{\mu} & \frac{c\beta_2\Lambda}{\mu} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, V = \begin{pmatrix} \mu + k_1 - \eta & -(\eta + \alpha) & 0 \\ -k_1 & \alpha + \mu + \rho + k_2 & 0 \\ 0 & -a & a_0 \end{pmatrix}$$

Now, FV^{-1} is said to be the next generation matrix of system (2). The basic reproduction number of system (2) will be the spectral radius of FV^{-1} which is denoted and defined as [55]:

$$R_0 = \frac{c\Lambda\{\beta_1(\alpha + \mu + \rho + k_2) + \beta_2 k_1\}}{\mu[(\mu + k_1 - \eta)(\alpha + \mu + \rho + k_2) - k_1(\eta + \alpha)]} > 0 \text{ (by assumption (11))}$$

The system has the following equilibrium points:
(1) Disease-free equilibrium (DFE) $E_0\left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right)$.
(2) Endemic equilibrium point $E_1(S^*, I_1^*, I_2^*, E^*, Z^*)$.

- **Existence of endemic equilibrium point** $E_1(S^*, I_1^*, I_2^*, E^*, Z^*)$

Let us examine the existence of the endemic equilibrium point of the system. For this we will consider

$$S > 0, I_1 > 0, I_2 > 0, E > 0, Z > 0$$

and

$$\begin{aligned}
\Lambda - c(\beta_1 I_1^* + \beta_2 I_2^*)S^* - \mu S + \theta E^* - u_1 d S^* Z^* &= 0,\\
c(\beta_1 I_1^* + \beta_2 I_2^*)S^* - (\mu + k_1)I_1^* + \eta(I_1^* + I_2^*) + \alpha I_2^* &= 0,\\
k_1 I_1^* - (\alpha + \mu + k_2)I_2^* - \rho I_2^* &= 0,\\
u_1 d S^* Z^* - (\mu + \theta)E^* &= 0,\\
\frac{a I_2^*}{1 + b I_2^*} - a_0 Z^* &= 0,
\end{aligned} \tag{3}$$

Solving the equations of (3):

$$I_2^* = \frac{k_1 I_1^*}{\alpha + \mu + k_2 + \rho}, \qquad Z^* = \frac{a k_1 I_1^*}{a_0(\alpha + \mu + k_2 + \rho + b k_1 I_1^*)}, \qquad E^* = \frac{u_1 d \Lambda}{\mu(\mu + \theta)R_0}\frac{a k_1 I_1^*}{a_0(\alpha + \mu + k_2 + \rho + b k_1 I_1^*)},$$
$$S^* = \frac{(\mu + k_1 - \eta)(\alpha + \mu + k_2 + \rho) - k_1(\eta + \alpha)}{c\{\beta_1(\alpha + \mu + k_2 + \rho) + \beta_2 k_1\}} = \frac{\Lambda}{\mu}\frac{1}{R_0} > 0 \qquad (\text{as } R_0 > 0)$$

and I_1^* is the positive solution of the equation: $A_1 I_1^2 + A_2 I_1 + A_3 = 0$, where $A_1 = S^* a_0(\mu + \theta) b k_1 c\{\beta_1(\alpha + \mu + k_2 + \rho) + \beta_2 k_1\}$,

$$\begin{aligned}
A_2 &= S^*[c\{\beta_1(\alpha + \mu + k_2 + \rho) + \beta_2 k_1\}a_0(\mu + \theta)(\alpha + \mu + k_2 + \rho) + a\mu k_1 u_1 d(\alpha + \mu + k_2 + \rho)]\\
&\quad - b k_1 a_0(\mu + \theta)(\alpha + \mu + k_2 + \rho)\Lambda\left(1 - \frac{1}{R_0}\right),\\
A_3 &= -a_0\Lambda\left(1 - \frac{1}{R_0}\right)(\mu + \theta)(\alpha + \mu + k_2 + \rho)^2.
\end{aligned}$$

Here, $A_1 > 0$ always. If $R_0 > 1$, then $A_3 < 0$. So, there exists exactly one positive root I_1^* of the equation. Hence we have the following theorem:

Theorem 4.1. *System (2) has a disease-free equilibrium point* $E_0\left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right)$. *If* $R_0 > 1$, *it admits a unique endemic equilibrium* $E_1(S^*, I_1^*, I_2^*, E^*, Z^*)$.

5. Sensitivity analysis

The basic reproduction number (R_0) of system (2) depends on ten parameters, namely, recruitment rate (Λ), natural mortality rate (μ), transmission rate by an infective in asymptomatic and symptomatic phase (β_1 and β_2 respectively), average contact rate with others (c), progression rate from I_1 to I_2 and I_2 to T (k_1 and k_2 respectively), amount of infective population in symptomatic phase who enter into A due to lack of treatment and awareness (ρ), transfer rate from I_2 to I_1 due to treatment (α) and vertical transmission rate (η). Among those parameters, we cannot control some of the parameters like Λ, ρ, α, η, μ, k_1. Here (using assumption (11)):

$$\begin{aligned}
\frac{\partial R_0}{\partial \beta_1} &= \frac{c\Lambda}{\mu}\frac{(\alpha + \rho + \mu + k_2)}{(\mu - \eta + k_1)(\alpha + \rho + \mu + k_2) - k_1(\eta + \alpha)} > 0\\
\frac{\partial R_0}{\partial \beta_2} &= \frac{c\Lambda}{\mu}\frac{k_1}{(\mu - \eta + k_1)(\alpha + \rho + \mu + k_2) - k_1(\eta + \alpha)} > 0\\
\frac{\partial R_0}{\partial c} &= \frac{\Lambda}{\mu}\frac{\{\beta_1(\alpha + \rho + \mu + k_2) + \beta_2 k_1\}}{(\mu - \eta + k_1)(\alpha + \rho + \mu + k_2) - k_1(\eta + \alpha)} > 0\\
\frac{\partial R_0}{\partial k_2} &= -\frac{c\Lambda}{\mu}\frac{\{\beta_1 k_1(\alpha + \eta) + \beta_2 k_1(\mu + k_1 - \eta)\}}{[(\mu - \eta + k_1)(\alpha + \rho + \mu + k_2) - k_1(\eta + \alpha)]^2} < 0
\end{aligned}$$

Hence, to examine the sensitivity of R_0 to the parameters β_1, β_2, k_2 and c, by the method of Arriola and Hyman [56], normalized forward sensitivity index with respect to each of those parameters are computed as follows:

$$\Theta_{\beta_1} = \left|\frac{\frac{\partial R_0}{R_0}}{\frac{\partial \beta_1}{\beta_1}}\right| = \left|\frac{\beta_1}{R_0}\frac{\partial R_0}{\partial \beta_1}\right| = \left|\beta_1 \frac{(\alpha+\rho+\mu+k_2)}{\{\beta_1(\alpha+\rho+\mu+k_2)+\beta_2 k_1\}}\right| < 1$$

$$\Theta_{\beta_2} = \left|\frac{\frac{\partial R_0}{R_0}}{\frac{\partial \beta_2}{\beta_2}}\right| = \left|\frac{\beta_2}{R_0}\frac{\partial R_0}{\partial \beta_2}\right| = \left|\frac{\beta_2 k_1}{\{\beta_1(\alpha+\rho+\mu+k_2)+\beta_2 k_1\}}\right| < 1$$

$$\Theta_{k_2} = \left|\frac{\frac{\partial R_0}{R_0}}{\frac{\partial k_2}{k_2}}\right| = \left|\frac{k_2}{R_0}\frac{\partial R_0}{\partial k_2}\right|$$

$$= \left|\frac{k_1 k_2\{\beta_1(\eta+\alpha)+\beta_2(\mu+k_1-\eta)\}}{\{\beta_1(\alpha+\rho+\mu+k_2)+\beta_2 k_1\}\{(\mu+k_1-\eta)(\alpha+\rho+\mu+k_2)-k_1(\eta+\alpha)\}}\right| < 1$$

$$\Theta_c = \left|\frac{\frac{\partial R_0}{R_0}}{\frac{\partial c}{c}}\right| = \left|\frac{c}{R_0}\frac{\partial R_0}{\partial c}\right| = 1$$

From the above discussion it is clear that the basic reproduction number (R_0) is most sensitive to changes in c, average number of contacts with others per unit time. If c will increase R_0 will increase in the same proportion and if c will decrease R_0 will also decrease in the same proportion. On the other hand, β_1, β_2 have an directly proportional relationship with R_0, i.e., the increase in any of them will cause an increase in R_0 and a decrease in any of them will cause a decrease in R_0. But decrease in β_1 will be more affective than β_2 to decrease the value of R_0. In this context, it is mentioned that β_1 represents the disease transmission rate by an infective in asymptomatic phase and β_2 denotes the disease transmission rate by an infective in symptomatic phase. So, it is better to focus either on c, the average contact rate and β_1, transmission rate by an infective in asymptomatic phase. Moreover, k_2 have an inversely proportional relationship with R_0, i.e., increment in k_2 will lead to a decrease in R_0 and if k_2 decreases R_0 will increase. As R_0 is more sensitive to changes in c than β_1 and k_2, so, it is sensible to focus on c, per capita contact rate to prevent the disease to escalate in population. This sensitivity analysis tells us that controlling average number of contacts with others (c) is more effective in controlling the disease transmission than controlling the transmission rate by an infective in any specific phase or treatment in symptomatic phase.

6. Stability analysis

In this section, we shall discuss the criterion for both local and global stability of the equilibrium points. Jacobian matrix of the corresponding system be

$$\tilde{J} = \begin{pmatrix} -c(\beta_1 I_1+\beta_2 I_2)-\mu-u_1 dZ & -c\beta_1 S & -c\beta_2 S & \theta & -u_1 dS \\ c(\beta_1 I_1+\beta_2 I_2) & c\beta_1 S-(\mu+k_1)+\eta & c\beta_2 S+\eta+\alpha & 0 & 0 \\ 0 & k_1 & -(\alpha+\mu+k_2+\rho) & 0 & 0 \\ u_1 dZ & 0 & 0 & -(\mu+\theta) & u_1 dS \\ 0 & 0 & \frac{a}{(1+bI_2)^2} & 0 & -a_0 \end{pmatrix} \tag{4}$$

6.1. Local stability of E_0

From (4), Jacobian matrix corresponding to E_0 is

$$\tilde{J}|_{E_0} = \begin{pmatrix} -\mu & -c\beta_1\frac{\Lambda}{\mu} & -c\beta_2\frac{\Lambda}{\mu} & \theta & -u_1 d\frac{\Lambda}{\mu} \\ 0 & c\beta_1\frac{\Lambda}{\mu}-(\mu+k_1-\eta) & c\beta_2\frac{\Lambda}{\mu}+\eta+\alpha & 0 & 0 \\ 0 & k_1 & -(\alpha+\mu+k_2+\rho) & 0 & 0 \\ 0 & 0 & 0 & -(\mu+\theta) & u_1 d\frac{\Lambda}{\mu} \\ 0 & 0 & a & 0 & -a_0 \end{pmatrix}$$

Here, eigenvalues of the characteristic equation of $\tilde{J}|_{E_0}$ are $\lambda_1 = -\mu$, $\lambda_2 = -(\mu+\theta)$, $\lambda_3 = -a_0$ and the solutions of the equation: $\lambda^2 + B_1\lambda + B_2 = 0$, where, $B_1 = 2\mu+\alpha+\rho+k_1+k_2-\eta-c\beta_1\frac{\Lambda}{\mu}$

$$\text{and } B_2 = -\left[(\alpha+\mu+k_2+\rho)\left\{c\beta_1\frac{\Lambda}{\mu}-(\mu-\eta+k_1)\right\}+k_1\left(c\beta_2\frac{\Lambda}{\mu}+\eta+\alpha\right)\right]$$

$$= -\frac{c\Lambda}{\mu}[\beta_1(\alpha+\mu+k_2+\rho)+k_1\beta_2]\left(1-\frac{1}{R_0}\right).$$

By Routh–Hurwitz criterion, this equation has two roots with negative real part iff $B_1, B_2 > 0$. Now $R_0 < 1$ implies $B_1, B_2 > 0$, therefore, we have the following theorem:

Theorem 6.1. *The disease free equilibrium E_0 is locally asymptotically stable (LAS) if $R_0 < 1$.*

6.2. Global stability of E_0

Theorem 6.2. *The disease free equilibrium E_0 is globally asymptotically stable (GAS) for $R_0 < 1$.*

Proof. For global continuation of DFE, let us consider a suitable Lyapunov function:

$$L(I_1, I_2) = (\alpha + \mu + k_2 + \rho)\, I_1 + \left(c\beta_2 \frac{\Lambda}{\mu} + \eta + \alpha\right) I_2$$

Here, $L(I_1, I_2)$ is a positive definite function for all (S, I_1, I_2, E, Z) other than E_0.

The time derivative of L computed along the solutions of the system (2) is given by

$$\begin{aligned}
\frac{dL}{dt} &= (\alpha + \mu + k_2 + \rho)\frac{dI_1}{dt} + \left(c\beta_2 \frac{\Lambda}{\mu} + \eta + \alpha\right)\frac{dI_2}{dt} \\
&= (\alpha + \mu + k_2 + \rho)\left[c(\beta_1 I_1 + \beta_2 I_2)\frac{\Lambda}{\mu} + \eta(I_1 + I_2) - (\mu + k_1)I_1 + \alpha I_2\right] \\
&+ \left(c\beta_2 \frac{\Lambda}{\mu} + \eta + \alpha\right)[k_1 I_1 - (\alpha + \mu + k_2 + \rho)I_2] \\
&\leq [c\beta_1(\alpha + \mu + k_2 + \rho) + c\beta_2 k_1]\frac{\Lambda}{\mu} I_1 - [(\alpha + \mu + k_2 + \rho)(\mu + k_1 - \eta) - k_1(\eta + \alpha)]\, I_1 \\
&= c\frac{\Lambda}{\mu}\{\beta_1(\alpha + \mu + k_2 + \rho) + \beta_2 k_1\}\left(1 - \frac{1}{R_0}\right) I_1 \\
&< 0 \qquad (\text{provided } R_0 < 1).
\end{aligned}$$

Furthermore $\frac{dL}{dt} = 0$ if and only if $I_1 = I_2 = 0$. Therefore, the largest compact invariant set in $\left\{(S, I_1, I_2, E, Z) \in: \frac{dL}{dt} = 0\right\}$, when $R_0 < 1$, is the singleton E_0. LaSalle's invariance principle [57] implies that E_0 is globally asymptotically stable in Ξ when $R_0 < 1$. □

6.3. Local stability of E_1

From (4), Jacobian matrix corresponding to E_1 is

$$\tilde{J}|_{E_1} = \begin{pmatrix} a_{11} & a_{12} & a_{13} & a_{14} & a_{15} \\ a_{21} & a_{22} & a_{23} & 0 & 0 \\ 0 & a_{32} & a_{33} & 0 & 0 \\ a_{41} & 0 & 0 & a_{44} & a_{45} \\ 0 & 0 & a_{53} & 0 & a_{55} \end{pmatrix}$$

where $a_{11} = -c(\beta_1 I_1^* + \beta_2 I_2^*) - \mu - u_1 dZ^*$, $a_{12} = -c\beta_1 S^*$, $a_{13} = -c\beta_2 S^*$,

$a_{14} = \theta$, $a_{15} = -u_1 dS^*$, $a_{21} = c(\beta_1 I_1^* + \beta_2 I_2^*)$, $a_{22} = c\beta_1 S^* - (\mu + k_1) + \eta$,
$a_{23} = c\beta_2 S^* + \eta + \alpha$, $a_{32} = k_1$, $a_{33} = -(\alpha + \mu + k_2 + \rho)$, $a_{41} = u_1 dZ^*$,
$a_{44} = -(\mu + \theta)$, $a_{45} = u_1 dS^*$, $a_{53} = \dfrac{a}{(1 + bI_2^*)^2}$, $a_{55} = -a_0$.

From the steady state conditions of E_1 we have

$$\begin{aligned}
\Lambda - c(\beta_1 I_1^* + \beta_2 I_2^*)S^* - \mu S + \theta E^* - u_1 dS^* Z^* &= 0, \\
c(\beta_1 I_1^* + \beta_2 I_2^*)S^* - (\mu + k_1)I_1^* + \eta(I_1^* + I_2^*) + \alpha I_2^* &= 0, \qquad k_1 I_1^* - (\alpha + \mu + k_2)I_2^* - \rho I_2^* \quad = 0, \\
u_1 dS^* Z^* - (\mu + \theta)E^* &= 0, \qquad \frac{aI_2^*}{1 + bI_2^*} - a_0 Z^* = 0.
\end{aligned}$$

Characteristic equation of $\tilde{J}|_{E_1}$ be

$$\lambda^5 + C_1\lambda^4 + C_2\lambda^3 + C_3\lambda^2 + C_4\lambda + C_5 = 0,$$

where

$$C_1 = -(a_{11} + a_{22} + a_{33} + a_{44} + a_{55}),$$
$$C_2 = a_{11}a_{22} + a_{33}(a_{11} + a_{22}) + (a_{44} + a_{55})(a_{11} + a_{22} + a_{33}) + a_{44}a_{55} - a_{12}a_{21} - a_{23}a_{32} - a_{14}a_{41},$$
$$C_3 = a_{14}a_{41}(a_{22} + a_{33} + a_{55}) + a_{32}(a_{11}a_{23} - a_{13}a_{21}) - a_{44}a_{55}(a_{11} + a_{22} + a_{33}) - a_{33}(a_{11}a_{22} - a_{12}a_{21}) - (a_{44} + a_{55})(a_{11}a_{22} + a_{11}a_{33} + a_{22}a_{33} - a_{12}a_{21} - a_{23}a_{32});$$
$$C_4 = a_{33}(a_{44} + a_{55})(a_{11}a_{22} - a_{12}a_{21}) + a_{44}a_{55}(a_{11}a_{22} + a_{22}a_{33} + a_{11}a_{33} - a_{12}a_{21}) + (a_{44} + a_{55})(a_{13}a_{21}a_{32} - a_{11}a_{23}a_{32}) - a_{23}a_{32}a_{44}a_{55} - a_{14}a_{41}(a_{22}a_{55} + a_{33}a_{55} + a_{22}a_{33}) + a_{23}a_{32} - a_{15}a_{21}a_{53}a_{32},$$
$$C_5 = a_{15}a_{44}a_{32}a_{21}a_{53} + a_{41}a_{14}a_{22}a_{33}a_{55} - a_{33}a_{44}a_{55}(a_{11}a_{22} - a_{12}a_{21}) - a_{23}a_{32}a_{55} - a_{44}a_{55}a_{32}(a_{13}a_{21} - a_{11}a_{23}) - a_{14}a_{45}a_{32}a_{21}a_{53}.$$

Now $a_{22} = c\beta_1 S^* - (\mu + k_1) + \eta$

$$= -\frac{k_1\left[\beta_1(\alpha + \eta) + \beta_2(\mu - \eta + k_1)\right]}{\beta_1(\alpha + \mu + \rho + k_2) + \beta_2 k_1} < 0\ (\because\ \mu > \eta)$$

Here $C_1 > 0$ for feasible S^*.

By Routh–Hurwitz criterion, E_1 is LAS if the following conditions hold:
(i) $C_i > 0$ for $i = 2, 3, 4, 5$;
(ii) $C_3\,(C_1C_2 - C_3) > C_1^2C_4$,
(iii) $(C_1C_4 - C_5)\left(C_1C_2C_3 - C_3^2 - C_1^2C_4\right) > C_5\,(C_1C_2 - C_3)^2 + C_1C_5^2$.

Hence we have the following theorem:

Theorem 6.3. *The endemic equilibrium E_1 is LAS for $R_0 > 1$ with the stated conditions* (i), (ii) *and* (iii).

6.4. Global stability of E_1

We investigate global stability of the endemic equilibrium point E_1 of system (2) when all the parameters are positive.

Theorem 6.4. *Assume that $R_0 > 1$. Then the endemic equilibrium E_1 of system (2) is globally asymptotically stable (GAS).*

Proof. Consider a function V as:

$$V(t) = \left(S - S^* - S^*\ln\frac{S}{S^*}\right) + A_1\left(I_1 - I_1^* - I_1^*\ln\frac{I_1}{I_1^*}\right) + A_2\left(I_2 - I_2^* - I_2^*\ln\frac{I_2}{I_2^*}\right) + A_3\left(E - E^* - E^*\ln\frac{E}{E^*}\right) + \left(Z - Z^* - Z^*\ln\frac{Z}{Z^*}\right)$$

The time derivative of V computed along the solutions of system (2) is given by

$$\begin{aligned}
So,\ \frac{dV}{dt} &= \left(1 - \frac{S^*}{S}\right)\frac{dS}{dt} + A_1\left(1 - \frac{I_1^*}{I_1}\right)\frac{dI_1}{dt} + A_2\left(1 - \frac{I_2^*}{I_2}\right)\frac{dI_2}{dt} + A_3\left(1 - \frac{E^*}{E}\right)\frac{dE}{dt} + \left(1 - \frac{Z^*}{Z}\right)\frac{dZ}{dt}\\
&= \left(1 - \frac{S^*}{S}\right)[\Lambda - c(\beta_1 I_1 + \beta_2 I_2)S - \mu S + \theta E - u_1 dSZ]\\
&+ A_1\left(1 - \frac{I_1^*}{I_1}\right)[c(\beta_1 I_1 + \beta_2 I_2)S - (\mu + k_1)I_1 + \eta(I_1 + I_2) + \alpha I_2]\\
&+ A_2\left(1 - \frac{I_2^*}{I_2}\right)[k_1 I_1 - (\alpha + \mu + k_2)I_2 - \rho I_2] + A_3\left(1 - \frac{E^*}{E}\right)[u_1 dSZ - (\mu + \theta)E]\\
&+ \left(1 - \frac{Z^*}{Z}\right)\left[\frac{aI_2}{1 + bI_2} - a_0 Z\right]\\
&= \left(1 - \frac{S^*}{S}\right)[c\beta_1\left(I_1^*S^* - I_1S\right) + c\beta_2\left(I_2^*S^* - I_2S\right) + \mu\left(S^* - S\right) - \theta\left(E^* - E\right)\\
&+ u_1 d\left(S^*Z^* - SZ\right)] + A_1\left(1 - \frac{I_1^*}{I_1}\right)\left[c\beta_1\left(I_1S - I_1^*S^*\right) + c\beta_2\left(I_2S - \frac{I_1}{I_1^*}I_2^*S^*\right)\right.\\
&\left. + (\eta + \alpha)\left(I_2 - \frac{I_1}{I_1^*}I_2^*\right)\right] + A_2\left(1 - \frac{I_2^*}{I_2}\right)\left[k_1\left(I_1 - \frac{I_2}{I_2^*}I_1^*\right)\right]\\
&+ A_3\left(1 - \frac{E^*}{E}\right)u_1 d\left(SZ - S^*Z^*\frac{E}{E^*}\right) + I_2^*\left(1 - \frac{Z^*}{Z}\right)\left[\frac{aI_2}{I_2^*(1 + bI_2)} - \frac{Z}{Z^*}\frac{a}{1 + bI_2^*}\right]
\end{aligned} \tag{5}$$

Let $\frac{S}{S^*} = x, \quad \frac{I_1}{I_1^*} = y, \quad \frac{I_2}{I_2^*} = z, \quad \frac{E}{E^*} = u, \quad \frac{Z}{Z^*} = v.$

So, (5) becomes

$$\begin{aligned}
\frac{dV}{dt} &= \left(1-\frac{1}{x}\right)\left[c\beta_1 I_1^* S^*(1-xy) + c\beta_2 I_2^* S^*(1-xz) + \mu S^*(1-x) - \theta E^*(1-u)\right.\\
&\left. + u_1 d S^* Z^*(1-xv)\right] + A_1\left(1-\frac{1}{y}\right)\left[c\beta_1 I_1^* S^*(xy-y) + c\beta_2 I_2^* S^*(xz-y)\right.\\
&\left. + (\eta+\alpha) I_2^*(z-y)\right] + A_2\left(1-\frac{1}{z}\right)\left[k_1 I_1^*(y-z)\right]\\
&+ A_3\left(1-\frac{1}{u}\right) u_1 d S^* Z^*(xv-u) + I_2^*\left(1-\frac{1}{v}\right)\left[\frac{az}{1+bI_2} - \frac{av}{1+bI_2^*}\right]\\
&= c\beta_1 I_1^* S^*\left(1-\frac{1}{x}-xy+y\right) + c\beta_2 I_2^* S^*\left(1-\frac{1}{x}-xz+z\right) - \mu S^*\left(\sqrt{x}-\frac{1}{\sqrt{x}}\right)^2\\
&- \theta E^*\left(1-\frac{1}{x}-u+\frac{u}{x}\right) + u_1 d S^* Z^*\left(1-\frac{1}{x}-xv+v\right) + A_1 c\beta_1 I_1^* S^*(xy-x-y+1)\\
&+ A_1 c\beta_2 I_2^* S^*\left(xz-\frac{xz}{y}-y+1\right) + A_1(\eta+\alpha) I_2^*\left(z-\frac{z}{y}-y+1\right)\\
&+ A_2 k_1 I_1^*\left(1-\frac{y}{z}-z+y\right) + A_3 u_1 d S^* Z^*\left(xv-\frac{xv}{u}-u+1\right)\\
&+ aI_2^*\left(1-\frac{1}{v}\right)\frac{(z-v)+bI_2^* z(1-v)}{I_2^*(1+bI_2^*)\left(\frac{1}{I_2^*}+bz\right)}.
\end{aligned}$$

It indicates a choice of values for A_i to make V as a Lyapunov function and so A_i have to satisfy the following equations:

$$A_1 - 1 = 0, \ -c\beta_2 I_2^* S^* - (\eta+\alpha) I_2^* + A_2 k_1 I_1^* = 0 \ \text{ and } \ \theta E^* - A_3 u_1 d S^* Z^* = 0.$$

Leading to

$$A_1 = 1, \qquad A_2 = \frac{c\beta_2 I_2^* S^* + (\eta+\alpha) I_2^*}{k_1 I_1^*}, \qquad A_3 = \frac{\theta E^*}{u_1 d S^* Z^*}.$$

$$\begin{aligned}
\text{Hence, } \frac{dV}{dt} &< c\beta_2 I_2^* S^*\left(3-\frac{1}{x}-\frac{xz}{y}-\frac{y}{z}\right) - \theta E^*\left(\frac{u}{x}-\frac{1}{x}+\frac{xv}{u}-xv\right) + (\eta+\alpha) I_2^*\left(2-\frac{y}{z}-\frac{z}{y}\right)\\
&- u_1 d S^* Z^*\left(x+\frac{1}{x}-v-1\right) - a\left(v+\frac{z}{v}-z-1\right)\frac{1}{\left(\frac{1}{I_2^*}+bz\right)}\\
&< 0.
\end{aligned}$$

Therefore, $\frac{dV}{dt} < 0$ and $\frac{dV}{dt} = 0$ if and only if $S = S^*, I_1 = I_1^*, I_2 = I_2^*, E = E^*$ and $Z = Z^*$ in Ξ. Thus the singleton set E_1 is the largest positively invariant set contained in $\left\{(S, I_1, I_2, E, Z) \in \Xi : \frac{dV}{dt} = 0\right\}$. Then by Lyapunov LaSalle's theorem [57], E_1 is globally asymptotically stable in the interior of Ξ for $R_0 > 1$. □

7. Direction of bifurcation at $R_0 = 1$

In order to establish the direction of bifurcation at the crucial threshold value $R_0 = 1$, the central manifold theory is used as discussed in Chavez and Song [58], and their result is stated in the following theorem:

Theorem 7.1. *Consider the following system of ODEs with a parameter φ:*

$$\frac{dx}{dt} = h(x, \varphi), \ h : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \text{ and } h \in C^2\left(\mathbb{R}^n \times \mathbb{R}\right),$$

with O is an equilibrium of this system and $h(O, \varphi) = O$ for all φ. Assume
(a) *$M = D_x h(O, 0) = (\frac{\partial h_i}{\partial x_j}(O, 0))$ is the linearization matrix of the above system around the equilibrium O with φ evaluated at 0. Zero is a simple eigenvalue of M and all other eigenvalues of M have negative real parts.*
(b) *Matrix M has a non-negative right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.*

Let h_k be the kth component of h and

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

$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 h_k}{\partial x_i \partial \varphi}(O,0),$$

The local dynamics of the system around O is totally determined by a and b.

1. *$a > 0, b > 0$. When $\varphi < 0$ with $|\varphi| \ll 1$, O is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \varphi \ll 1$, O is unstable and there exists a negative and locally asymptotically stable equilibrium.*
2. *$a < 0, b < 0$. When $\varphi < 0$ with $|\varphi| \ll 1$, O is unstable; when $0 < \varphi \ll 1$, O is locally asymptotically stable, and there exists a positive unstable equilibrium.*
3. *$a > 0, b < 0$. When $\varphi < 0$ with $|\varphi| \ll 1$, O is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \varphi \ll 1$, O is stable, and a positive unstable equilibrium appears.*
4. *$a < 0, b > 0$. When φ changes from negative to positive, O changes its stability from stable to unstable. Corresponding a negative unstable equilibrium becomes positive and locally asymptotically stable.*

The non-negativity of components of the eigenvector w is not necessary if corresponding component of equilibrium is positive and has been mentioned as **Remark 1** in [58].

The requirement that w is non-negative in the previous theorem is not necessary. When some components in w are negative, we still can apply the theorem, but one has to compare w with the equilibrium because the general parameterization of the centre manifold before the coordinate change is

$$W^c = \{x_0 + c(t)y + k(c,\varphi) : \ v \cdot k(c,\varphi), |c| \le c_0, c(0) = 0\}$$

provided that x_0 is a non-negative equilibrium of system (usually x_0 is the DFE). Hence, $x_0 - 2\frac{b\varphi}{a} > 0$ requires that $w(j) > 0$ whenever $x_0(j) = 0$. If $x_0(j) > 0$, then $w(j)$ need not be positive.

Let us redefine $S = x_1,\ I_1 = x_2,\ I_2 = x_3,\ E = x_4$ and $Z = x_5$ then the system (2) can be rewritten as

$$\begin{aligned}
\frac{dx_1}{dt} &= \Lambda - c(\beta_1 x_2 + \beta_2 x_3)x_1 - \mu x_1 + \theta x_4 - u_1 d x_1 x_5 \equiv h_1,\\
\frac{dx_2}{dt} &= c(\beta_1 x_2 + \beta_2 x_3)x_1 - (\mu + k_1)x_2 + \eta(x_2 + x_3) + \alpha x_3 \equiv h_2,\\
\frac{dx_3}{dt} &= k_1 x_2 - (\alpha + \mu + k_2)x_3 - \rho x_3 \equiv h_3,\\
\frac{dx_4}{dt} &= u_1 d x_1 x_5 - (\mu + \theta)x_4 \equiv h_4,\\
\frac{dx_5}{dt} &= \frac{a x_3}{1 + b x_3} - a_0 x_5 \equiv h_5.
\end{aligned} \tag{6}$$

We have considered $\varphi = c$ as bifurcation parameter for $R_0 = 1$. Thus at $\varphi = \varphi^* = c^*$, $R_0 = 1$ gives $c^* = \frac{\mu[(\mu+k_1-\eta)(\alpha+\mu+\rho+k_2)-k_1(\eta+\alpha)]}{\Lambda\{\beta_1(\alpha+\mu+\rho+k_2)+\beta_2 k_1\}}$. The linearization matrix of the model system (6) at $E_0(\frac{\Lambda}{\mu}, 0, 0, 0, 0)$ with bifurcation parameter $c = c^*$ is given by

$$\tilde{J}|_{E_0} = \begin{pmatrix}
-\mu & -c^*\beta_1\frac{\Lambda}{\mu} & -c^*\beta_2\frac{\Lambda}{\mu} & \theta & -u_1 d\frac{\Lambda}{\mu}\\
0 & c^*\beta_1\frac{\Lambda}{\mu} - (\mu + k_1 - \eta) & c^*\beta_2\frac{\Lambda}{\mu} + \eta + \alpha & 0 & 0\\
0 & k_1 & -(\alpha + \mu + k_2 + \rho) & 0 & 0\\
0 & 0 & 0 & -(\mu + \theta) & u_1 d\frac{\Lambda}{\mu}\\
0 & 0 & a & 0 & -a_0
\end{pmatrix}$$

Here, $\lambda_1 = -\mu,\ \lambda_2 = -(\mu + \theta),\ \lambda_3 = -a_0,\ \lambda_4 = \frac{c\beta_1\Lambda}{\mu} + \eta - 2\mu - \alpha - \rho - k_1 - k_2$, and $\lambda_5 = 0$. So, $\tilde{J}|_{E_0}(c^*)$ has a zero eigenvalue at $R_0 = 1$ and it is simple eigenvalue and all remaining eigenvalues are negative. The right eigenvector corresponding to the zero eigenvalue of $\tilde{J}|_{E_0}(c^*)$ is denoted by $w = (w_1, w_2, w_3, w_4, w_5)^T$ where $w_1 = -\Lambda[c\beta_1 a_0(\mu+\theta)(\alpha+\mu+k_2+\rho)+c\beta_2 a_0 k_1(\mu+\theta)+a\mu d k_1 u_1],\ w_2 = a_0\mu^2(\mu+\theta)(\alpha+\mu+k_2+\rho),\ w_3 = a_0 k_1\mu^2(\mu+\theta),\ w_4 = \Lambda a\mu d k_1 u_1$, and $w_5 = a k_1\mu^2(\mu+\theta)$. Also the left eigenvector of $\tilde{J}|_{E_0}(c^*)$ corresponding to zero eigenvalue is $v = (v_1, v_2, v_3, v_4, v_5)^T$ where $v_1 = 0,\ v_2 = k_1,\ v_3 = (\mu + k_1 - \eta) - \frac{c\beta_1\Lambda}{\mu},\ v_4 = 0$, and $v_5 = 0$. Hence

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 h_k}{\partial x_i \partial x_j}(E_0) = -2k_1 a_0 \mu^4(\mu + \theta)X\left[a d u_1 k_1 + \frac{a_0(\mu + \theta)}{X}\right] < 0,$$

where $X = (\mu + k_1 - \eta)(\alpha + \mu + k_2 + \rho) - k_1(\eta + \alpha) > 0$, by our assumption (11).

Table 1
Parameter values used for numerical simulation of system (2).

Parameter	Λ	β_1	β_2	μ	θ	u_1	d	k_1	η	α
Value	5	0.000481	0.000581	0.07	0.001	0.1	0.002	0.125 [59]	0.05	0.33 [60]

Parameter	k_2	ρ	γ	δ	a	b	a_0
Value	0.1 [60]	0.07	0.01	0.1	0.01	1	0.06

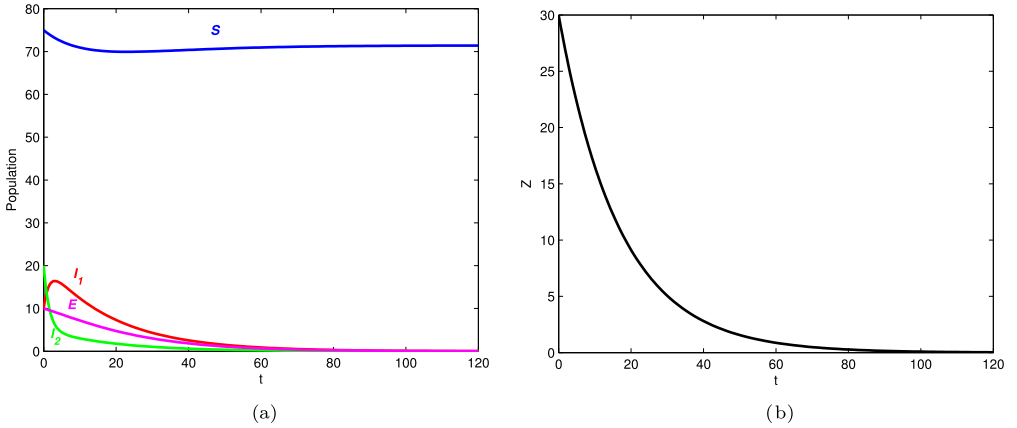

Fig. 2. (a) Stability of the populations around disease-free equilibrium E_0. (b) Information level when the system is disease-free.

$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 h_k}{\partial x_i \partial \varphi}(E_0) = \frac{k_1 \Lambda}{\mu}(\beta_1 + \beta_2) > 0$$

Now applying the last condition of Theorem 7.1, it is observed that the direction of bifurcation is forward.

Theorem 7.2. *The DFE: $E_0\left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right)$ changes its stability from stable to unstable at $R_0 = 1$ and there exists a positive equilibrium as R_0 crosses one. Hence, system (2) undergoes a transcritical bifurcation with bifurcation parameter $c = c^*$ at $R_0 = 1$.*

8. Numerical simulation without any optimal control

In the section, we illustrate the dynamics of the system (2) graphically for the set of parameter values given in Table 1.

For $c = 0.01$, system (2) converges to $E_0 = (71.43, 0, 0, 0, 0)$ when $R_0 = 0.007 < 1$, which is depicted in Fig. 2. For $c = 3$, $R_0 = 2.11 > 1$ and $E_1 = (S^* = 33.7855, I_1^* = 42.7201, I_2^* = 9.3684, E^* = 0.0143, Z^* = 0.1505)$. Fig. 3 provides the stability behaviour around the endemic equilibrium E_1 when $R_0 > 1$. In Fig. 4, the sensitivity of some of the system parameters have been observed which leads to the fact that the rate of contact of susceptible with infective population plays a crucial role in the disease transmission. It is noted that the disease can be eradicated by reducing the basic reproduction number below unity. In Fig. 5(b), only the stable region of the equilibrium points have been drawn and it can be observed that for $c < c^*$ the disease-free equilibrium is stable while after crossing the threshold vale $c^* = 1.418$, the endemic equilibrium will be stable. So, at $c = c^*$ the system undergoes a transcritical bifurcation around E_1. Now d is the information interaction rate by which individuals can bring changes in their behaviour. As days go by, people become more aware about the use of PREP and can protect themselves in a higher rate by taking it before getting infected. In early days the population density of asymptomatic infected population hardly change for different values of d but later it can be observed that d plays an important role to reduce the disease transmission. So, increasing d can reduce the number of overall infected individuals which is reflected in Fig. 6.

9. Optimal control problem

In this section, we formulate an optimal control problem corresponding to the model system (1) considering both (i) the effect of information of PrEP and other preventions and (ii) the effect of treatment on the population as control policies. We try to look over the influence of these control parameters on the progression of disease and also to optimize the cost incurred in their implementation. Let us first describe these two control policies and then determine the cost corresponding to those policies.

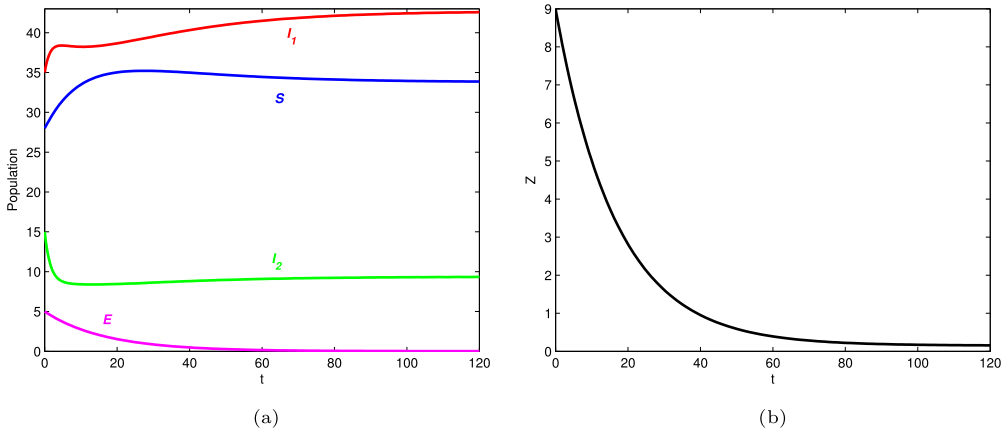

Fig. 3. Stability of the populations around endemic equilibrium E^*. (b) Information level when the system is infected with HIV.

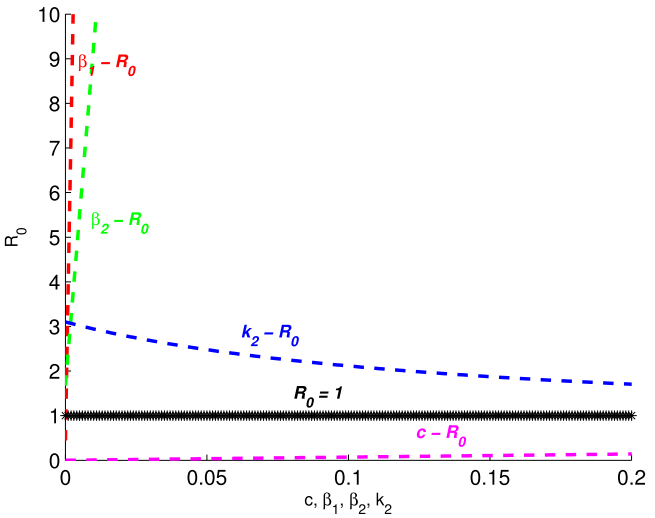

Fig. 4. Relationship between basic reproduction number R_0 with c, β_1, β_2 and k_2.

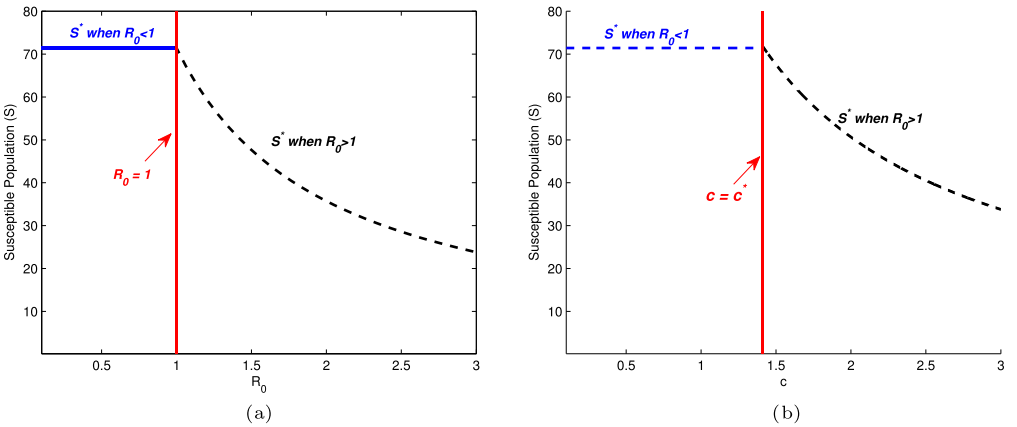

Fig. 5. (a) Dynamical behaviour of susceptible population (S) with respect to R_0. (b) Stable branch of the equilibrium points with variation of c.

(i) To raise the response of susceptible population through information: Providing the information about a disease and its prevention can instigate behavioural change among susceptible individuals. This information here we have considered

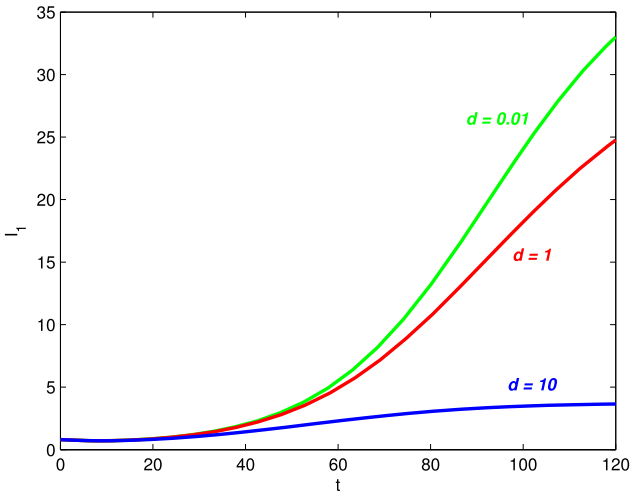

Fig. 6. Profiles of asymptomatic infective population for various d without any control policy.

as a possible tool mainly to activate the sensibility of the susceptible individuals. In our model system (1), u_1 is the response intensity function through information satisfying $0 \leq u_1 \leq 1$. Here 0 means no response whereas 1 indicates the full response of informed individuals. Hence, $u_1(t)$ will change accordingly as individual's behavioural response. We take this response intensity $u_1(t)$ as a control variable. Cost will be involved as a non-linear function of $u_1(t)$ to enhance the response of individuals, so that they change their behaviour. Spread of information shall help us to find the optimal response of susceptible individuals.

(ii) Medical treatment of infective population: The disease prevalence can be lowered by proper treatment to infective individuals and it also affects disease progression. It is assumed that the treatment is available and is provided to infected (symptomatic) individuals. Now the availability of resources mainly depend on medical diagnosis, treatment etc. that cannot be unlimited. In the model system (1), we have incorporated saturated treatment rate function as $\frac{\epsilon u_2 I_2}{1+\alpha_1 I_2}$ and thereby obtained system (8). Here ϵ is treatment rate with intensity u_2 along with saturation constant α_1. We have also included different costs such as vaccination, diagnosis, medicines, hospitalization, health care and other related costs at the time of providing treatment to the infected. Thus we also consider the treatment intensity u_2 as control variable with the restriction $0 \leq u_2 \leq 1$.

We mainly try to determine optimal treatment and optimal response intensity by dint of information with minimum cost. From the above discussion we have got that the acceptable set for the control variables $u_1(t)$ and $u_2(t)$ is given by

$$\Omega = \{(u_1(t), u_2(t)) \,|(u_1(t), u_2(t)) \in [0, 1] \times [0, 1], t \in [0, T_1]\}\,.$$

Here T_1 represents the final time that control policies can be executed, and $u_1(t)$ and $u_2(t)$ both are measurable and bounded functions.

9.1. Determination of total cost

First we determine the total cost that has to be minimized for control interventions in the system.

(i) Cost involved in spread of information: The total cost incurred for the processing of information transmission is as follows:

$$\int_0^{T_1} w_2 u_1^4(t) dt$$

Here $w_2 u_1^4(t)$ represents the cost for spreading information regarding the disease and its prevention through the use of PrEP and treatment via educational programs, campaigns, television, newspapers, social networks etc. By convention w_2 mainly represents the positive weight (constant) associated with spreading of information. The term includes the cost of associated efforts to convince the individual and this cost is comparatively higher. Some researchers analysed the impact of the cost which is associated with social mitigation strategies such as awareness programs, screening and self protective measures but they have taken the non-linearity up to order two [47,29,19]. Now the cost of efforts to spread the information to induce behavioural changes for a fraction of population will be much higher for those who is already at higher response intensity than in case of cost in efforts at a low response intensity. Consequently this cost increases rapidly for people with high response to information. Hence we consider non-linearity of order four as $u_1^4(t)$ [49].

Table 2
Parametric values used in the model system.

Parameters	Value	Source
Λ	0.02 person day^{-1}	[15]
ϵ	0.6 day^{-1}	[15]
ρ	0.1 day^{-1}	[60]
d	0.017 day^{-1}	[48]
k_2	0.1 day^{-1}	[60]
δ	0.01 day^{-1}	[15]
a	0.01	[22,61]
a_0	0.06	[22,61]
c	4 person day^{-1}	Assumed
γ	0.01 day^{-1}	Assumed
k_1	0.3 day^{-1}	Assumed
η	0.0005 day^{-1}	Assumed
α	0.0003 day^{-1}	Assumed
θ	0.001 day^{-1}	Assumed
μ	0.004 day^{-1}	Assumed
β_1	0.0005 person^{-1}day^{-1}	Assumed
β_2	0.0005 person^{-1}day^{-1}	Assumed
b	1	Assumed
α_1	0.045	Assumed

(ii) Cost involved in disease and treatment: The total cost associated with disease burden and treatment policy for infected (symptomatic) people is given by

$$\int_0^{T_1} \left[w_1 I_2(t) + w_3 u_2^2(t)\right] dt$$

The cost associated with infected population for losing man power and corresponding wealth is represented by $w_1 I_2(t)$ [15,29,18]. It also expresses the opportunity loss which includes the lose of productivity due to illness. The term $w_3 u_2^2(t)$ denotes the cost regarding the treatment policy such as medication charges, diagnosis charges, expenditure of hospitalization etc. As a result, quadratic non-linearity $u_2^2(t)$ in cost for treatment is incorporated [15,29,18]. In this case w_1 and w_3 are the positive weights (constants) associated with infected population and treatment respectively.

The following control problem is considered based on previous discussions along with the cost functional J_1 to be minimized:

$$J_1[u_1(t), u_2(t)] = \int_0^{T_1} \left[w_1 I_2(t) + w_2 u_1^4(t) + w_3 u_2^2(t)\right] dt \tag{7}$$

subject to the following model system:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - c(\beta_1 I_1 + \beta_2 I_2)S - \mu S + \theta E - u_1(t) dSZ,\\
\frac{dI_1}{dt} &= c(\beta_1 I_1 + \beta_2 I_2)S - (\mu + k_1) I_1 + \eta(I_1 + I_2) + \alpha I_2,\\
\frac{dI_2}{dt} &= k_1 I_1 - (\alpha + \mu + k_2) I_2 - \rho I_2 - \frac{\epsilon u_2(t)}{1 + \alpha_1 I_2} I_2,\\
\frac{dT}{dt} &= k_2 I_2 - (\mu + \gamma) T + \frac{\epsilon u_2(t)}{1 + \alpha_1 I_2} I_2,\\
\frac{dE}{dt} &= u_1(t) dSZ - (\mu + \theta) E,\\
\frac{dZ}{dt} &= \frac{a I_2}{1 + b I_2} - a_0 Z,
\end{aligned} \tag{8}$$

with the initial conditions $S_0 > 0,\ I_{1,0} > 0,\ I_{2,0} > 0,\ T_0 > 0,\ E_0 > 0$ and $Z_0 > 0$. Here the functional J_1 represents the total cost, i.e., sum of the costs as stated. The integrand is

$$L(S, I_1, I_2, T, E, Z, u_1(t), u_2(t)) = w_1 I_2(t) + w_2 u_1^4(t) + w_3 u_2^2(t)$$

that denotes the current value of cost at any time t. Parameters w_1, w_2 and w_3 are positive weights (assumed as constants) which balance the units of integrand also [15,29]. Let us denote $u_1(t) = u_1$ and $u_2(t) = u_2$. The existence of optimal control pair u_1^* and u_2^* in Ω is guaranteed which mainly minimizes the cost functional J_1.

Theorem 9.1. *There exists an optimal control pair u_1^* and u_2^* in Ω such that $J_1(u_1^*, u_2^*) = \min\{J_1(u_1, u_2)\}$ corresponding to the control system (7)–(8).*

Proof. Proof has been given in Appendix . □

Further, with the help of **Pontryagin's Maximum Principle** we characterize the optimal control pair u_1^* and u_2^* of the system in the following.

Theorem 9.2. *Let u_1^* and u_2^* be optimal control variables and $S^*, I_1^*, I_2^*, T^*, E^*, Z^*$ are corresponding optimal state variables of the control system (7)–(8). Then there exists adjoint variable $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6) \in \mathbb{R}^6$ that satisfies the following canonical equations:*

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= \lambda_1 \{c(\beta_1 I_1 + \beta_2 I_2) + \mu + u_1(t)dZ\} - \lambda_2 c(\beta_1 I_1 + \beta_2 I_2) - \lambda_5 u_1(t)dZ,\\
\frac{d\lambda_2}{dt} &= c\lambda_1\beta_1 S - \lambda_2 \{c\beta_1 S - (\mu + k_1) + \eta\} - \lambda_3 k_1,\\
\frac{d\lambda_3}{dt} &= -w_1 + c\lambda_1\beta_2 S - \lambda_2 \{c\beta_2 S + (\alpha + \eta)\} + \lambda_3 \left\{\alpha + \mu + \rho + k_2 + \frac{\epsilon u_2(t)}{(1+\alpha_1 I_2)^2}\right\}\\
&\quad - \lambda_4 \left\{k_2 + \frac{\epsilon u_2(t)}{(1+\alpha_1 I_2)^2}\right\} - \lambda_6 \frac{a}{(1+bI_2)^2},\\
\frac{d\lambda_4}{dt} &= \lambda_4(\mu + \gamma),\\
\frac{d\lambda_5}{dt} &= -\lambda_1\theta + (\mu + \theta)\lambda_5,\\
\frac{d\lambda_6}{dt} &= \lambda_1 u_1(t) dS - \lambda_5 u_1(t) dS + a_0\lambda_6,
\end{aligned} \tag{9}$$

with transversality conditions $\lambda_i(T_1) = 0$ for $i = 1, 2, \ldots, 6$. The corresponding optimal controls u_1^* and u_2^* are given as

$$\begin{aligned}
u_1^* &= \min\left\{\max\left\{0, \left(\frac{dS^*Z^*}{4w_2}(\lambda_1 - \lambda_5)\right)^{\frac{1}{3}}\right\}, 1\right\},\\
\text{and} \quad u_2^* &= \min\left\{\max\left\{0, \frac{\epsilon I_2^*}{2w_3\left(1+\alpha_1 I_2^*\right)}(\lambda_3 - \lambda_4)\right\}, 1\right\}.
\end{aligned} \tag{10}$$

Proof. Proof is given in Appendix . □

10. Numerical results and discussion

Till now we have analysed the stability conditions of the equilibrium points and also find the optimal control variables for corresponding optimal control problem. These control variables mainly minimize the total cost that has been considered. Here we shall perform the numerical simulations to validate our analytical findings and to see the involvement of control variables in the system dynamics. We shall consider the cases for implementation of one or both control strategies to find the minimal cost.

We shall numerically solve the control system-(8) along with (7) for the set of parameter values provided in Table 2 with the initial size of populations and information as: $S(0) = 56.18$, $I_1(0) = 5.11$, $I_2(0) = 1.43$, $T(0) = 0.45$, $E(0) = 1.12$ and $Z(0) = 1$. MATLAB plays an important role to obtain the graphical scenarios for various cases. Forward–backward sweep method has been used here for the optimal control problem. We have to solve the optimal state system forward in time and then we need to solve the adjoint state system backward in time. In the next step these optimal controls are updated using Hamiltonian for optimality of the optimal system and for doing this we need to use the steepest descent method [62,63]. The process will continue until the convergence criterion is satisfied. Time period of study and application of control interventions is around 1 month, i.e., 30 days.

Fig. 7 shows the population graphs with respect to time in absence of both the controls, i.e., $u_1 = 0$, $u_2 = 0$. For this situation, at $T_1 = 30$, the population is $(S^*, I_1^*, I_2^*, T^*, E^*) = (37.439, 0.716, 1.499, 7.353, 0.964)$. It is observed that the growth of infective population slowly decreases after around a week. It is also noted that there are more infective population in symptomatic phase than in asymptomatic phase. Moreover, there are a significant number of infective present in the scenario around 5th day which will create the economic burden in terms of productivity loss, morbidity, mortality and in procuring protective measures during the period.

Now we shall discuss about the effects of single control. The positive weights have been considered as $w_1 = 1.64$, $w_2 = 100$ and $w_3 = 10$ [15,29]. In Fig. 8, the population profiles have been considered by taking only the response regarding PrEP via information (u_1) as control parameter. The optimality of the system has been determined only for u_1 (taking $u_2 = 0$). For this situation, at $T_1 = 30$, the population is $(S^*, I_1^*, I_2^*, T^*, E^*) = (36.680, 0.655, 1.404, 7.198, 2.252)$. It is observed that the behavioural response can stimulate the population awareness. Both the infected population are lower than the case when control has not been incorporated. But the population, who are taking PrEP as a precaution, has increased in a higher rate.

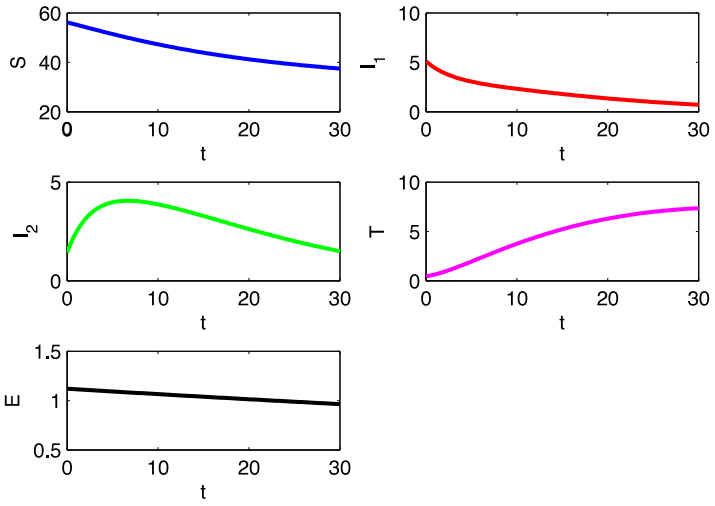

Fig. 7. Profiles of populations in absence of controls i.e. both $u_1 = 0$ and $u_2 = 0$. Parameters are as in Table 2.

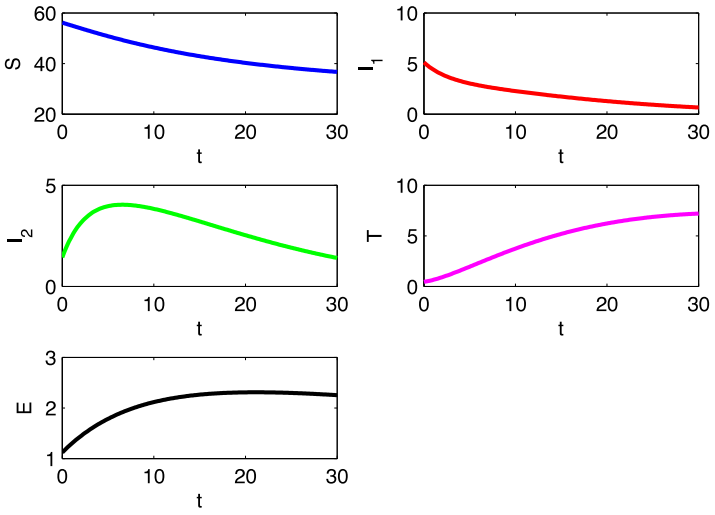

Fig. 8. Profiles of populations with applied optimal control of response regarding PrEP via information u_1^* only and $u_2 = 0$. Parameters are as in Table 2.

As people become more aware about PrEP day by day, so the number of susceptible (S) has also been decreased and the number of people with PrEP (E) will increase. This will lead to a lower growth rate of infective population also. Though the count of both infective population are reduced throughout the entire period, still the population remains high enough for almost a week. Henceforth, PrEP can reduce the disease burden although the time duration of disease prevalence is almost unaffected. Fig. 9(a) depicts the path of optimal intensity of response about PrEP. So, the effect of taking PrEP plays a crucial role to reduce the disease burden during outbreak of the epidemic.

To obtain the population trajectories in Fig. 10, the optimality of the system is solved for treatment only ($u_1 = 0$). For this situation, at $T_1 = 30$, the population is $(S^*, I_1^*, I_2^*, T^*, E^*) = (44.249, 0.172, 0.279, 7.559, 0.964)$. Parameters have been taken from Table 2 along with weights as mentioned. The optimal treatment works better to reduce the prevalence of disease and also it reduces the infective population (both asymptomatic and symptomatic). The span of symptomatic infective population reduces early in this case. The corresponding intensity profile of optimal treatment has been shown in Fig. 9(b). From Fig. 9, it is observed that the intensity of treatment works with a higher capacity for around one week and then slowly decline through the rest of the time period. So, it can be concluded that if the pharmaceutical control (u_2) is not available due to some reasons during epidemic outbreak, then the health organizations can focus on the behavioural response via information to control the epidemic, i.e., taking PrEP as a precaution can control the disease prevalence in absence of any treatment.

Let us give a brief description about the need of the control policies in the underlying system. In system-(8), u_1 reduces susceptible population and decreases the disease transmission from susceptible to asymptomatic infective population

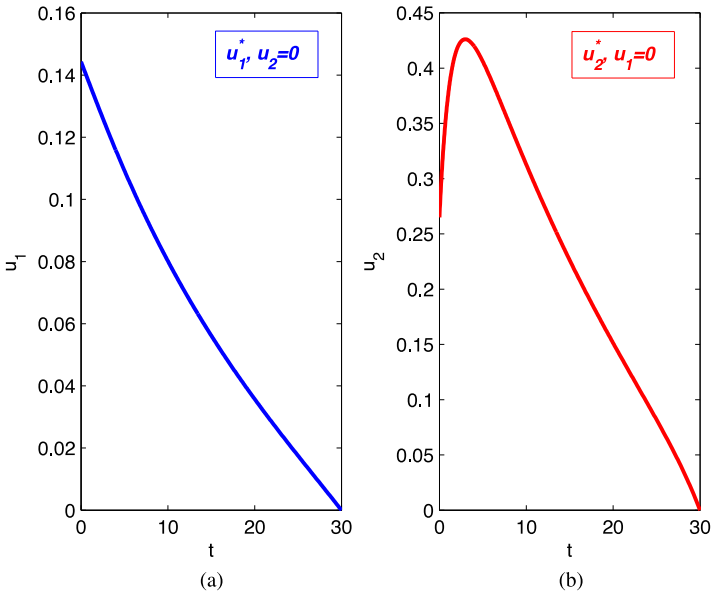

Fig. 9. (a) Optimal intensity of response about PrEP via information u_1^* and $u_2 = 0$. (b) Optimal intensity of treatment u_2^* and $u_1 = 0$. Parameters are as in Table 2.

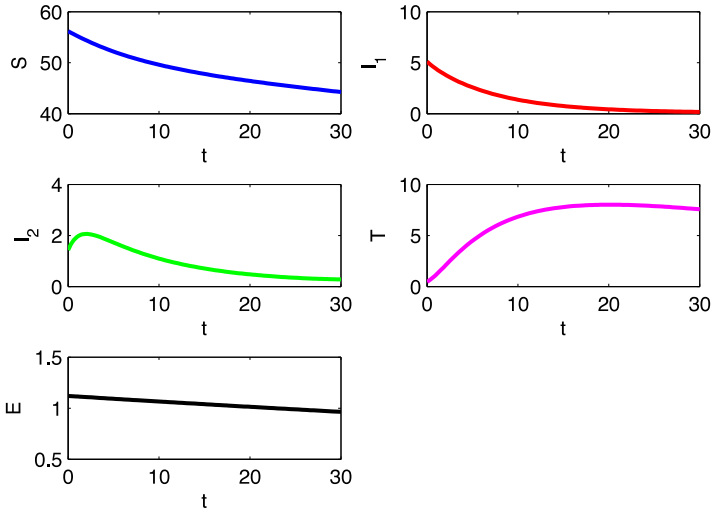

Fig. 10. Profiles of populations with optimal treatment u_2^* only and $u_1 = 0$. Parameters are as in Table 2.

through $c(\beta_1 I_1 + \beta_2 I_2)S$. But u_1 does not effect the average life time of infectious individuals. So, the time period of disease prevalence will remain unchange by increasing the response of susceptible population regarding PrEP. Moreover, providing treatment to symptomatic infective reduces the overall symptomatic infective population as a result of conversion of I_2 to I_1.

Now we consider a combination of both the control policies simultaneously, i.e., a system has been taken where a portion of population is responding to the advantages PrEP and taking it as a precaution from being infected as well as a pharmaceutical treatment is applied to symptomatic infective population. Fig. 11 depicts the population profiles. For this situation, at $T_1 = 30$, the population is $(S^*, I_1^*, I_2^*, T^*, E^*) = (42.267, 0.241, 0.426, 7.585, 1.897)$. It is observed that the implementation of both the controls will work better. The combined effect not only reduces the overall infective population but also increases the awareness among people about the advantages of taking PrEP. Implementation of both the controls can reduce the duration of prevalence of overall infective population also. The paths of the optimal controls have been plotted in Fig. 12(a). It can be noted that the treatment can work with a better intensity for quite a long time period to control the infective individuals. The response for PrEP works with higher intensity at the initial stage to control the disease outbreak. Fig. 12(b) shows that under the effect of optimal control the level of information gradually decreases.

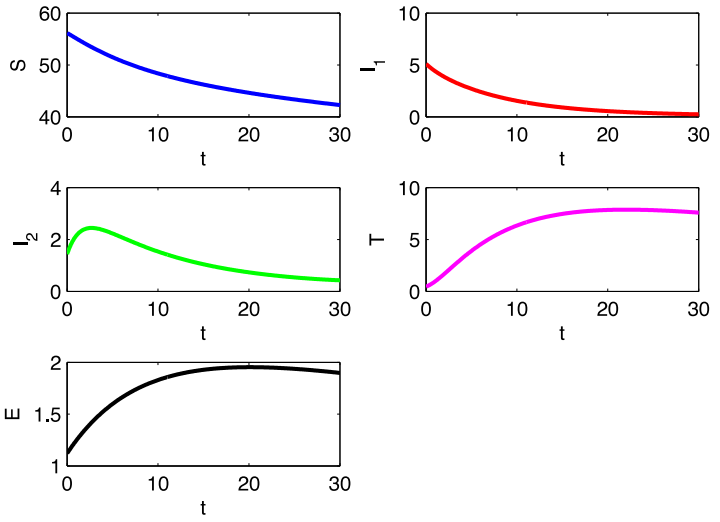

Fig. 11. Profiles of populations with both optimal control policies u_1^* and u_2^*. Parameters are as in Table 2.

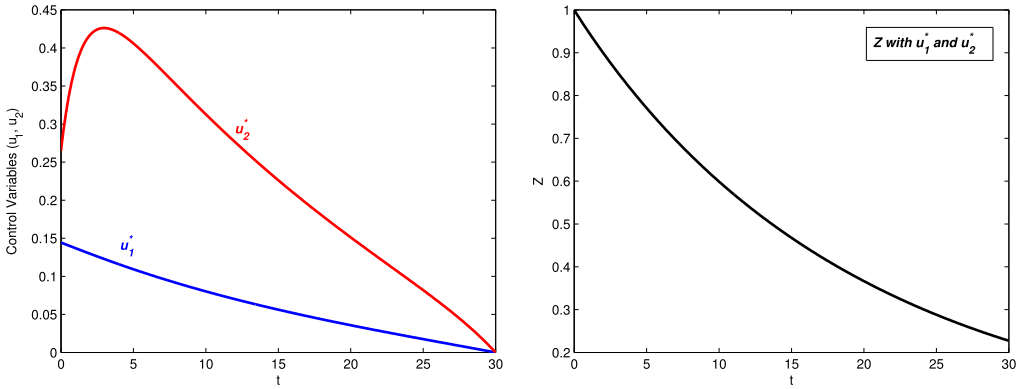

Fig. 12. (a) Profiles of optimal controls u_1^* and u_2^*. (b) Optimal information level under the influence of u_1^* and u_2^*. Other parameters are as in Table 2.

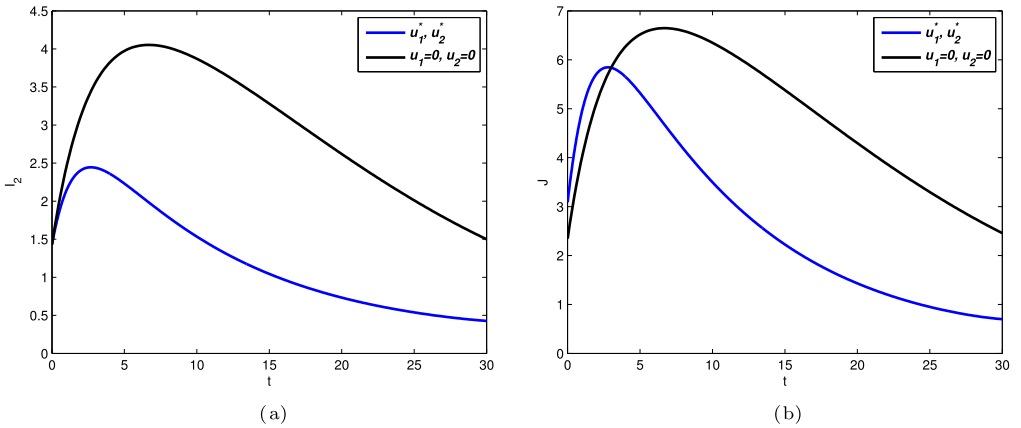

Fig. 13. (a) Cost distribution with various control policies. (b) Profiles of symptomatic infective population under various control policies. Other parameters are as in Table 2.

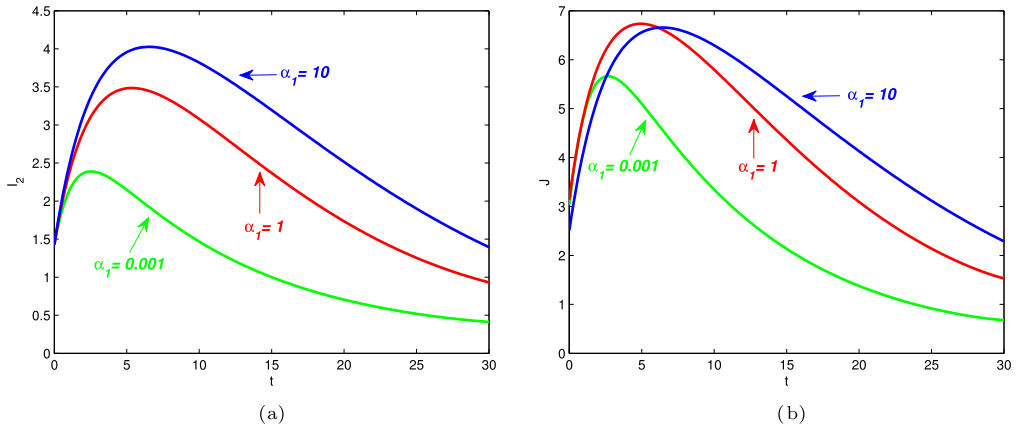

Fig. 14. (a) Profiles of symptomatic infective population for various α_1 with u_1^* and u_2^*. (b) Profiles of cost for various α_1 with u_1^* and u_2^*. Other parameters are as in Table 2.

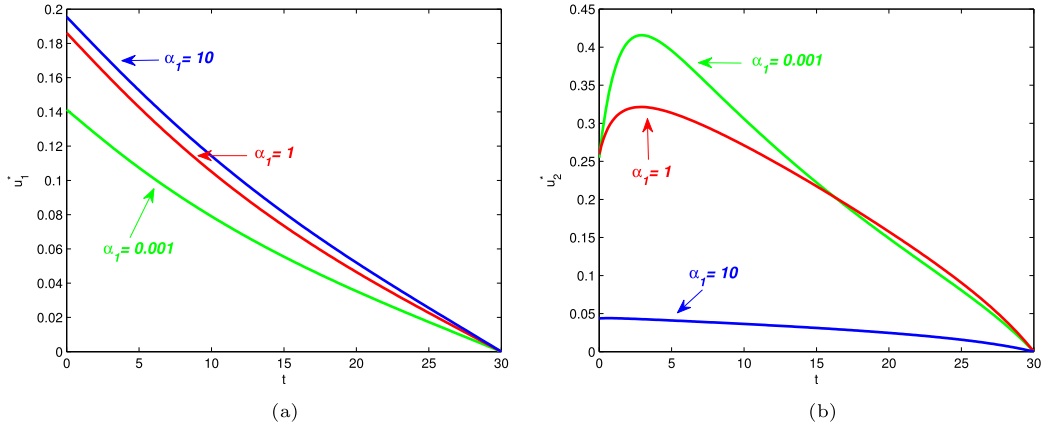

Fig. 15. (a) Plots of control u_1^* for various α_1. (b) Plots of control u_2^* for various α_1. Other parameters are as in Table 2.

We have performed the cost design analysis for different cases because cost effectiveness is one of the important characteristics to decide the fitness (see Fig. 13). Both the optimal cost profiles for these control policies along with the trajectory of symptomatic infective individuals for different cases can be observed from Fig. 13(a) and (b). It is noted that in absence of any control policies, the cost will be due to the productivity loss which will be influenced by symptomatic infective population. The cost is quite high and hence in absence of any control the disease will spread out and infective population will be higher. So, opportunity loss will increase and it will sum up to economic burden. Moreover, when both control policies are used, the optimal cost will be comparatively low. Smaller number of infective individuals will reduce the overall total cost via opportunity loss in this case.

10.1. Effect of saturated treatment on optimal control variables

This section contains how the limited treatment resources effect the disease dynamics when both the control policies are applied with their optimal intensities. The saturation on treatment (α_1) as well as the treatment rate (ϵ) have been varied in the subsequent figures. Fig. 14 depict the profiles of symptomatic infective population and corresponding cost for various values of α_1. Associated optimal controls have been drawn in Fig. 15. Increasing α_1 will lead to an increased value of symptomatic infectives and associated cost also, because higher level of infective population is related to productivity loss. From the optimal profiles of control variables, it is concluded that higher saturation in treatment (*i.e.* smaller value of α_1) will provide lower efforts on the control variables. Therefore, if the saturation in treatment is sufficiently high, then it will be economically viable and needs comparatively lesser efforts to implement the controls.

On the other hand when treatment rate (ϵ) is varied from 0.01 to 1, the infective (symptomatic) population decreases following a reduction in associated cost also (Fig. 16). From Fig. 17, it can be observed that with increasing value of ϵ, the maximum intensity can be reduced for the control that represents the behavioural response regarding PrEP via information. Also, higher treatment rate helps the optimal treatment to work with comparatively higher intensity. It is also true that

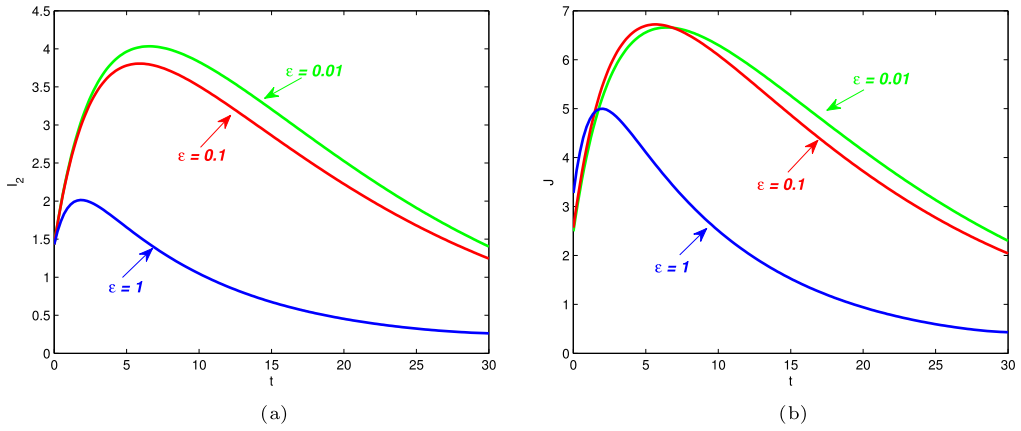

Fig. 16. (a) Profiles of symptomatic infective population for various ϵ with u_1^* and u_2^*. (b) Profiles of cost for various ϵ with u_1^* and u_2^*. Other parameters are as in Table 2.

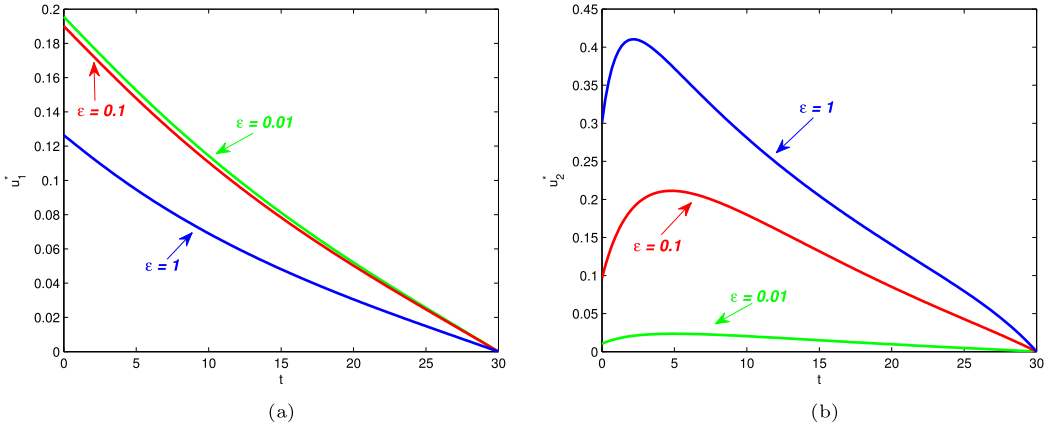

Fig. 17. (a) Plots of control u_1^* for various ϵ. (b) Plots of control u_2^* for various ϵ. Other parameters are as in Table 2.

higher treatment rate decreases the time period during which optimal treatment can be implemented with maximum intensity.

11. Conclusion

In this work, we have sketched a mathematical model of population dynamics of HIV considering treatment and pre-exposure prophylaxis (PrEP). The model includes the effect of information (regarding PrEP) induced behavioural response of susceptible individuals. Here we have incorporated a separate rate equation to model the dynamics of information where a saturated functional for information growth has been considered. The growth of information mainly depends on symptomatic infective population, social media, awareness programs conducted by government and other social activities. Stability theory has been used to analyse the model system qualitatively. The system has mainly two equilibrium points: disease-free equilibrium which exists always and the endemic equilibrium that exists when basic reproduction number (R_0) be greater than 1. Local and global stability of the equilibria have been proved in Section 6. Global stabilities have been proved by constructing suitable Lyapunov functions and with the help of Lyapunov LaSalle's theorem.

In the later part, we have redefined our model to an optimal control problem by taking the combination of treatment and impact of information about PrEP as control variables and determined the total cost. Existence of the optimal control functions have also been proven. Pontryagin's Maximum Principle plays an important role in finding of analytical characterization of optimal control paths. The analytical results and simulations are quite meaningful as the work presented here is dealt with current HIV trends. Through the numerical computations, we can deduce certain observations that have already been discussed. The disease transmission can be reduced by taking precautions in an early stage that decrease the number of AIDS related death also.

These days a large number of population is exposed to HIV due to various reasons. The portion which is at high-risk includes young girls and women, sex workers, discordant couples and truckers etc. [64]. These populations can be considered

as the focal point for PrEP. Because by considering them as susceptible population, it will be comparatively easier to assess how best to introduce PrEP in the model. The model qualifies the impact of PrEP on susceptible population, because through numerical simulations we have come to the conclusion that PrEP can potentially reduce the number of new HIV infectious. Moreover, the effect of optimal response due to information, PrEP and optimal treatment can minimize the cost burden as well as the number of infective individual and duration of disease prevalence. It is observed that, if we apply any one of the control policies, that should be effective but with certain restrictions. The control of response via information (u_1) is economically beneficial for before getting infected, but the treatment policy which is given to symptomatic infective is economical for a long time duration. It is observed that, the effect of information regarding PrEP plays an important role in reduction of disease burden even if there is no pharmaceutical treatment given to the symptomatic patients. It has no doubt that the combination of both the control policies can reduce the disease transmission and disease prevalence as well as duration of disease prevalence. These policies can minimize the over all economic load also. So, implementation of both control policies is more effective and economical during epidemic outbreak.

Acknowledgements

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Appendix

A.1. Existence of optimal control functions

In this section, we shall discuss the existence of optimal control pair which minimizes the cost function in finite time. To establish the existence of this type of pair, we shall take the help of results proved in [65,15,46].

Proof of Theorem 9.1. For existence of optimal controls, the following conditions have to be satisfied:
(i) Set of solutions of the system (7) with control variables in $\Omega \neq \phi$.
(ii) Ω is closed, convex and state system can be expressed as a linear function of control variables where the coefficients will depend on time and state variables.
(iii) The integrand L of Eq. (7) is convex on Ω and $L(S, I_1, I_2, T, E, Z, u_1, u_2) \geq g(u_1, u_2)$ where $g(u_1, u_2)$ is continuous and $|(u_1, u_2)|^{-1} g(u_1, u_2) \to \infty$ whenever $|(u_1, u_2)| \to \infty$, here $|.|$ represents the $L^2(0, T_1)$ norm.

From (8), the total population $N = S + I_1 + I_2 + T + E$.

$$\text{So, } \frac{dN}{dt} = \Lambda - \mu N + \eta\,(I_1 + I_2) - \rho I_2 - \gamma T \leq \Lambda - (\mu - \eta)N.$$

The solution $N(t)$ of the above differential equation has the following property:

$$0 < N(t) \leq N(0)e^{-(\mu-\eta)t} + \frac{\Lambda}{\mu - \eta}\left(1 - e^{-(\mu-\eta)t}\right),$$

where $N(0)$ represents the sum of the initial values of the variables (S, I_1, I_2, T, A, E).

As $t \to \infty$, $0 < N(t) \leq \frac{\Lambda}{\mu-\eta}$.

$$\text{Now, } \frac{dZ}{dt} = \frac{aI_2}{1 + bI_2} - a_0 Z \leq aI_2 - a_0 Z$$

$$\Rightarrow \frac{dZ}{dt} + a_0 Z \leq \frac{a\Lambda}{\mu - \eta} \text{ (for large time } t\text{)}.$$

The solution $Z(t)$ will be of the form:

$$0 < Z(t) \leq Z(0)e^{-a_0 t} + \frac{a\Lambda}{a_0(\mu - \eta)}\left(1 - e^{-a_0 t}\right),$$

where $Z(0)$ represents the initial value of Z.

As $t \to \infty$, $0 < Z(t) \leq \frac{a\Lambda}{a_0(\mu-\eta)}$.

For each control variable in Ω, the solution of (8) is bounded and also the right hand side functions are Lipschitzian with respect to state variables. So condition (i) holds by *Picard–Lindelöf* theorem [66]. Now the control set Ω is closed and convex by definition. Also system-(3) can be written as a linear equation in control variables u_1 and u_2 with coefficients depending

on state variables which proves that condition (ii) is also satisfied. Now the bi-quadratic nature of control variable u_1 and quadratic nature of u_2 ensure that the integrand $L(S, I_1, I_2, T, E, Z, u_1, u_2)$ is convex.

$$\begin{aligned}\text{Also } L(S, I_1, I_2, T, E, Z, u_1, u_2) &= w_1 I_2 + w_2 u_1^4 + w_3 u_2^2 \\ &\geq w_2 u_1^4 + w_3 u_2^2\end{aligned}$$

Let, $\tilde{c} = \min(w_2, w_3) > 0$ and $g(u_1, u_2) = \tilde{c}(u_1^4 + u_2^2)$.

Then $L(S, I_1, I_2, T, E, Z, u_1, u_2) \geq g(u_1, u_2)$.

Here g is continuous and $|(u_1, u_2)|^{-1} g(u_1, u_2) \to \infty$ whenever $|(u_1, u_2)| \to \infty$. So, condition (iii) holds. Hence from [65,15,46], it can be concluded that there exists a control pair u_1^* and u_2^* such that $J_1[u_1^*, u_2^*] = \min[J_1[u_1, u_2]]$. □

A.2. Characterization of optimal control functions

In this section, we derive the necessary conditions for optimal control functions with the help of Pontryagin's Maximum Principle for the system (7)–(8) [65,67,68]. For this purpose, we define Hamiltonian as

$$\begin{aligned}H(S, I_1, I_2, T, E, Z, u_1, u_2, \lambda) &= L(S, I_1, I_2, T, E, Z, u_1, u_2) + \lambda_1 \dot{S} + \lambda_2 \dot{I}_1 + \lambda_3 \dot{I}_2 \\ &\quad + \lambda_4 \dot{T} + \lambda_5 \dot{E} + \lambda_6 \dot{Z}\end{aligned}$$

$$\begin{aligned}\text{So, } H &= w_1 I_2 + w_2 u_1^4 + w_3 u_2^2 + \lambda_1 [\Lambda - c(\beta_1 I_1 + \beta_2 I_2)S - \mu S + \theta E - u_1(t) d S Z] \\ &\quad + \lambda_2 [c(\beta_1 I_1 + \beta_2 I_2)S - (\mu + k_1) I_1 + \eta(I_1 + I_2) + \alpha I_2] \\ &\quad + \lambda_3 \left[k_1 I_1 - (\alpha + \mu + k_2) I_2 - \rho I_2 - \frac{\epsilon u_2(t)}{1 + \alpha_1 I_2} I_2 \right] \\ &\quad + \lambda_4 \left[k_2 I_2 - (\mu + \gamma) T + \frac{\epsilon u_2(t)}{1 + \alpha_1 I_2} I_2 \right] + \lambda_5 [u_1(t) d S Z - (\mu + \theta) E] \\ &\quad + \lambda_6 \left[\frac{a I_2}{1 + b I_2} - a_0 Z \right]\end{aligned} \tag{11}$$

Here $\lambda = (\lambda_1, \lambda_2, \ldots, \lambda_6)$ is called adjoint variable. By Pontryagin's Maximum Principle, we shall get minimized Hamiltonian that minimizes cost functional. Pontryagin's Maximum Principle plays an important role in adjoining the cost functional with the state equations by introducing adjoint variables.

Proof of Theorem 9.2. Let u_1^* and u_2^* be optimal control variables and $S^*, I_1^*, I_2^*, T^*, E^*, Z^*$ are corresponding optimal state variables of the control system (8) which minimize the cost functional (7). Then by Pontryagin's Maximum Principle, there exist adjoint variables $\lambda_1, \lambda_2, \ldots, \lambda_6$ which satisfy following canonical equations:

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S}, \quad \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial I_1}; \quad \frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial I_2}, \quad \frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial T},$$
$$\frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial E}, \quad \frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial Z}.$$

So, we have

$$\begin{aligned}\frac{d\lambda_1}{dt} &= \lambda_1 [c(\beta_1 I_1 + \beta_2 I_2) + \mu + u_1(t) d Z] - \lambda_2 c(\beta_1 I_1 + \beta_2 I_2) - \lambda_5 u_1(t) d Z, \\ \frac{d\lambda_2}{dt} &= c\lambda_1 \beta_1 S - \lambda_2 [c\beta_1 S - (\mu + k_1) + \eta] - \lambda_3 k_1, \\ \frac{d\lambda_3}{dt} &= -w_1 + c\lambda_1 \beta_2 S - \lambda_2 [c\beta_2 S + (\alpha + \eta)] + \lambda_3 \left(\alpha + \mu + \rho + k_2 + \frac{\epsilon u_2(t)}{(1 + \alpha_1 I_2)^2} \right) \\ &\quad - \lambda_4 \left(k_2 + \frac{\epsilon u_2(t)}{(1 + \alpha_1 I_2)^2} \right) - \lambda_6 \frac{a}{(1 + b I_2)^2}, \\ \frac{d\lambda_4}{dt} &= \lambda_4(\mu + \gamma), \\ \frac{d\lambda_5}{dt} &= -\lambda_1 \theta + (\mu + \theta)\lambda_5, \\ \frac{d\lambda_6}{dt} &= \lambda_1 u_1(t) d S - \lambda_5 u_1(t) d S + a_0 \lambda_6,\end{aligned} \tag{12}$$

with transversality conditions $\lambda_i(T_1) = 0$ for $i = 1, 2, \ldots, 6$.

Now from optimality conditions, $\left.\frac{\partial H}{\partial u_1}\right|_{u_1 = u_1^*} = 0$, and $\left.\frac{\partial H}{\partial u_2}\right|_{u_2 = u_2^*} = 0$.

So, $u_1^* = \left[\frac{dS^*Z^*}{4w_2}(\lambda_1 - \lambda_5)\right]^{\frac{1}{3}}$, and $u_2^* = \frac{\epsilon I_2^*}{2w_3(1+\alpha_1 I_2^*)}(\lambda_3 - \lambda_4)$. Now from the above findings along with the characteristics of control set Ω, we have

$$u_1^* = \begin{cases} 0, & \text{if } \left(\frac{dS^*Z^*}{4w_2}(\lambda_1 - \lambda_5)\right)^{\frac{1}{3}} < 0 \\ \left[\frac{dS^*Z^*}{4w_2}(\lambda_1 - \lambda_5)\right]^{\frac{1}{3}}, & \text{if } 0 \le \left(\frac{dS^*Z^*}{4w_2}(\lambda_1 - \lambda_5)\right)^{\frac{1}{3}} \le 1 \\ 1, & \text{if } \left(\frac{dS^*Z^*}{4w_2}(\lambda_1 - \lambda_5)\right)^{\frac{1}{3}} > 1 \end{cases}$$

and

$$u_2^* = \begin{cases} 0, & \text{if } \frac{\epsilon I_2^*}{2w_3(1+\alpha_1 I_2^*)}(\lambda_3 - \lambda_4) < 0 \\ \frac{\epsilon I_2^*}{2w_3(1+\alpha_1 I_2^*)}(\lambda_3 - \lambda_4), & \text{if } 0 \le \frac{\epsilon I_2^*}{2w_3(1+\alpha_1 I_2^*)}(\lambda_3 - \lambda_4) \le 1 \\ 1, & \text{if } \frac{\epsilon I_2^*}{2w_3(1+\alpha_1 I_2^*)}(\lambda_3 - \lambda_4) > 1 \end{cases}$$

which is equivalent as (10). □

A.3. Optimality system

In this part, we state the corresponding optimality system using the optimal control functions u_1^* and u_2^* which are characterized above. The optimality system with minimized Hamiltonian H^* at $(S^*, I_1^*, I_2^*, T^*, E^*, Z^*, \lambda)$ is given as

$$\begin{aligned} \frac{dS^*}{dt} &= \Lambda - c(\beta_1 I_1^* + \beta_2 I_2^*)S^* - \mu S^* + \theta E^* - u_1^* dS^* Z^*, \\ \frac{dI_1^*}{dt} &= c(\beta_1 I_1^* + \beta_2 I_2^*)S^* - (\mu + k_1)I_1^* + \eta(I_1^* + I_2^*) + \alpha I_2^*, \\ \frac{dI_2^*}{dt} &= k_1 I_1^* - (\alpha + \mu + k_2)I_2^* - \rho I_2^* - \frac{\epsilon u_2^*}{1 + \alpha_1 I_2^*} I_2^*, \\ \frac{dT^*}{dt} &= k_2 I_2^* - (\mu + \gamma)T^* + \frac{\epsilon u_2^*}{1 + \alpha_1 I_2^*} I_2^*, \\ \frac{dE^*}{dt} &= u_1^* dS^* Z^* - (\mu + \theta)E^*, \\ \frac{dZ^*}{dt} &= \frac{aI_2^*}{1 + bI_2^*} - a_0 Z^*, \end{aligned} \tag{13}$$

with the initial conditions, $S_0^* > 0$, $I_{1,0}^* > 0$, $I_{2,0}^* > 0$, $T_0^* > 0$, $E_0^* > 0$, and $Z_0^* > 0$. The corresponding adjoint system is

$$\begin{aligned} \frac{d\lambda_1}{dt} &= \lambda_1\left[c(\beta_1 I_1^* + \beta_2 I_2) + \mu + u_1^* dZ^*\right] - \lambda_2 c(\beta_1 I_1^* + \beta_2 I_2^*) - \lambda_5 u_1^* dZ^*, \\ \frac{d\lambda_2}{dt} &= c\lambda_1\beta_1 S^* - \lambda_2\left[c\beta_1 S^* - (\mu + k_1) + \eta\right] - \lambda_3 k_1, \\ \frac{d\lambda_3}{dt} &= -w_1 + c\lambda_1\beta_2 S^* - \lambda_2\left[c\beta_2 S^* + (\alpha + \eta)\right] + \lambda_3\left(\alpha + \mu + \rho + k_2 + \frac{\epsilon u_2^*}{(1 + \alpha_1 I_2^*)^2}\right) \\ &\quad - \lambda_4\left(k_2 + \frac{\epsilon u_2^*(t)}{(1 + \alpha_1 I_2^*)^2}\right) - \lambda_6\frac{a}{(1 + bI_2^*)^2}, \\ \frac{d\lambda_4}{dt} &= \lambda_4(\mu + \gamma), \\ \frac{d\lambda_5}{dt} &= -\lambda_1\theta + (\mu + \theta)\lambda_5, \\ \frac{d\lambda_6}{dt} &= \lambda_1 u_1^* dS^* - \lambda_5 u_1^* dS^* + a_0\lambda_6, \end{aligned} \tag{14}$$

with transversality conditions $\lambda_i(T_1) = 0$ for $i = 1, 2, \ldots, 6$ and u_1^* and u_2^* are same as (10).

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