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MODELLING THE IMPACT OF DIFFERENT HEALTH CARE SYSTEMS AND DROPOUTS ON THE INFECTION DYNAMICS OF HIV/AIDS

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Abstract. Side effects from antiretroviral drugs (ARVs) over time, present a major challenge to individuals on treatment and is a major cause of dropouts from treatment programs. The provision of treatment for infected individuals varies depending on their levels of affordability in many developing countries. In this paper, we formulate a mathematical model to determine the impact of dropouts on the dynamics of HIV/AIDS which depends on different health care systems. We categorize the health care systems into two, private and public with the dropout rates being dependent on the health care system. The model's steady states are determined and their stabilities presented in terms of the reproduction number $\mathfrak{R}_o$. Numerical simulations are carried out and results suggest that the management of dropouts is significant to the dynamics and management of HIV/AIDS. The role of essential parameters is also investigated through sensitivity analysis that employs the Latin Hypercube Sampling technique. The results have implications to the management and policy designs with regards to health care systems, dropouts and disease progression.

Keywords: HIV/AIDS; side effects; dropouts; global stability; sensitivity analysis; simulations.

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1. INTRODUCTION

The world is faced with a diverse number of health problems in which the human immunodeficiency syndrome (HIV/AIDS) is one of the leading global health problems [3, 5]. The rate at which HIV infection has been spreading and the mortality due to the disease over the years have led to significant medical and scientific research [3]. According to the global HIV statistics, 76.1 million [$65.2-88.0$ million] people have become infected with HIV and 35.0 million [$28.9-41.5$ million] people have died from AIDS-related illnesses since the start of the epidemic. As at 2018, 37.9 million [32.7 million–44.0 million] people globally were living with HIV, 1.7 million [1.4 million–2.3 million] people became newly infected with HIV and 770 000 [570 000–1.1 million] people died from AIDS-related illnesses [1]. National Institute of Allergy and Infectious Diseases (NIAID) has helped in fostering and promoting the development of highly active antiretroviral therapy (HAART) that has led HIV infection from being fatal to a chronic condition that can be managed [8, 9]. As a result of HAART, an HIV infected person can live a near-normal lifespan if they start the antiretroviral treatment early regardless of the CD4 count [7, 12]. The use of antiretroviral treatment will slow down the progression of HIV to AIDS [10, 11, 13]. Globally, 20.9 million people are on antiretroviral therapy as of 2017 and AIDS related deaths have fallen by 48% since the peak in 2005 [1].

Health care systems can be categorized into two, in many of the developing nations; private and public health care systems. Private health care is provided by institutions other than the government in order to meet the health needs of the people that can afford it, while public health care system is provided or funded entirely by the government [38]. Public health care, apart from the fact that the services rendered to people are free (or almost free) in most countries, it has some disadvantages. People who go for public health care often experience long waiting periods before they are attended to, the facilities are sometimes old and poorly managed, the quality of care is poor and there is poor disease control and prevention [37]. Private health care, on the other hand, can largely transform these negative experiences by providing better facilities and extended care [37]. Therefore, the majority of people who can afford prefer to turn to private health care because of its accessibility, availability, and convenience of services[39, 40]. Care is essential to individuals living with HIV/AIDS, but when the care is limited, it can contribute

to dropouts from the treatment. As a result, private health care has less of dropouts when compared to public health care.

Zimbabwe has been grossly affected by HIV over the years, with the first reported HIV infection case in 1985 [22]. In 2012, the Zimbabwe Demographic and Health Survey (ZDHS) had a national estimate of HIV prevalence at 15% [21]. Despite the fact that HIV/AIDS is a severe epidemic, prevalence has begun to show signs of decline in Zimbabwe, albeit the country is still ranked among the top 10 HIV-infected countries in the world [34].

The importance of staying on the ARV treatment has been highlighted by many researchers, see for instance [14, 18]. Despite the advocacy and media campaigns on the need to stay on treatment once started, patient dropouts are still being recorded especially in resource constrained communities. Schilkowsky et al [15] investigated factors associated with HIV/AIDS treatment with dropouts.They considered two models in which health care dropouts was consistently associated with being unemployed or having an unstable job, using illicit drugs and having psychiatric background and having used multiple antiretroviral regimens. Su et al cite16 also considered dropouts in their model as a result of loss of treatment follow-up from the health care system. Chikomo [17] considered dropouts as a result of death and loss of follow-up from the health care system for Warren Park Poly Clinic in Harare, Zimbabwe. In this paper, the model is extended by including a class of those that drop out of treatment and inclusion of different health care systems.

We consider side effects of antiretroviral drugs as the driving force behind dropouts. Side effects to ARV drugs can arise as a result of taking drugs for a longer period of time, other medications interacting with HIV drugs and non-adherence to an ARV treatment plans [42, 43]. Therefore, we assume that dropouts from private and public health care systems respectively are influenced by the side effects of the antiretroviral drugs. In this work, we develop a deterministic mathematical model that describes the dynamics of HIV/AIDS with the aim of investigating the impact of different health care systems and dropouts on the dynamics of HIV/AIDS, in which side effects of ARV drugs is assumed as the propelling force that causes the dropouts.

This work is arranged as follows: In the next section, the model is formulated. In section 3,

the basic properties are detailed and in section 4, the model equilibria and their global stability are respectively investigated. In section 5, the numerical simulations are carried out. The paper ends with some discussions and conclusions in section 6.

2. MODEL FORMULATION

Following many of the compartmental model formulations, we partitioned the entire population into seven classes or compartments. The susceptibles, $S(t)$ which are those at risk of getting infected at any time t; the infectives, $I(t)$ are those infected with the HIV virus; $T_1(t)$ represents, those on antiretroviral therapy in a private health care system; $T_2(t)$ represents, those on antiretroviral therapy but in a public health care system; $D_1(t)$, the dropout from antiretroviral therapy in the private health care system; $D_2(t)$, dropout from antiretroviral therapy in the public health care system; and $A(t)$, those with full blown AIDS, whom we assume, once they are in that class the health care system to which they came from is immaterial. Thus, at any time $t \geq 0$, the total population size is given by

$$N(t) = S(t) + I(t) + T_1(t) + T_2(t) + D_1(t) + D_2(t) + A(t). \tag{1}$$

Susceptible individuals $S(t)$ are recruited at a rate π, through births and immigration. Individuals in all classes die naturally at a rate μ. Susceptible individuals acquire HIV infection at a rate λ, referred to as the force of infection, such that

$$\lambda = \frac{\beta(I(t) + \eta_1 T_1(t) + \eta_2 T_2(t) + \eta_3 D_1(t) + \eta_4 D_2(t) + \eta_5 A(t))}{N}, \tag{2}$$

where η_i, $i = 1,2,3,4,5$, are modification parameters to infectivity of all the other classes relative to I. The parameter β is the effective contact rate i.e the contact that results in infection per unit time. We shall assume that $\eta_1, \eta_2 \in (0,1]$ due to the effect of treatment in reducing the spread of HIV while $\eta_3, \eta_4, \eta_5 = 1$ due to increased viral loads as a result of dropping out from treatment programs and development of AIDS. The rate at which infected individuals are absorbed into treatment is γ with a proportion ρ moving into private health care and the remainder move into public health care. Those that are not screened for the disease will eventually progress to the AIDS class at a rate α_1. Individuals in both treatment classes can drop out of treatment as a result of side effects of the drugs or non compliance.

Functional responses have been used to model human behavior, see for instance [23, 35]. One functional response proposed by Njagarah [23] has been used to model person-to-person contact in cholera transmission. Here we propose to use a similar functional response $f(\xi)$ that denotes the side effects of ARV drugs. It is plausible to believe that the dropout rate will increase with increased levels of side effects. We assume that individuals that drop out, return to treatment in their respective categories in relation to the health care system they can afford. We also assume that individuals do not change their health care systems. We argue that individuals access the type of health care, especially HIV treatment, depending on their level of affordability. In this model, we propose a dropout function that is dependent on the side effects of antiretroviral drugs. We suggest a function of the form

$$f(\xi_i) = \frac{\omega_0 + \omega_{max}\xi_i^q}{k + \xi_i^q}, \tag{3}$$

where q is the shape parameter and $q > 1$ for the dropout rate to be sigmoidal, k is the half saturated constant, ω_0 is the minimum dropout rate, ω_{max} is the maximum dropout rate, ξ_i, $i = 1,2$ denotes the side effects level of the antiretroviral drugs, with $f(\xi_1) < f(\xi_2)$. A typical example of curve that depicts the change in the dropout rate is shown in Figure 1.

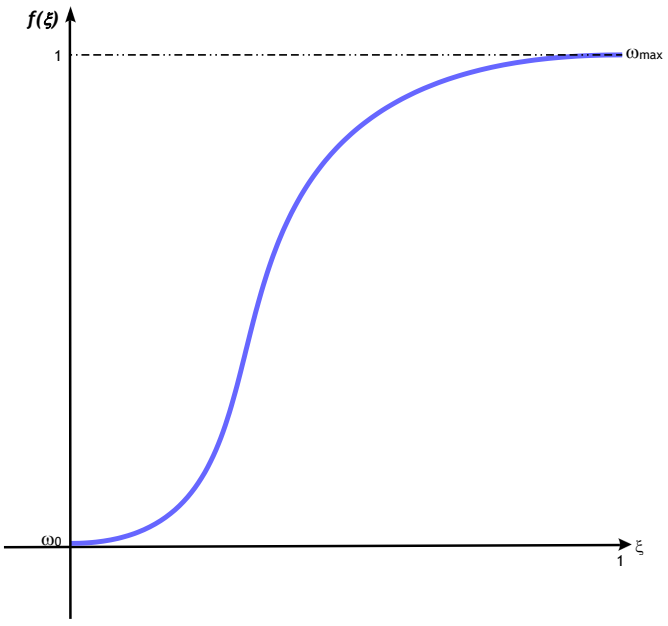

FIGURE 1. Dropout rate as a function of side effects level for people on antiretroviral drugs.

The drop out rates are modelled by the function (3). We allow the drop outs to re-enter treatment programs at rates θ_1 and θ_2 for the private and public health care systems respectively although at different rates. Individuals under treatment in the private and public health care systems eventually develop AIDS at rates α_2 and α_3 respectively. Those who drop out will also develop AIDS at rates α_4 and α_5 for the private and public health care systems respectively. We assume a disease related mortality δ for those in the AIDS class.

The model description presented is visualized by the model diagram in Figure 2. The model

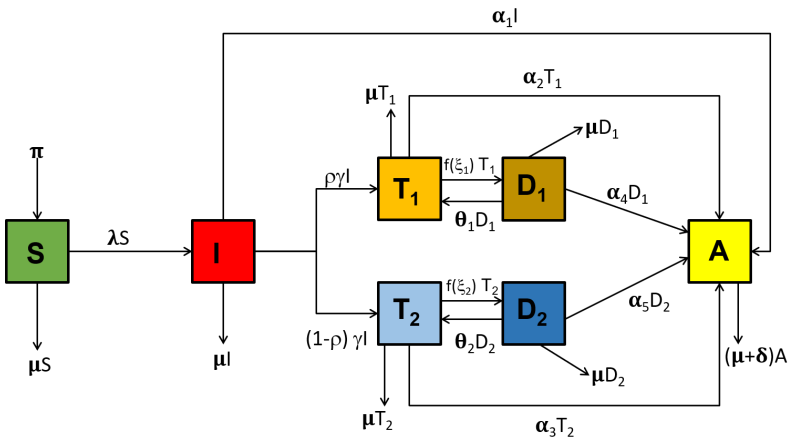

FIGURE 2. The flow diagram showing the HIV/AIDS infection dynamics

can be described by the following set of nonlinear ordinary differential equations (4)

$$
\left.
\begin{aligned}
\frac{dS}{dt} &= \pi - (\lambda + \mu)S, \\
\frac{dI}{dt} &= \lambda S - (\mu + \alpha_1 + \gamma)I, \\
\frac{dT_1}{dt} &= \gamma\rho I - (\mu + \alpha_2 + f(\xi_1))T_1 + \theta_1 D_1, \\
\frac{dT_2}{dt} &= \gamma(1-\rho)I - (\mu + \alpha_3 + f(\xi_2))T_2 + \theta_2 D_2, \\
\frac{dD_1}{dt} &= f(\xi_1)T_1 - (\mu + \theta_1 + \alpha_4)D_1, \\
\frac{dD_2}{dt} &= f(\xi_2)T_2 - (\mu + \theta_2 + \alpha_5)D_2, \\
\frac{dA}{dt} &= \alpha_1 I + \alpha_2 T_1 + \alpha_3 T_2 + \alpha_4 D_1 + \alpha_5 D_2 - (\mu + \delta)A,
\end{aligned}
\right\} \tag{4}
$$

with initial conditions $S(0) = S_0$, $I(0) = I_0$, $T_1(0) = T_{1(0)}$, $T_2(0) = T_{2(0)}$, $D_1(0) = D_{1(0)}$, $D_2(0) = D_{2(0)}$, $A(0) = A_0$, where we assume that all the model parameters are positive.

3. BASIC PROPERTIES

3.1. Positivity of solutions. It is important to show that the solutions of system (4) remain positive for any given non negative initial conditions for all $t \in [0,\infty)$.

Theorem 3.1. *Given that the initial conditions of the model system* (4) *are* $S(0) > 0, I(0) > 0, T_1(0) > 0, T_2(0) > 0, D_1(0) > 0, D_2(0) > 0, A(0) > 0$. *The resulting solutions are all non-negative for all* $t \in [0,\infty)$.

Proof. It follows from the first equation of the model system (4) that

$$\frac{dS}{dt} = \pi - (\lambda + \mu)S \geq -(\lambda + \mu)S.$$

Therefore

$$\frac{dS}{dt} \geq -(\lambda + \mu)S. \tag{5}$$

Integrating both sides of equation (5) gives

$$S(t) \geq S(0) \exp\left[\int_0^t -(\lambda + \mu)dt\right] > 0.$$

Hence $S(t)$ is always positive for $S(0) > 0$.

Similarly, from the second equation of the model system (4), we obtain

$$\frac{dI}{dt} = \lambda S - (\alpha_1 + \mu + \gamma)I \geq -(\alpha_1 + \mu + \gamma)I,$$

whose solution is given by

$$I(t) \geq I(0)e^{-(\alpha_1+\mu+\gamma)} > 0.$$

Similarly, it can be shown that the state variables $T_1(0) > 0, T_2(0) > 0$,
$D_1(0) > 0, D_2(0) > 0, A(0) > 0$, for all $t > 0$ respectively.
This completes the proof. □

3.2. Invariant region.

Theorem 3.2. *The set* $\Omega = \left\{(S,I,T_1,T_2,D_1,D_2,A) \in \mathbb{R}^7_+ | 0 \leq N \leq \frac{\pi}{\mu}\right\}$ *is positively invariant as a globally attractive set of model* (4).

Proof. The rate of change of the total population given by

$$\frac{dN}{dt} = \pi - \mu N - \delta A \leq \pi - \mu N. \tag{6}$$

Solving equation (6) gives

$$N(t) \leq \frac{\pi}{\mu} + \left(N(0) - \frac{\pi}{\mu}\right) e^{-\mu t}. \tag{7}$$

It is important to note that if $N(0) < \frac{\pi}{\mu}$ then $N(t) \leq \frac{\pi}{\mu}$. This implies that the set Ω is a positively invariant set for model (4). On the other hand, if $N(0) > \frac{\pi}{\mu}$ then $\lim_{t\to\infty} N(t) = \frac{\pi}{\mu}$. So the set Ω is a globally attractive set for the model (4). □

4. Model analysis

4.1. Model equilibria. In this section we consider the model equilibria found by setting the right hand side of model system (4) to zero so that

$$\pi - (\lambda^* + \mu)S^* = 0, \tag{8}$$

$$\lambda^* S^* - (\alpha_1 + \mu + \gamma)I^* = 0, \tag{9}$$

$$\gamma\rho I^* - (\mu + \alpha_2 + f(\xi_1))T_1^* + \theta_1 D_1^* = 0, \tag{10}$$

$$\gamma(1-\rho)I^* - (\mu + \alpha_3 + f(\xi_2))T_2^* + \theta_2 D_2^* = 0, \tag{11}$$

$$f(\xi_1)T_1^* - (\theta_1 + \mu + \alpha_4)D_1^* = 0, \tag{12}$$

$$f(\xi_2)T_2^* - (\theta_2 + \mu + \alpha_5)D_2^* = 0, \tag{13}$$

$$\alpha_1 I^* + \alpha_2 T_1^* + \alpha_3 T_2^* + \alpha_4 D_1^* + \alpha_5 D_2^* - (\mu + \delta)A^* = 0. \tag{14}$$

From equation (12) we have

$$D_1^* = \frac{f(\xi_1)T_1^*}{(\mu + \theta_1 + \alpha_4)} = \psi_1 T_1^*, \text{ where } \psi_1 = \frac{f(\xi_1)}{(\mu + \theta_1 + \alpha_4)}. \tag{15}$$

Equation (13) gives

$$D_2^* = \frac{f(\xi_2)T_2^*}{(\mu + \theta_2 + \alpha_5)} = \psi_2 T_2^*, \text{ where } \psi_2 = \frac{f(\xi_2)}{(\mu + \theta_2 + \alpha_5)}. \tag{16}$$

Substituting equation (15) into (10) we have

$$T_1^* = \frac{\gamma\rho I^*}{(\mu + \alpha_2 + f(\xi_1) - \theta_1\psi_1)} = \psi_3 I^*, \tag{17}$$

with

$$\psi_3 = \frac{\gamma\rho}{(\mu + \alpha_2 + f(\xi_1))(1 - \phi_1)}, \quad \text{where} \quad \phi_1 = \frac{\theta_1 f(\xi_1)}{(\mu + \theta_1 + \alpha_4)(\mu + \alpha_2 + f(\xi_1))}.$$

Substituting equation (16) into (11) we have

$$T_2^* = \frac{\gamma(1-\rho))I^*}{(\mu + \alpha_3 + f(\xi_2) - \theta_2\psi_2)} = \psi_4 I^*, \tag{18}$$

with

$$\psi_4 = \frac{\gamma(1-\rho}{(\mu + \alpha_3 + f(\xi_2))(1 - \phi_2)}, \quad \text{where,} \quad \phi_2 = \frac{\theta_2 f(\xi_2)}{(\mu + \theta_2 + \alpha_5)(\mu + \alpha_3 + f(\xi_2))}.$$

Substituting equation (17) into (15) we have

$$D_1^* = \psi_1\psi_3 I^* = \psi_5 I^*, \tag{19}$$

where

$$\psi_5 = \frac{f(\xi_1)\gamma\rho}{(\mu + \theta_1 + \alpha_4)(\mu + \alpha_2 + f(\xi_1))(1 - \phi_1)}.$$

Substituting equation (18) into (16) yield

$$D_2^* = \psi_2\psi_4 I^* = \psi_6 I^*, \tag{20}$$

where

$$\psi_6 = \frac{f(\xi_2)\gamma(1-\rho)}{(\mu+\theta_2+\alpha_5)(\mu+\alpha_3+f(\xi_2))(1-\phi_2)}.$$

Substituting equations (17), (18), (19) and (20) into (14) gives

$$A^* = \frac{(\alpha_1+\alpha_2\psi_3+\alpha_3\psi_4+\alpha_4\psi_5+\alpha_5\psi_6)I^*}{(\mu+\delta)} = \psi_7 I^*, \tag{21}$$

where

$$\psi_7 = \frac{(\alpha_1+\alpha_2\psi_3+\alpha_3\psi_4+\alpha_4\psi_5+\alpha_5\psi_6)}{(\mu+\delta)},$$

$$= \frac{1}{(\mu+\delta)}\left[\alpha_1 + \frac{\alpha_2\gamma\rho}{(1-\phi_1)(\mu+\alpha_2+f(\xi_1))} + \frac{\alpha_3\gamma(1-\rho)}{(1-\phi_2)(\mu+\alpha_3+f(\xi_2))} + \right.$$
$$\left. \frac{f(\xi_1)\alpha_4\gamma\rho}{(1-\phi_1)(\mu+\theta_1+\alpha_4)(\mu+\alpha_2+f(\xi_1))} + \frac{f(\xi_2)\alpha_5\gamma(1-\rho)}{(1-\phi_2)(\mu+\theta_2+\alpha_5)(\mu+\alpha_3+f(\xi_2))}\right].$$

Substituting equations (17), (18), (19), (20) and (21) into (2) we have

$$\lambda^* = \frac{\beta I^*(1+\eta_1\psi_3+\eta_2\psi_4+\eta_3\psi_5+\eta_4\psi_6+\eta_5\psi_7)}{N^*} = \frac{\psi_8 I^*}{N^*}, \tag{22}$$

where

$$\psi_8 = \beta(1+\eta_1\psi_3+\eta_2\psi_4+\eta_3\psi_5+\eta_4\psi_6+\eta_5\psi_7).$$

Substituting equation (22) into (9) we have

$$\left[\frac{\psi_8 S^*}{N^*} - (\mu+\gamma+\alpha_1)\right] I^* = 0.$$

We thus have

$$I^* = 0 \qquad \text{or} \qquad \frac{S^*}{N^*} = \frac{(\mu+\gamma+\alpha_1)}{\psi_8} = \frac{1}{\mathfrak{R}_o}. \tag{23}$$

Note that, $\mathfrak{R}_o$ is the model reproduction number. We thus have

$$\mathfrak{R}_o = R_I + R_{T_1} + R_{T_2} + R_{D_1} + R_{D_2} + R_A, \tag{24}$$

where

$$R_I = \frac{\beta}{(\mu+\gamma+\alpha_1)}, \qquad R_{T_1} = \frac{\beta\eta_1\gamma\rho}{(\mu+\alpha_2+f(\xi_1))(1-\phi_1)(\mu+\gamma+\alpha_1)},$$

$$R_{T_2} = \frac{\beta\eta_2\gamma(1-\rho)}{(\mu+\alpha_3+f(\xi_2))(1-\phi_2)(\mu+\gamma+\alpha_1)},$$

$$R_{D_1} = \frac{\beta\eta_3 f(\xi_1)\gamma\rho}{(\mu+\theta_1+\alpha_4)(1-\phi_1)(\mu+\gamma+\alpha_1)(\mu+\alpha_2+f(\xi_1))},$$

$$R_{D_2} = \frac{\beta\eta_4 f(\xi_2)\gamma(1-\rho)}{(\mu+\theta_2+\alpha_5)(1-\phi_2)(\mu+\gamma+\alpha_1)(\mu+\alpha_3+f(\xi_2))}, \qquad R_A = \frac{1}{(\mu+\delta)}$$
$$\left[\frac{\beta\alpha_1\eta_5}{(\mu+\gamma+\alpha_1)} + \frac{\beta f(\xi_1)\alpha_4\gamma\rho\eta_5}{(1-\phi_1)(\mu+\gamma+\alpha_1)(\mu+\alpha_2+f(\xi_1))(\mu+\theta_1+\alpha_4)} + \right.$$
$$\frac{\beta\alpha_3\gamma(1-\rho)\eta_5}{(1-\phi_2)(\mu+\gamma+\alpha_1)(\mu+\alpha_3+f(\xi_2))} + \frac{\beta\alpha_2\gamma\rho\eta_5}{(1-\phi_1)(\mu+\gamma+\alpha_1)(\mu+\alpha_2+f(\xi_1))}$$
$$\left. + \left(\frac{\beta f(\xi_2)\gamma(1-\rho)\eta_5}{(1-\phi_2)(\mu+\gamma+\alpha_1)(\mu+\alpha_3+f(\xi_2))}\right) \times \left(\frac{\alpha_5}{(\mu+\theta_2+\alpha_5)}\right)\right].$$

The basic reproductive number $\Re_o$ generated in equation (24) can be define as the average number of secondary infections caused by an infectious individual during the period of infection[24]. In epidemiology modelling the purpose of basic reproduction number is to give conditions necessary for the eradication and elimination of the disease [33]. The method proposed in [24], [25] can also be use to derive $\Re_o$.

If $I^* = 0$ then from (8) we have $S^* = \frac{\pi}{\mu}$. A back substitution of $I^* = 0$ into (17), (18), (19), (20) and (21) results in the disease free equilibrium

$$E_0 = \left(\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0\right).$$

Substituting equations (17), (18), (19) and (20) into (1) we have;

$$N = S^* + (1+\psi_3+\psi_4+\psi_5+\psi_6)I^* = S^* + \psi_9 I^*, \tag{25}$$

where

$$\psi_9 = (1 + \psi_3 + \psi_4 + \psi_5 + \psi_6).$$

Substituting equation (25) into (23) we have

$$\frac{S^*}{S^* + \psi_9 I^*} = \frac{1}{\mathfrak{R}_o} \Rightarrow I^* = \frac{S^*(\mathfrak{R}_o - 1)}{\psi_9}. \tag{26}$$

Substituting Eqs. (22), (25) and (26) into (8) we obtain

$$S^* = \frac{\pi \mathfrak{R}_o \psi_9}{(\mathfrak{R}_o - 1)\psi_8 + \mu \mathfrak{R}_o \psi_9}, \qquad I^* = \frac{\pi(\mathfrak{R}_o - 1)\mathfrak{R}_o}{(\mathfrak{R}_o - 1)\psi_8 + \mu \mathfrak{R}_o \psi_9}$$

Substituting I^* into (17), (18), (19), (20) and (21) we have the following

$$T_1^* = \frac{\psi_3 \pi(\mathfrak{R}_o - 1)\mathfrak{R}_o}{(\mathfrak{R}_o - 1)\psi_8 + \mu \mathfrak{R}_o \psi_9}, \qquad T_2^* = \frac{\psi_4 \pi(\mathfrak{R}_o - 1)\mathfrak{R}_o}{(\mathfrak{R}_o - 1)\psi_8 + \mu \mathfrak{R}_o \psi_9},$$
$$D_1^* = \frac{\psi_5 \pi(\mathfrak{R}_o - 1)\mathfrak{R}_o}{(\mathfrak{R}_o - 1)\psi_8 + \mu \mathfrak{R}_o \psi_9}, \qquad D_2^* = \frac{\psi_6 \pi(\mathfrak{R}_o - 1)\mathfrak{R}_o}{(\mathfrak{R}_o - 1)\psi_8 + \mu \mathfrak{R}_o \psi_9},$$
$$A^* = \frac{\psi_7 \pi(\mathfrak{R}_o - 1)\mathfrak{R}_o}{(\mathfrak{R}_o - 1)\psi_8 + \mu \mathfrak{R}_o \psi_9}.$$

The expressions $(S^*, I^*, T_1^*, T_2^*, D_1^*, D_2^*, A^*)$ give the endemic equilibrium E_1. Note that if $\mathfrak{R}_o = 1$, the endemic equilibrium collapses to the disease free equilibrium. We thus have the following theorem on the existence of the endemic equilibrium.

Theorem 4.1. *If $\mathfrak{R}_o \leq 1$, model* (4) *always has a disease free equilibrium E_0. If $\mathfrak{R}_o > 1$ the model has a unique endemic equilibrium E_1.*

4.2. Global stability of the equilibria. In this section we prove the global stability of our equilibria E_0 and E_1.

4.2.1. *Global stability of the disease free equilibrium.*

Theorem 4.2. *The disease free equilibrium of the model system* (4) *is globally asymptotically stable in Ω if $\mathfrak{R}_o < 1$ and unstable otherwise.*

The proof of the theorem is given in A.

4.2.2. *Global stability of the endemic equilibrium.* To prove the global stability of the endemic equilibrium, we make an assumption that the population does not change over the modelling time. That is,
$\pi = \mu N + \delta A$ holds. This assumption is made for mathematical tractability and may not be reflective of what would happen in reality especially in developing countries.

Theorem 4.3. *The endemic equilibrium of the model system* (4) *is globally asymptotically stable in* Ω *if* $\pi = \mu N + \delta A$ *and* $\mathfrak{R}_o > 1$.

The proof of the theorem is given in B.

5. NUMERICAL SIMULATIONS

In this section, to illustrate the dynamic behavior of model system (4), simulations are carried out in Matlab by using the range of parameters in Table 1 which are also used for the data fitting. We determine the population of dropouts from treatment when the reproduction number $\mathfrak{R}_o$ is greater than one and when it is less than one. A few parameters are known. The unknown parameters are therefore estimated. Therefore, it is important to carefully study the disease dynamics, putting into consideration individual differences, location, social-economic status while selecting parameter values. Our focus is on Zimbabwe given that the model will be validated using data from Warren Park in Zimbabwe. The death rate $\mu = 0.016$ was calculated from the life expectancy in Zimbabwe which was taken to be 61.16years [27] given that the model will be validated using data from Zimbabwe. We used the following initial conditions for the classes in model system (4): $S(0) = 59840$, $I(0) = 10$, $T_1(0) = 6$, $T_2(0) = 5$, $D_1(0) = 4$, $D_2(0) = 6$, $A(0) = 0$. The values of the initial conditions were hypothetically chosen based on the HIV prevalence rates in Harare, Zimbabwe [28], considering the population of Warren park in Harare, Zimbabwe [29] and the data collected from Warren park polyclinic in Zimbabwe.

5.1. Application of the model to data from Warren Park in Zimbabwe. In this section, we fit the model system (4) to the data of individuals that dropout from treatments which was recorded from Warren Park from $(2000-2017)$. Warren Park polyclinic in Harare, Zimbabwe, is one of the clinics that treats HIV/AIDS patients. The Ministry of Health in Zimbabwe classified Warren Park as a Level 5 clinic (the highest ranking when it comes to data quality). The

clinic has the Electronic Patient Monitoring System (EPMS) that contains information of all HIV/AIDS-related patients since 2000. For data fitting, parameters that give the best fit were estimated with the use of Least Square method in Matlab, where the other parameters were estimated by assigning upper and lower bounds. The coefficient of determination R^2 (which is used to determine how well the model fits the data) is 0.773, this implies that the model fits the data reasonably well.

From Figure 3, the results show that the total number of people who dropout of treatments each year in Warren Park, has been increasing. This also shows that, each year there is always a record of individuals that are on ARV drugs that drop out of treatment, a clear indication of the consistent data recording. Therefore, strategies must be put in place to make individuals that dropout of treatment return back to treatment. Please note that the data use does not differentiate between private and public health care systems. Therefore, in the model fitting, we added together both the private and public health care systems.

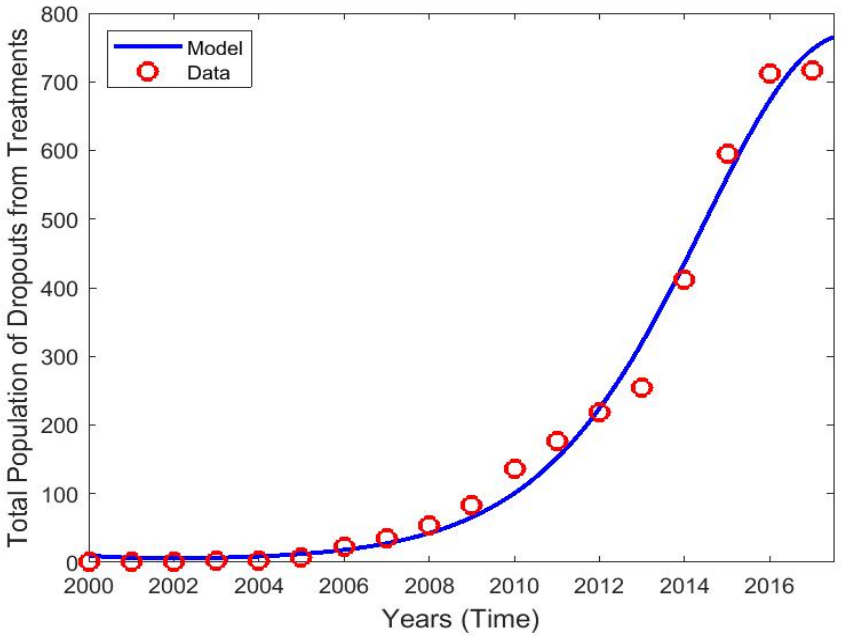

FIGURE 3. Model system (4) fitted to data for individuals that dropout from treatment from $(2000-2017)$. The solid line indicates the model fit to the data and the circles indicate the actual data.

TABLE 1. Range of values used for the parameters and the estimated values that give the best fit. Units are year^{-1} with $R^2 = 0.773$

Parameter	Description	Range	Source
π	Recruitment	(2000 - 2500)	Estimated
μ	Natural mortality rate	0.016	[27]
γ	Rate at which I proceed to T_1 and T_2	(0 - 0.6)	Estimated
ρ	Proportion of γ to T_1 and T_2	(0.1 - 0.73)	Estimated
α_1	Progression rate to AIDS from infected individuals I	(0.05 - 0.2)	Estimated
α_2	Progression rate to AIDS from T_1	(0 - 0.5)	Estimated
α_3	Progression rate to AIDS from T_2	(0.0998 - 0.4)	Estimated
α_4	Progression rate to AIDS from D_1	(0.001 - 0.7)	Estimated
α_5	Progression rate to AIDS from T_2	(0.001 - 0.090)	Estimated
θ_1	Rate at which D_1 move back to T_1	0.02 - 0.099	Estimated
θ_2	Rate at which D_2 move back to T_2	(0.05 - 0.099)	Estimated
$f(\xi_1)$	Rate at which T_1 move to D_1 due to side effect of ART	(0 - 0.06)	Estimated
$f(\xi_2)$	Rate at which T_2 move to D_2 due to side effect of ART	(0 - 0.069)	Estimated
β	Effective transmission rate	(0.1 - 0.8)	Estimated
η_1	Relative infectivity due to T_1 class	(0.1 - 0.5)	Estimated
η_2	Relative infectivity due to T_2 class	(0.15 - 0.7)	Estimated
η_3	Relative infectivity due to D_1 class	(1 - 1.05)	Estimated
η_4	Relative infectivity due to D_2 class	(1 - 1.08)	Estimated
η_5	Relative infectivity due to AIDS class	(1 - 1.10)	Estimated
δ	Disease induced death rate	(0.001 - 0. 07)	Estimated

5.2. Time series plot of the classes in model system (4)**.** In Figure 4, it can be observed that model system (4) approaches a stable disease free state when reproduction number $\mathfrak{R}_o = 0.0496$. The time series plots for the infected and dropouts reduce to zero asymptotically. The same trends are depicted for the treatments and AIDS compartments. Also, Figure 4 shows that the model system (4) is at a stable endemic state when the reproduction number $\mathfrak{R}_o = 5.1739$. The infected and dropouts compartments increases due to the fact that the disease persist in the population.

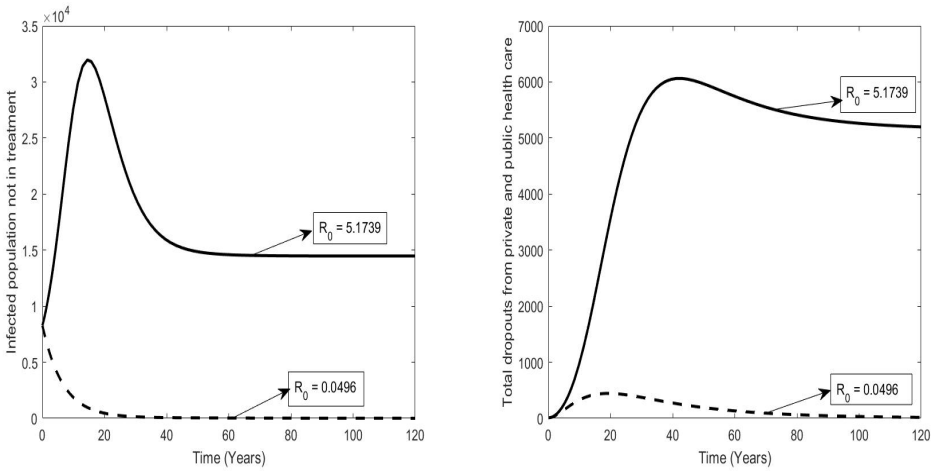

FIGURE 4. The result of simulations of the dynamics of model system (4) for the estimated parameter values $\pi = 2413, \mu = 0.016, \gamma = 0.1501, \rho = 045, \alpha_1 = 0.0412, \alpha_2 = 0.0114, \alpha_3 = 0.0319, \alpha_4 = 0.0521, \alpha_5 = 0.068, \theta_1 = 0.076, \theta_2 = 0.071, \rho = 0.45, \delta = 0.043, f(\xi_1) = 0.021, f(\xi_2) = 0.034, \eta_1 = 0.257, \eta_2 = 0.345, \eta_3 = 1.016, \eta_4 = 1.03, \eta_5 = 1.04$. When $\beta = 0.313, \mathfrak{R}_o = 5.1739$ and when $\beta = 0.003, \mathfrak{R}_o = 0.0496$. The value of $\mathfrak{R}_o > 1$ describes an endemic state and $\mathfrak{R}_o < 1$ describes a disease free state.

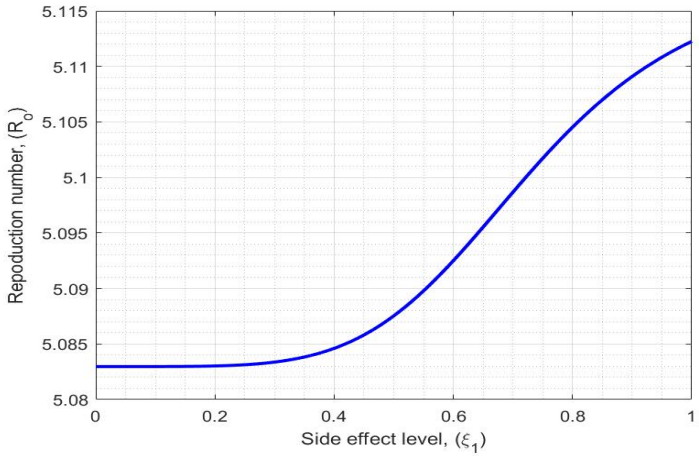

FIGURE 5. $\mathfrak{R}_o$ as a function of side effect level of people on ARV drugs in the private health care system. The rest of the parameter values are: $\omega_{max} = 0.7$, $\omega_0 = 0.1$, $k = 0.1, q = 0.6$, $\pi = 2412, \mu = 0.016, \gamma = 0.098, \rho = 0.45, \alpha_1 = 0.0412, \alpha_2 = 0.0214, \alpha_3 = 0.0312, \alpha_4 = 0.0521, \alpha_5 = 0.052, \theta_1 = 0.076, \theta_2 = 0.071, \rho = 0.45, \delta = 0.043, f(\xi_1) = 0.021, \eta_1 = 0.257, \eta_2 = 0.345, \eta_3 = 1.016, \eta_4 = 1.03, \eta_5 = 1.04, \beta = 0.313$.

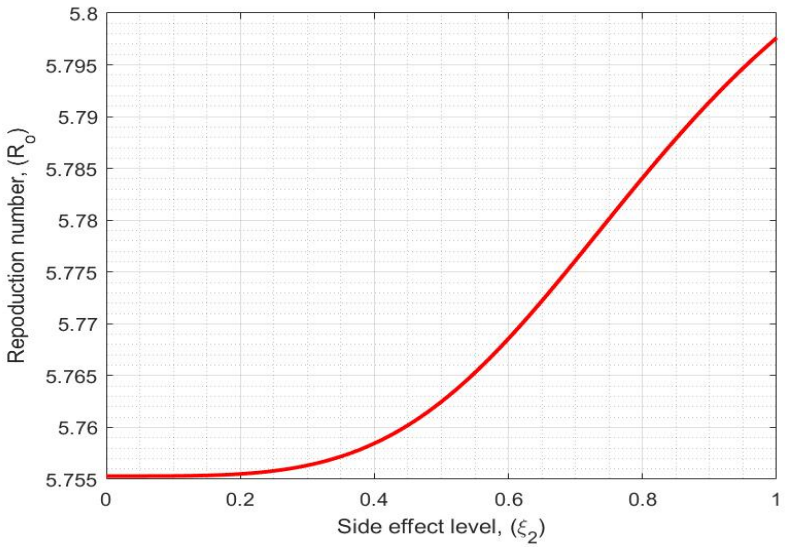

FIGURE 6. $\mathfrak{R}_o$ as a function of side effect level of people on ARV drugs in the public health care system. The rest of the parameter values are: $\omega_{max} = 0.9$, $\omega_0 = 0.2$, $k = 0.1, q = 0.6$, $\pi = 2412, \mu = 0.016, \gamma = 0.098, \rho = 0.45, \alpha_1 = 0.0412, \alpha_2 = 0.0214, \alpha_3 = 0.0312, \alpha_4 = 0.0521, \alpha_5 = 0.052, \theta_1 = 0.076, \theta_2 = 0.071, \rho = 0.45, \delta = 0.043, f(\xi_1) = 0.021, \eta_1 = 0.257, \eta_2 = 0.345, \eta_3 = 1.016, \eta_4 = 1.03, \eta_5 = 1.04, \beta = 0.313$.

Figures 5 and 6 are obtained by replacing the estimated values of $f(\xi_1)$ and $f(\xi_2)$ respectively with the functional response $f(\xi_i)$ in the expression in (3) for variables ξ_1 and ξ_2. In Figure 5 it is observed that there is an inverse relationship between $\mathfrak{R}_o$ and ξ_1, this shows that as the side effect level of people on antitroviral drugs increases, the reproductive number increases. Also, Figure 6 shows an inverse relationship between $\mathfrak{R}_o$ and ξ_2. Therefore, it is important to reduce the toxicity of ARV drugs so as to reduce it's side effects on infected individuals on antiretroviral treatment. This will in turn help in fighting the AIDS epidemic.

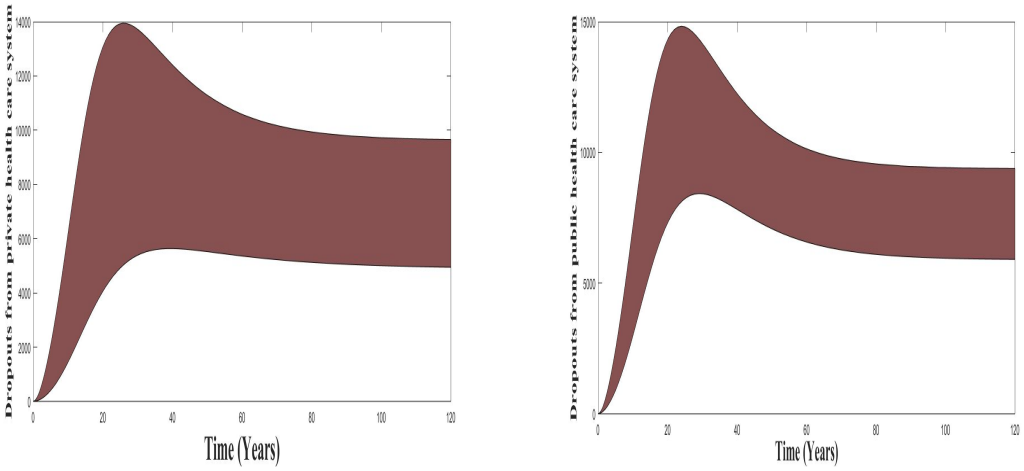

FIGURE 7. Potential number of dropouts over time, which is the population that dropout from private and public health care systems respectively with $\omega_{max} = 0.5$ and $\omega_0 = 0.01$.

In Figure 7, the impact of the dropout rate parameters $f(\xi_1)$ and $f(\xi_2)$ due to side effects of the antiretroviral drugs on the infected population under treatment was investigated. It was paramount to know how side effects affect the dropouts in order to design interventions on how to reduce them. The shaded area in Figure 7 represents the potential number of dropouts over time. As side effect increases, the number of dropouts from treatment classes increases significantly. In such a scenario, we are able to see the impact of side effects on the number of dropouts.

5.3. Sensitivity analysis. Sensitivity analysis is the study of how the changes in parameters or variation in parameter inputs in a model system can lead to response in the output [30]. We use sensitivity analysis to show which parameter has a great effect on the reproduction number $\mathfrak{R}_o$ either with a positive or negative correlation [2]. Sensitivity analysis also enables us to know important parameters that are capable of altering the value of the output or that can cause a change in the structure of the model [31]. We use the Latin Hypercube Sampling (LHS) method. In this work, we estimated the effect of variation of parameters to the sensitivity of the reproduction number $\mathfrak{R}_o$ using Matlab. This enabled us to determine the impact of each parameters in model system (4) on a chosen outcome variable.

h!]

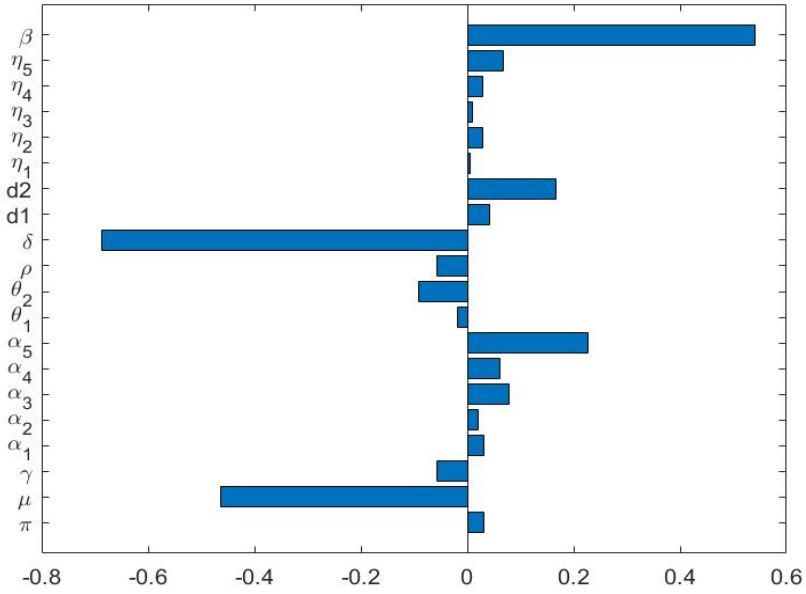

FIGURE 8. The Latin Hypercube Sampling-Partial Rank Correlation Coefficients (LHS/PRCCs) for the range of parameters from. Note d1 and d2 represent $f(\xi_1)$ and $f(\xi_2)$ respectively.

The estimated range of parameters used for the simulations are found in Table 1. Parameters with positive sensitivity indices imply that there will be increase in the reproduction number $\mathfrak{R}_o$ whenever they are increased (positive correlation) while parameters with negative sensitivity indices imply the opposite.

From Figure 8, it shows that positive correlation exists between $\mathfrak{R}_o$ and $f(\xi_1)$, also positive correlation exists between $\mathfrak{R}_o$ and $f(\xi_2)$. It indicates that side effects of antiretroviral drugs play an important role in increasing the epidemic and hence adequate measures must be put in place to reduce the side effects of the ARV drugs so to reduce the rate of dropout from treatment.

Also from Figure 8, it can be seen that negative correlation exist between $\mathfrak{R}_o$ and γ, θ_1, θ_2. This implies that treatment intervention that has been put in place should be sustained and drop outs should be traced and encouraged to move back to treatment programs for the control of the epidemics.

5.4. Effects of varying θ_1, θ_2, $f(\xi_1)$, $f(\xi_2)$ on the dynamics of the dropout compartments. In order to determine the effects of θ_1, θ_2, $f(\xi_1)$, $f(\xi_2)$ on the dynamics of the dropouts of the model system (4) we varied the parameters and explored how the time series plot change as the parameters change. The results of the simulations are shown in Figs. 9 and 10.

Figure 9 shows that as θ_1 and θ_2 increases, the population of D_1 and D_2 decreases respectively. This implies that when the rate at which people move back into treatment after dropout increases, then the reproduction number $\mathfrak{R}_o$ decreases. So it is very expedient that individuals that dropout from treatment be encouraged to move back to treatment so as to control the disease escalation.

Figure 10 shows that increasing $f(\xi_1)$ and $f(\xi_2)$ increases the number of D_1 and D_2 individuals. This imply that when side effects to ARV drugs increases, individuals that dropout of treatment increases which also in turn makes the reproduction number $\mathfrak{R}_o$ to increase. As a result adequate efforts must be put in place for individuals on ART to adhere to treatment in order to reduce side effects. Also tips on managing side effects should be emphasized in order to avoid people from dropping out of treatment.

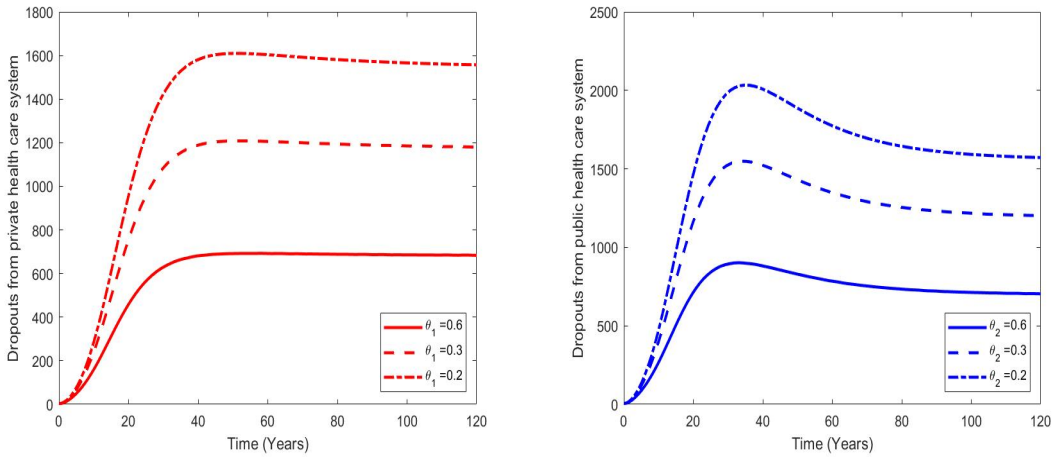

FIGURE 9. Variation of the model system (4) time series plots when θ_1 and θ_2 are varied as shown.

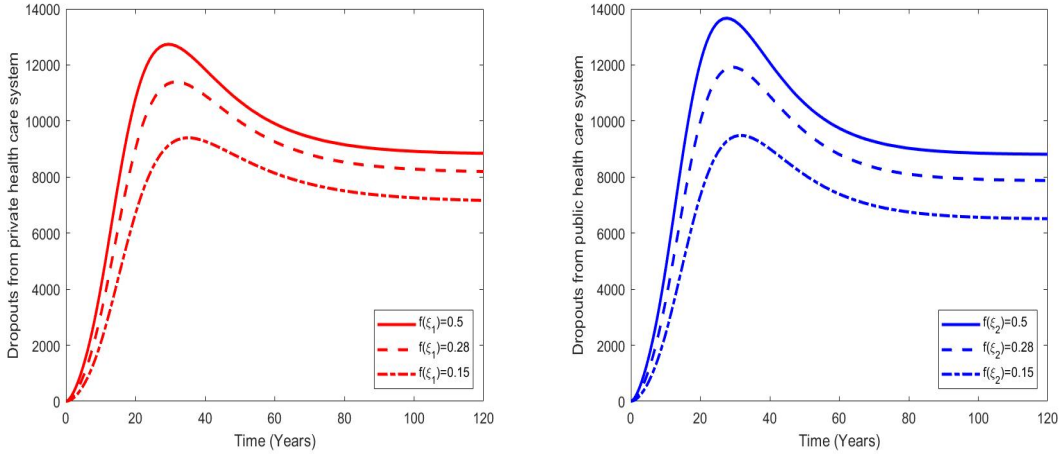

FIGURE 10. Variation of the model system (4) time series plots when $f(\xi_1)$ and $f(\xi_2)$ are varied.

Contour plots in Figure 11 are used to ascertain the relationship between some selected pairs of parameters and $\mathfrak{R}_o$. Figure 11 shows that when both θ_1 and θ_2 (rate at which individuals that dropout of treatment return back to treatment) are increased, they decrease the reproduction number $\mathfrak{R}_o$. Biologically, moving back to treatment after dropout has a positive impact on the reproduction number $\mathfrak{R}_o$. However, from Figure 11 when both $f(\xi_1)$ and $f(\xi_2)$ (side effects to ART) are increased, the reproduction number increases. Also, we can notice that the reproduction number $\mathfrak{R}_o$ increases significantly as side effects increases. Therefore, we can conclude that the rate at which individuals dropout from treatment is a major concern for the health policy makers. Thus, adequate public health measures such as sensitizing individuals on ART and managing side effects should be escalated in order to control people from dropping out of treatment, so as to control HIV/AIDS. We note from Figure 12 that as γ increases the reproduction number decreases. This is an indication that a lot of efforts must be made so as to increase compliance to treatment which is already in place and to enroll more people living with HIV/AIDS into treatment and also to encourage individuals not to drop out from treatment in Warren park, Zimbabwe in order to reduce the burden of the disease.

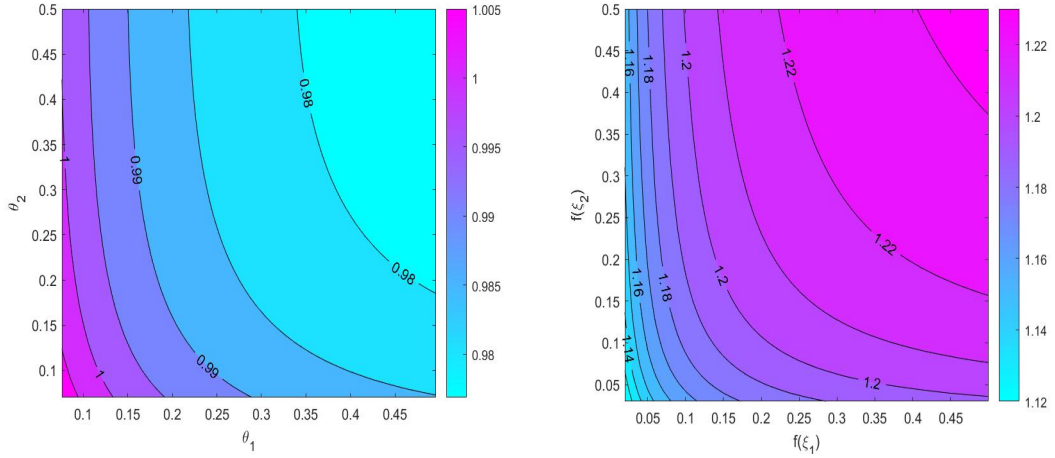

FIGURE 11. Contour plots of $\mathfrak{R}_o$ as a function of θ_1, θ_2 and $f(\xi_1), f(\xi_2)$ using the parameter values shown in Figure 4.

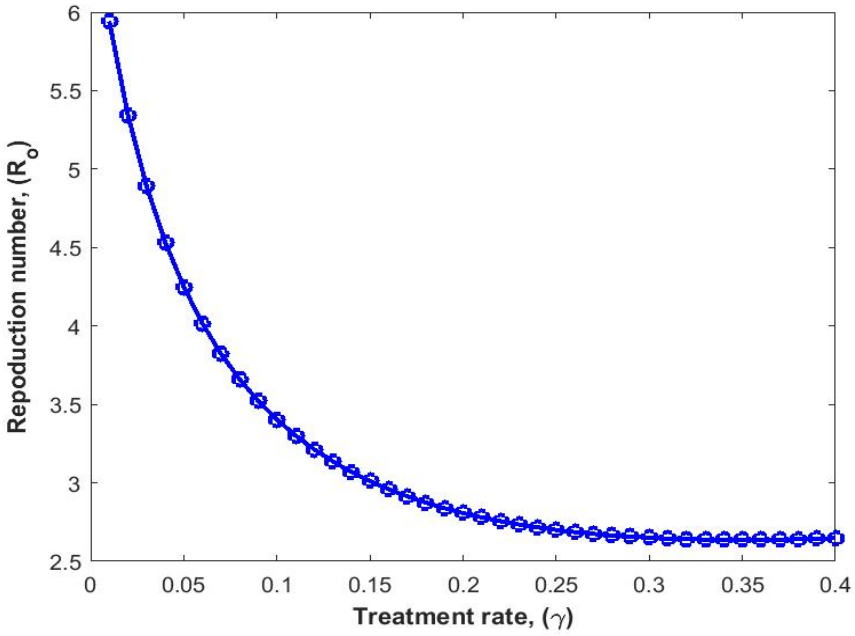

FIGURE 12. Effect of varying γ on $\mathfrak{R}_o$. Using the parameter values as indicated in Figure 4.

6. Concluding Remarks

In this paper, we propose a deterministic model for HIV/AIDS. We included the treatment of individuals with respect to the type of health care system (private or public) in which they are enrolled. Dropouts from treatment are as a result of side effects to ARV drugs. We explicitly computed the steady states: the disease-free and endemic equilibrium points of the model system (4). The basic reproduction number $\mathfrak{R}_o$ was obtained from the analysis of the steady states. Apart from proving the existence of the endemic state of model system (4), we also established theorems that provide the global stability of the disease and endemic states. Lyapunov functions are presented to prove the global stabilities of the disease-free and endemic equilibrium points of the model system (4). The results show that disease-free equilibrium point is globally asymptotically stable for $\mathfrak{R}_o < 1$ and endemic equilibrium is globally stable for $\mathfrak{R}_o > 1$. The global stability result suggests that the model has a forward transcritical bifurcation as shown in Figure 13.

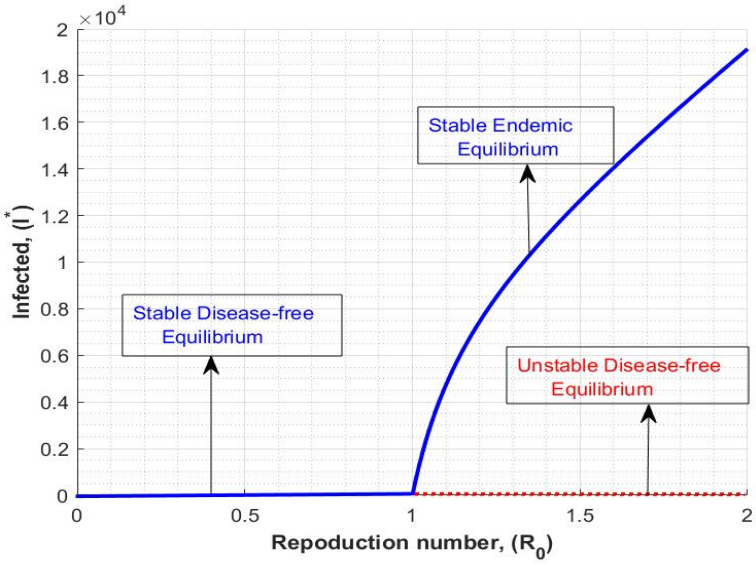

FIGURE 13. Forward transcritical bifurcation for R_0.

Simulations were carried out to track the dynamics of the model system (4) at both the disease and endemic equilibrium points. The results obtained from the sensitivity analysis enable us to determine the parameters which have a significant impact on the disease. Sensitivity indices

were obtained for various parameters. We note that reducing parameters with positive signs of their sensitivity indices reduces the reproduction number $\mathfrak{R}_o$. Therefore, interventions should target on reducing such parameters. The sensitivity analysis and numerical results also show that the side effects of ARV drugs have a positive correlation with the reproduction number $\mathfrak{R}_o$. This implies that decreasing side effects of ARV drugs decreases $\mathfrak{R}_o$. Therefore when side effects to ARV drugs decrease, individuals that drop out from treatment also decreases and individuals that are in treatment increases, thus reducing the transmission of the disease. This, in turn, also will reduce the rate at which individuals develop AIDS and as a result help in the control of the disease. Thus, when the number of individuals that return to treatment after dropout increases, this will in turn help in reducing the reproduction number $\mathfrak{R}_o$.

The model system (4) was fitted to data of individuals that drop out of treatment in order to see the trends of individuals that drop out of treatment as shown in Figure 3. This implies that individuals will dropout from treatment if the situation remains as it has been before 2017. If adequate measures are not put in place, the effective transmission rate β will increase which will lead to an increase in the reproduction number $\mathfrak{R}_o$ in Warren Park, Zimbabwe. Also, the modelling framework presented in this paper suggests that data from the private and public health care system should be presented separately for the sole purpose of monitoring HIV/AIDS in both systems. It is, however, important to note that most of the data collected are donor-funded and as such, donors deal directly with the public health care systems.

In conclusion, in this study increase in side effects of ARV drugs could bring about an increase of individuals that dropout from treatment, which will have a great impact on the dynamics of HIV/AIDS. However, getting individuals that dropout to move back to treatment could be of great help in the control of HIV/AIDS epidemics. Also, the type of health care system that individuals are receiving treatment plays a great role in the drop out of the infected individuals from ARV drugs. Therefore, interventions on how to manage side effects must be implemented so as to encourage individuals that drop out of treatment to move back. As a result, helps to fight against the HIV/AIDS epidemic.

In this work, there are some limitations. The majority of the parameters are estimated. We had to use an iterative method using Matlab in order to get an estimated value for the parameters

as a result of the fact that there is no availability of published data on the parameters. We use data from just one clinic but data from both private and public health care systems could give a better estimate of our parameters. Also, the model we use does not put into consideration vertical transmission and direct recruitment into infected class. In addition, the drop out rate may not necessarily be constant throughout the epidemic period. Stochasticity that can be attributed to the side effect level of people on ARV drugs could also have an influence on the pattern of the infection. Therefore, considering a stochastic approach could give a better picture of the dynamics of the dropout classes.

APPENDIX A. PROOF THEOREM 4.2

Proof. Let us consider the following Lyapunov function

$$V = I + \nu_1 T_1 + \nu_2 T_2 + \nu_3 D_1 + \nu_4 D_2 + \nu_5 A, \tag{27}$$

where $\nu_i, i = 1, \cdots, 5$ are positive constants that will be determined.

Differentiating equation (27) with respect to t gives

$$\dot{V} = \dot{I} + \nu_1 \dot{T_1} + \nu_2 \dot{T_2} + \nu_3 \dot{D_1} + \nu_4 \dot{D_2} + \nu_5 \dot{A}. \tag{28}$$

Substituting (4) into (28), we have

$$\begin{aligned} \dot{V} = {} & \lambda S - Q_1 I + \nu_1[\gamma\rho I - Q_2 T - 1 + \theta_1 D - 1] + \nu_2[\gamma(1-\rho)I - Q_3 T_2 + \theta_2 D_2] + \\ & \nu_3[f(\xi_1)T_1 - Q_4 D - 1] + \nu_4[f(\xi_2)T_2 - Q_5 D_2] + \nu_5[\alpha_1 I + \alpha_2 T_1 + \alpha_3 T_2 + \alpha_4 D_1 + \\ & \alpha_5 D_2 - Q_6 A], \end{aligned} \tag{29}$$

where

$$Q_1 = \mu + \alpha_1 + \gamma, \quad Q_2 = \mu + \alpha_2 + f(\xi_1), \quad Q_3 = \mu + \alpha_3 + f(\xi_2),$$

$$Q_4 = \mu + \theta_1 + \alpha_4 \quad Q_5 = \mu + \theta_2 + \alpha_5, \quad Q_6 = \mu + \delta.$$

Substituting equation (2) into (29), gives

$$\begin{aligned}\dot{V} = &\left[\frac{\beta S}{N} - Q_1 + \nu_1\gamma\rho + \nu_2(\gamma(1-\rho)) + \nu_5\alpha_1\right] I + \left[\frac{\eta_1\beta S}{N} - \nu_1 Q_2 + \nu_3 f(\xi_1) + \right.\\ &\left.\nu_5\alpha_2\right] T_1 + \left[\frac{\eta_2\beta S}{N} - \nu_2 Q_3 + \nu_4 f(\xi_2) + \nu_5\alpha_3\right] T_2 + \left[\frac{\eta_3\beta S}{N} + \nu_1\theta_1 - \nu_3 Q_4 + \right.\\ &\left.\nu_5\alpha_4\right] D_1 + \left[\frac{\eta_4\beta S}{N} + \nu_2\theta_2 - \nu_4 Q_5 + \nu_5\alpha_5\right] D_2 + \left[\frac{\eta_5\beta S}{N} - \nu_5 Q_6\right] A. \qquad (30)\end{aligned}$$

From equation (7), we know that $\frac{N}{S} \leq 1$. Substituting it into equation (30) gives

$$\begin{aligned}\dot{V} \leq &\, Q_1\left[\frac{\beta}{Q_1} + \frac{\nu_1\gamma\rho}{Q_1} + \frac{\nu_2(\gamma(1-\rho))}{Q_1} + \frac{\nu_5\alpha_1}{Q_1} - 1\right] I + [\eta_1\beta - \nu_1 Q_2 + \nu_3 f(\xi_1) + \\ &\nu_5\alpha_2] T_1 + [\eta_2\beta - \nu_2 Q_3 + \nu_4 f(\xi_2) + \nu_5\alpha_3] T_2 + [\eta_3\beta + \nu_1\theta_1 - \nu_3 Q_4 + \nu_5\alpha_4] D_1 + \\ &[\eta_4\beta + \nu_2\theta_2 - \nu_4 Q_5 + \nu_5\alpha_5] D_2 + [\eta_5\beta - \nu_5 Q_6] A. \qquad (31)\end{aligned}$$

Solving for $\nu_i, i = 1, \cdots, 5$ so that the coefficients of T_1, T_2, D_1, D_2, A are zero, we have

$$\begin{aligned}\nu_1 &= \frac{\beta[Q_4(Q_6\eta_1 + \alpha_2\eta_5) + f(\xi_1)(Q_6\eta_3 + \alpha_4\eta_5)]}{Q_6[Q_2Q_4 - f(\xi_1)\theta_1]}, \qquad \nu_5 = \frac{\beta\eta_5}{Q_6}.\\ \nu_2 &= \frac{\beta[Q_5(Q_6\eta_2 + \alpha_3\eta_5) + f(\xi_2)(Q_6\eta_4 + \alpha_5\eta_5)]}{Q_6[Q_3Q_5 - f(\xi_2)\theta_2]}\\ \nu_3 &= \frac{\beta[Q_2(Q_6\eta_3 + \alpha_4\eta_5) + \theta_1(Q_6\eta_1 + \alpha_2\eta_5)]}{Q_6[Q_2Q_4 - f(\xi_1)\theta_1]},\\ \nu_4 &= \frac{\beta[Q_3(Q_6\eta_4 + \alpha_5\eta_5) + \theta_2(Q_6\eta_2 + \alpha_3\eta_5)]}{Q_6[Q_3Q_5 - f(\xi_2)\theta_2]},\end{aligned}$$

Substituting the expressions for $\nu_1, \nu_2, \nu_3, \nu_4, \nu_5$ into (31) gives

$$\begin{aligned}\dot{V} &\leq Q_1[(R_I + R_{T_1} + R_{T_2} + R_{D_1} + R_{D_2} + R_A) - 1]I,\\ &= Q_1(\mathfrak{R}_o - 1)I.\end{aligned}$$

Note that $\dot{V} \leq 0$ for $\mathfrak{R}_o$ with a strict inequality when $\mathfrak{R}_o < 1$. So the largest invariant set of $\frac{dv}{dt} = 0$ is $(0,0,0,0,0,0)$. By Lasalle's invariant principle from [36], we conclude that model (4) is globally asymptotically stable at E_0. This result means that the disease dies out eventually regardless of the initial states of the system. □

APPENDIX B. PROOF THEOREM 4.3

Proof. Lets consider equation (8) - (14) at steady states, so that

$$\pi = \lambda^* S^* + \mu S^*, \tag{32}$$

$$(\alpha_1 + \mu + \gamma) = \frac{\lambda^* S^*}{I^*}, \tag{33}$$

$$(\mu + \alpha_2 + f(\xi_1)) = \frac{\gamma\rho I^*}{T_1^*} + \frac{\theta_1 D_1^*}{T_1^*}, \tag{34}$$

$$(\mu + \alpha_3 + f(\xi_2)) = \frac{\gamma(1-\rho) I^*}{T_2^*} + \frac{\theta_2 D_2^*}{T_2^*}, \tag{35}$$

$$(\theta_1 + \mu + \alpha_4) = \frac{f(\xi_1) T_1^*}{D_1^*}, \tag{36}$$

$$(\theta_2 + \mu + \alpha_5) = \frac{f(\xi_2) T_2^*}{D_2^*}, \tag{37}$$

$$(\mu + \delta) = \frac{\alpha_1 I^*}{A^*} + \frac{\alpha_2 T_1^*}{A^*} + \frac{\alpha_3 T_2^*}{A^*} + \frac{\alpha_4 D_1^*}{A^*} + \frac{\alpha_5 D_2^*}{A^*}. \tag{38}$$

Let us consider the following Lyapunov function

$$\begin{aligned} V = (S - S^* \ln S) + \tau_1 (I - I^* \ln I) + \tau_2 (T_1 - T_1^* \ln T_1) + \tau_3 (T_2 - T_2^* \ln T_2) + \\ \tau_4 (D_1 - D_1^* \ln D_1) + \tau_5 (D_2 - D_2^* \ln D_2) + \tau_6 (A - A^* \ln A), \end{aligned} \tag{39}$$

where τ_i, $i = 1, \cdots, 6$ are constants to be determined.

Differentiating V with respect to time (t) yields

$$\begin{aligned} \dot{V} = \left(1 - \frac{S^*}{S}\right) \dot{S} + \tau_1 \left(1 - \frac{I^*}{I}\right) \dot{I} + \tau_2 \left(1 - \frac{T_1^*}{T_1}\right) \dot{T}_1 + \tau_3 \left(1 - \frac{T_2^*}{T_2}\right) \dot{T}_2 + \\ \tau_4 \left(1 - \frac{D_1^*}{D_1}\right) \dot{D}_1 + \tau_5 \left(1 - \frac{D_2^*}{D_2}\right) \dot{D}_2 + \tau_6 \left(1 - \frac{A^*}{A}\right) \dot{A}. \end{aligned} \tag{40}$$

Substituting the expressions for $\dot{S},\dot{I},\dot{T_1},\dot{T_2},\dot{D_1},\dot{D_2},\dot{A}$ from the model system (4) into (40), we have

$$\begin{aligned}\dot{V} = &\left(1-\frac{S^*}{S}\right)(\pi-(\lambda+\mu)S)+\tau_1\left(1-\frac{I^*}{I}\right)(\lambda S-(\alpha_1+\mu+\gamma)I)+\tau_2\left(1-\frac{T_1^*}{T_1}\right)\\
&(\gamma\rho I-(\mu+\alpha_2+f(\xi_1))T_1+\theta_1 D_1)+\tau_3\left(1-\frac{T_2^*}{T_2}\right)(\gamma(1-\rho)I-(\mu+\alpha_3+\\
&f(\xi_2))T_2+\theta_2 D_2)+\tau_4\left(1-\frac{D_1^*}{D_1}\right)(f(\xi_1)T_1-(\theta_1+\mu+\alpha_4)D_1)+\tau_5\left(1-\frac{D_2^*}{D_2}\right)\\
&(F(\xi_2)T_2-(\theta_2+\mu+\alpha_5)D_2)+\tau_6\left(1-\frac{A^*}{A}\right)(\alpha_1 I+\alpha_2 T_1+\alpha_3 T_2+\alpha_4 D_1\\
&+\alpha_5 D_2-(\mu+\delta)A).\end{aligned} \tag{41}$$

Substituting the expressions from equation (32) - (38), we have

$$\begin{aligned}\dot{V} = &\left(1-\frac{S^*}{S}\right)(\mu S^*+\lambda^* S^*-\mu S-\lambda S)+\tau_1\left(1-\frac{I^*}{I}\right)\left(\lambda S-\frac{\lambda^* S^* I}{I^*}\right)+\\
&\tau_2\left(1-\frac{T_1^*}{T_1}\right)\left(\gamma\rho I-\frac{\gamma\rho I^* T_1}{T_1^*}-\frac{\theta_1 D_1^* T_1}{T_1^*}+\theta_1 D_1\right)+\tau_3\left(1-\frac{T_2^*}{T_2}\right)(\gamma(1-\rho)I-\\
&\frac{\gamma(1-\rho)I^* T_2}{T_2^*}-\frac{\theta_2 D_2^* T_2}{T_2^*}+\theta_2 D_2\Big)+\tau_4\left(1-\frac{D_1^*}{D_1}\right)\left(f(\xi_1)T_1-\frac{f(\xi_1)T_1^* D_1}{D_1^*}\right)+\\
&\tau_5\left(1-\frac{D_2^*}{D_2}\right)\left(f(\xi_2)T_2-\frac{f(\xi_2)T_2^* D_2}{D_2^*}\right)+\tau_6\left(1-\frac{A^*}{A}\right)(\alpha_1 I+\alpha_2 T_1+\alpha_3 T_2+\\
&\alpha_4 D_1+\alpha_5 D_2-\frac{\alpha_1 I^* A}{A^*}-\frac{\alpha_2 T_1^* A}{A^*}-\frac{\alpha_3 T_2^* A}{A^*}-\frac{\alpha_4 D_1^* A}{A^*}-\frac{\alpha_5 D_2^* A}{A^*}\Big).\end{aligned} \tag{42}$$

Let

$$\frac{S}{S^*}=r,\quad \frac{I}{I^*}=u,\quad \frac{T_1}{T_1^*}=v,\quad \frac{T_2}{T_2^*}=w,\quad \frac{D_1}{D_1^*}=x,\quad \frac{D_2}{D_2^*}=y,\quad \frac{A}{A^*}=z,$$
$$\text{and}\quad \frac{\beta}{N}=\beta_0.$$

After some tedious algebraic manipulations we have

$$\dot{V}=-\mu\left(\frac{(S-S^*)^2}{S}\right)+f(r,u,v,w,x,y,z),$$

where

$$
\begin{aligned}
f(r,u,v,w,x,y,z) = {} & \beta_0 I^* S^* \left(2 - r - \frac{1}{r}\right) + \beta_0 \eta_1 T_1^* S^* \left(3 - \frac{1}{r} - \frac{rv}{u} - \frac{u}{v}\right) + \\
& \beta_0 \eta_2 T_2^* S^* \left(3 - \frac{1}{r} - \frac{rw}{u} - \frac{u}{w}\right) + \beta_0 \eta_3 D_1^* S^* \left(4 - \frac{1}{r} - \frac{rx}{u}\right. \\
& \left. - \frac{u}{v} - \frac{v}{x}\right) + \beta_0 \eta_4 D_2^* S^* \left(4 - \frac{1}{r} - \frac{ry}{u} - \frac{u}{w} - \frac{w}{y}\right) + \beta_0 \eta_5 A^* S^* \\
& \left(2 - \frac{1}{r} - \frac{rz}{u}\right) + \frac{\beta_0 \eta_5 \alpha_2 \theta_1 D_1^* T_1^* A^* S^*}{\gamma \rho I^* P} \left(2 - \frac{x}{v} - \frac{v}{x}\right) + \\
& \frac{\beta_0 \eta_5 \alpha_4 \theta_1 D_1^* A^* S^* D_1^*}{\gamma \rho I^* f(\xi_1) T_1^* P} \left(2 - \frac{x}{v} - \frac{v}{x}\right) + \frac{\beta_0 \eta_5 \alpha_2 A^* S^* T_1^*}{P} \left(2 - \frac{v}{z} - \frac{u}{v}\right) \\
& + \frac{\beta_0 \eta_5 \alpha_3 \theta_2 D_2^* T_2^* A^* S^*}{\gamma (1-\rho) I^* P} \left(2 - \frac{y}{w} - \frac{w}{y}\right) + \frac{\beta_0 \eta_5 \alpha_5 \theta_2 D_2^* A^* S^* D_2^*}{\gamma (1-\rho) I^* P} \\
& \left(2 - \frac{y}{w} - \frac{w}{y}\right) + \frac{\beta_0 \eta_5 \alpha_3 A^* S^* T_2^*}{P} \left(2 - \frac{w}{z} - \frac{u}{w}\right) + \frac{\beta_0 \eta_1 \theta_1 D_1^* S^* T_1^*}{\gamma \rho I^*} \\
& \left(2 - \frac{x}{v} - \frac{v}{x}\right) + \frac{\beta_0 \eta_5 \alpha_4 A^* S^* D_1^*}{P} \left(3 - \frac{x}{z} - \frac{u}{v} - \frac{v}{x}\right) + \\
& \frac{\beta_0 \eta_5 \alpha_5 A^* S^* D_2^*}{P} \left(3 - \frac{y}{z} - \frac{u}{w} - \frac{w}{y}\right) + \frac{\beta_0 \eta_3 \theta_1 D_1^* S^* D_1^*}{\gamma \rho I^*} \\
& \left(2 - \frac{x}{v} - \frac{v}{x}\right) + \frac{\beta_0 \eta_2 \theta_2 D_2^* S^* T_2^*}{\gamma (1-\rho) I^*} \left(2 - \frac{y}{w} - \frac{w}{y}\right) + \frac{\beta_0 \eta_5 \alpha_1 A^* S^* I^*}{P} \\
& \left(1 - \frac{u}{z}\right) + \frac{\beta_0 \eta_2 \theta_2 D_2^* S^* T_2^* D_2^*}{\gamma (1-\rho) I^*} \left(2 - \frac{y}{w} - \frac{w}{y}\right). \qquad (43)
\end{aligned}
$$

By the arithmetic-mean-geometric mean inequality, we note that

$$
\begin{aligned}
& \left(2 - r - \frac{1}{r}\right) \le 0, \left(3 - \frac{1}{r} - \frac{rv}{u} - \frac{u}{v}\right) \le 0, \left(3 - \frac{1}{r} - \frac{rw}{u} - \frac{u}{w}\right) \le 0, \\
& \left(4 - \frac{1}{r} - \frac{rx}{u} - \frac{u}{v} - \frac{v}{x}\right) \le 0, \left(4 - \frac{1}{r} - \frac{ry}{u} - \frac{u}{w} - \frac{w}{y}\right) \le 0, \quad \left(2 - \frac{1}{r} - \frac{rz}{u}\right) \le 0, \\
& \left(2 - \frac{x}{v} - \frac{v}{x}\right) \le 0, \left(2 - \frac{v}{z} - \frac{u}{v}\right) \le 0, \left(2 - \frac{y}{w} - \frac{w}{y}\right) \le 0, \left(2 - \frac{w}{z} - \frac{u}{w}\right) \le 0, \\
& \left(3 - \frac{x}{z} - \frac{u}{v} - \frac{v}{x}\right) \le 0, \left(3 - \frac{y}{z} - \frac{u}{w} - \frac{w}{y}\right) \le 0, \left(1 - \frac{u}{z}\right) \le 0.
\end{aligned}
$$

Thus, it implies that

$$
\dot{V} = -\mu \left(\frac{(S - S^*)^2}{S}\right) + f(r,u,v,w,x,y,z) \le 0.
$$

Also $\dot{V} = 0$ only if $r = 1, u = v = w = x = y = z$. Thus, the function V satisfies the Lyapunov stability theorem. This implies that the set
$\{(S,I,T_1,T_2,D_1,D_2,A) \in \Omega | \dot{V}(S,I,T_1,T_2,D_1,D_2,A) = 0\}$ consist only the point E_1 (Endemic equilibrium). Therefore, by Lyapunov's direct method, E_1 is globally asymptotically stable in the region Ω. By Lasalle's invariant principle from [36] we conclude that model (4) is globally asymptotically stable at E_1. Epidemiologically this means that the disease persist regardless of the initial states of the system. □

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CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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