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Research article

Modeling the population dynamics of HIV/AIDS with opportunistic infections at the severe stage of HIV

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Abstract: In this paper, we present a deterministic model for the population dynamics of HIV/AIDS, wherein some individuals at the severe symptomatic phase of HIV develop serious opportunistic infections (OIs) such cryptococcal, tuberculous, pneumococcal, and other bacterial meningitis due to an inappropriate treatment or lack of counseling. OIs are responsible for significant mortality and disability on individuals with HIV in many countries. Cryptococcal meningitis (CM) is among frequent OIs responsible for significant mortality and disability of individuals with HIV in limited resource settings. However, there are also cases of high mortality due to CM on HIV-uninfected individuals, but the burden of CM is more frequent in people living with HIV. We proved the global stability of the disease-free as well as the endemic equilibrium points. In addition, we performed the study of sensitivity analysis of the basic reproduction number with the parameters of the model as well as with some compartmental classes. We illustrated our theoretical results by way of numerical simulations using a projection on the HIV historical data of South Africa since 2024. Our analysis showed that a combination of ART and OI specific treatments may reduce the number of death related cases.

Keywords: mathematical modeling; HIV; opportunistic infections (OIs); cryptococcal meningitis (CM); stability analysis; sensitivity analysis

1. Introduction

The epidemic of human immunodeficiency virus (HIV)/AIDS remains a devastating disease in human history despite recent advancements in research. The prevalence of HIV infection is extremely high, and the number of people living with HIV continues to grow rapidly, especially in southern Africa. In South Africa, HIV increased from an estimated 4.14 million in 2002 to 8 million by 2024 [1]. The use of pre-exposure prophylaxis (PREP) and Antiretroviral therapy (ART) to combat HIV have proven efficiency in many countries. However, without ART, HIV can gradually destroy the immune

system and open doors to opportunistic infections (OIs). Cryptococcal meningitis (CM) is the most common OI in HIV-1/AIDS, and its disease mechanism has been extensively studied. The key steps for fungi to infect the brain and cause meningitis after establishment of local infection are the spread of fungal cells to the bloodstream and invasion through the blood-brain barrier to reach the central nervous system [2]. This fungal meningitis is often fatal without proper treatment, and the mortality rate remains unacceptably high even with antifungal drug interventions. During the progression of HIV and mostly at the severe stage, OIs such as CM, influenza, or coronavirus disease (COVID-19) occur in people with weakened immune systems, and this stage can be very fatal. Fungal meningitis does not spread from person to person. Instead, an individual acquires CM when they inhale soil particles contaminated by bird droppings [3]. OIs are less common now than they were in the early days of HIV because better treatments reduce the amount of HIV in a person's body and keep the immune system stronger. Therefore, people living with HIV (PLWH) remain at risk of OIs if they are diagnosed with late-stage HIV infection and have developed profound immunosuppression, or due to lack of adherence to ART. They are at risk of common infections such as COVID-19 infection and bacterial pneumonia [4]. However, there are also cases of high mortality due to CM that arise in HIV-uninfected individuals, especially in the population with very limited resources. Globally, approximately 152,000 incident cases of HIV-associated CM occur each year, accounting for 19% of AIDS-related deaths, and Africa has most (54%) of these incident cases, and South Africa has the highest estimated burden (i.e., 23,000 cases per annum) [5]. People with HIV-associated CM face negative impacts prior to and after diagnosis. These patients struggled to access timely quality healthcare. Patients starting or restarting ART, and thus at risk for CM, should receive CM education as part of HIV counselling [6]. Among people with cryptococcal CM shortly after initiating ART, the symptom onset can be more acute, likely related to an unmasking immune reconstitution inflammatory syndrome (IRIS) [7].

Mathematical models have insightful tools available to help understand the dynamics of infectious disease outbreaks and to support public health decision-making. Deterministic mathematical models have been formulated and analyzed by many scholars. In [8], the authors formulated a syphilis and HIV co-infection model to study the dynamics of syphilis and HIV transmission, and also calibrated the model using yearly confirmed syphilis and HIV data from the US Centers for Disease Control and Prevention. In [9], a mathematical co-infection model that fronts vaccination and treatment against pneumococcal pneumonia and ART for HIV/AIDS in the management of the co-infection burden is presented. In [10], a study on the epidemiology of meningitis among adults was investigated in a South African Province. The authors found that over a 4-year period, there was a significant decrease in an incidence of cryptococcal due to an expansion of the national ART program. In [11], the Southern African HIV Clinicians Society provided a guideline for the prevention, diagnosis, and management of cryptococcal disease among HIV-infected persons: 2019 update. In [12], the authors analyzed a mathematical model that describes the dynamics of HIV infection among the immigrant youths and how parental care can minimize or prevent the spread of the disease in the population. The authors identified the combination of screening of immigrants and parental care that gives the most efficient results in controlling the spread of HIV/AIDS. The researchers in [13] studied the impact of the President's emergency plan for AIDS relief (PEPFAR), a new USA executive order funding freeze on HIV deaths and infections in seven countries in sub-Saharan Africa. The authors argued that the sudden cessation of PEPFAR funding has immediate and far-reaching impact, likely resulting in tens of thousands of excess HIV deaths and new infections for the seven PEPFAR priority countries. The researchers

in [14] proposed a new mathematical model for the transmission dynamics of meningitis to investigate the effects of vaccine and treatment as control techniques to reduce the disease's prevalence in the population. There was a little evidence on how HIV infection affects risk of poor outcomes from COVID-19 [15]. A large population-based cohort study in South Africa revealed that the COVID-19 mortality risk among people living with HIV is double the risk of those without HIV [16]. There are also several fractional models, and the most relevant to this research can be found in [17–20]. In [19], a fractional model for the interactions of HIV-TB co-infection with treatment was examined and investigated, and the authors found that effective HIV prevention significantly lowers the rate of TB co-infections, and efficient TB treatment boosts the immune system, thereby reducing the risk of co-infections with opportunistic infections such as HIV/AIDS. The researchers in [20] present the transmission dynamics of HIV/AIDS using fractional order (FO) and a fractal-fractional order compartmental model with the power-law kernel.

Our main model is related to some models illustrated in [21–23]. However, in this research, our model has three rates of transfer in the form of treatment such as α_1 rate of transfer of individuals from the moderate symptomatic phase to the asymptomatic phase due to ART, α_2 rate of transfer of individuals from the severe symptomatic phase to the moderate symptomatic phase due to a combination of both ART and CM treatments, and α_3 rate of transfer of individuals from the severe symptomatic phase to the asymptomatic phase due to a combination of both ART and CM treatments. In addition, it is assumed in the model that the full-blown HIV individuals are not sexually active and cannot transmit the disease. In the model, a particular focus is featured at the severe symptomatic phase of HIV where people develop CM among these opportunistic infections due to a lack of ART treatment, before developing full-blown HIV/AIDS. This research shows how OIs can accelerate the risk of deaths among HIV individuals. Moreover, CM has been identified as the highest global burden among other OIs, because of its widespread morbidity and mortality. Furthermore, Infection occurs mostly at the severe stage of HIV. Thus, HIV patients need to be aware of common opportunistic infections so that they receive the best advice and necessary treatment recommendations.

The remainder of this paper is sectioned as follows: In Section 2, we present the model and use the next-generation method to find the basic reproduction number. We deal with equilibria and stability analysis in Section 3. In Section 4, we provide numerical simulations to illustrate our theoretical results. In Section 5, we study the sensitivity, and in Section 6, we give some concluding remarks.

2. The model

2.1. Model description

We consider a population of size $N(t)$ at time t that is subdivided into the susceptibles class $S(t)$, the asymptomatic phase $I_1(t)$, the moderate symptomatic phase $I_2(t)$, the severe symptomatic phase I_3, and the HIV/AIDS people $A(t)$. The population size $N(t)$ is given by

$$N(t) = S(t) + I_1(t) + I_2(t) + I_3(t) + A(t).$$

For the mathematical formulation of the model, we use the following notation:

μ	Birth and mortality rates by natural causes,
N	Size of the total population,
$\Lambda = \mu N$	Recruitment rate of susceptibles into the population,
c	An individual's average number of sexual contacts with others per unit time,
β_1	Probability of disease transmission in the asymptomatic phase,
β_2	Probability of disease transmission in the moderate symptomatic phase,
β_3	Probability of disease transmission in the severe symptomatic phase,
α_1	Rate of transfer from I_2 to I_1 due to ARV treatment
α_2	Rate of transfer from I_3 to I_1 due to a combination of both ARV and CM treatment
α_3	Rate of transfer from I_3 to I_2 due to a combination of both ARV and CM treatment
k_1	Progression rate from I_1 to I_2
k_2	Progression rate from the symptomatic phase I_2 to A
k_3	Progression rate from the severe symptomatic phase I_3 to A
σ	Progression rate from phase I_2 phase I_3
μ_m	HIV and CM disease induced mortality rate
μ_n	HIV/AIDS and CM disease induced mortality rate
δ	HIV/AIDS disease induced mortality rate

Our model is formulated from the flow diagram of Figure 1 below:

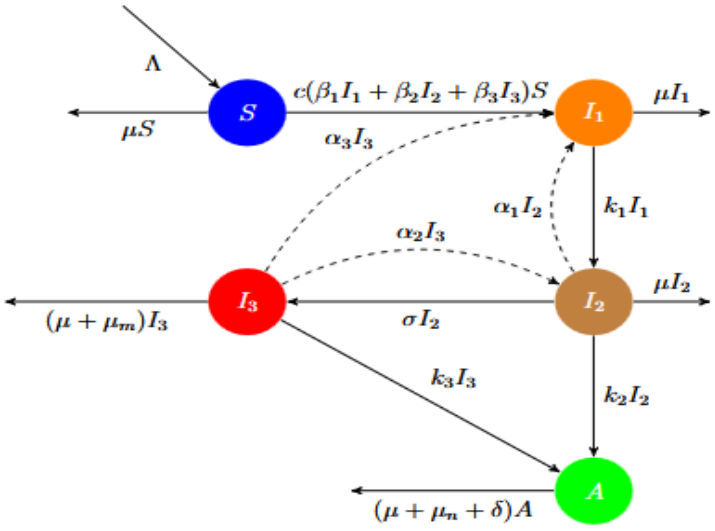

Figure 1. Flow diagram of an HIV/AIDS model.

These assumptions give rise to the following system of ordinary differential equations, with all the parameters being non-negative:

$$\frac{dS}{dt} = \Lambda - c(\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3)S - \mu S,$$

$$\begin{aligned}
\frac{dI_1}{dt} &= c(\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3)S - (\mu + k_1)I_1 + \alpha_1 I_2 + \alpha_2 I_3,\\
\frac{dI_2}{dt} &= k_1 I_1 - (\mu + k_2 + \alpha_1 + \sigma)I_2 + \alpha_3 I_3,\\
\frac{dI_3}{dt} &= \sigma I_2 - (\mu + \mu_m + k_3 + \alpha_2 + \alpha_3)I_3\\
\frac{dA}{dt} &= k_2 I_2 + k_3 I_3 - (\mu + \mu_n + \delta)A. \qquad (2.1)
\end{aligned}$$

$S(0) = S_0 > 0$, $I_1(0) = I_{1,0} > 0$, $I_2(0) = I_{2,0} > 0$, $I_3(0) = I_{3,0} > 0$, $A(0) = A_0 > 0$.
We note that A does not appear in the first four equations of model 2.1. Thus, we ignore the first equation to result in the following reduced system 2.2 below:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - c(\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3)S - \mu S,\\
\frac{dI_1}{dt} &= c(\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3)S - (\mu + k_1)I_1 + \alpha_1 I_2 + \alpha_2 I_3,\\
\frac{dI_2}{dt} &= k_1 I_1 - (\mu + k_2 + \alpha_1 + \sigma)I_2 + \alpha_3 I_3,\\
\frac{dI_3}{dt} &= \sigma I_2 - (\mu + \mu_m + k_3 + \alpha_2 + \alpha_3)I_3 \qquad (2.2)
\end{aligned}$$

Model system 2.2 admits a disease-free equilibrium $\Sigma_0 = (\frac{\Lambda}{\mu}, 0, 0, 0)$.

Following the method illustrated in [24], the basic reproduction number for model 2.2, which represents the expected average number of new HIV infections produced by a single HIV-infected individual when in contact with a completely susceptible population, is computed as

$$\mathcal{R}_0 = \frac{\Gamma_0}{\Gamma_1}$$

where

$$\Gamma_0 = c\Lambda\Big[\sigma k_1\beta_3 + \beta_1\Big((\alpha_1 + \mu + \sigma + k_2)(\mu + k_3 + \alpha_2 + \mu_m) + \alpha_3(\alpha_1 + k_2 + \mu)\Big) + \beta_2 k_1(\mu + k_3 + \alpha_2 + \alpha_3 + \mu_m)\Big],$$

$$\Gamma_1 = \mu\Big[(\mu + k_3 + \alpha_2 + \alpha_3 + \mu_m)\Big(\mu(\alpha_1 + \mu + k_2) + k_1(\mu + k_2)\Big) + \mu\sigma(\mu + k_3 + \alpha_2 + \mu_m) + k_1\sigma(\mu + k_3 + \mu_m)\Big].$$

2.2. Feasible solutions

Let us introduce the set Ω,

$$\Omega = \left\{x \in \mathbb{R}^5 |\ x_i > 0,\ i = 1, 2, 3, 4, 5 \text{ and } x_1 + x_2 + x_3 + x_4 + x_5 < \frac{\Lambda}{\mu}\right\}.$$

We now prove that all state variables of the model stay positive at all times $t > 0$.

Proposition 1. *Given any $t_0 > 0$, suppose that $X(t)$ is a local solution for which $X(t) \in \mathbb{R}^5_+$ for $0 < t \le t_0$. If $N(0) \le \frac{\Lambda}{\mu}$, then $N(t) < \frac{\Lambda}{\mu}$ for all $0 < t \le t_0$.*

Proof. Given any local solution with $X(t) \in \mathbb{R}^5_+$ for all $0 < t \le t_0$, we have

$$\frac{d(N(t)-\frac{\Lambda}{\mu})}{dt} = \Lambda - \mu N(t) - \mu_m I_3(t) - (\mu_n+\delta)A(t) < -\mu\left[N(t) - \frac{\Lambda}{\mu}\right].$$

Therefore, $N(0) < \frac{\Lambda}{\mu}$ implies that $N(t) < \frac{\Lambda}{\mu}$ for all $0 < t \leq t_0$. This completes the proof.

Theorem 1. *Given any solution $X(.)$ with $X(0) \in \Omega$, then $X(t) = (S(t), I_1(t), I_2(t), I_3(t), A(t))$ is positive for all $t > 0$.*

Proof. Consider any point $y \in \Omega$. Then, there exists a local solution $X(t)$ in Ω with initial value $X(0) = y$. Suppose that t_1 is the exit time from $\mathbb{R}^5_+$. We prove by contradiction that $t_1 = \infty$.
Thus, we suppose to the contrary that $t_1 < \infty$. Let us define the following function for $0 < t \leq t_1$.

$$V_0(X(t)) = \ln\Big(\frac{\Lambda}{\mu S(t)}\Big) + \ln\Big(\frac{\Lambda}{\mu I_1(t)}\Big) + \ln\Big(\frac{\Lambda}{\mu I_2(t)}\Big) + \ln\Big(\frac{\Lambda}{\mu I_3(t)}\Big) + \ln\Big(\frac{\Lambda}{\mu A(t)}\Big)$$

Then, in view of Proposition 1, each of the terms in $V_0(t)$ is a positive-valued function. In particular, if $t_1 < \infty$, then $V_0(X)$ tends to ∞ as $t \to t_1$. We prove that this cannot happen if t_1 is finite.
We calculate the derivative:

$$\begin{aligned}
\frac{dV_0(t)}{dt} &= -\frac{1}{S}\left(\Lambda - c(\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3)S - \mu S\right) \\
&\quad -\frac{1}{I_1}\Big(c(\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3)S - (\mu + k_1)I_1 + \alpha I_2 + \alpha_2 I_3\Big) \\
&\quad -\frac{1}{I_2}\Big(k_1 I_1 - (\mu + k_2 + \alpha_1 + \sigma)I_2 + \alpha_3 I_3\Big) \\
&\quad -\frac{1}{I_3}\Big(\sigma I_2 - (\mu + \mu_m + k_3 + \alpha_2 + \alpha_3)I_3\Big) \\
&\quad -\frac{1}{A}\Big(k_2 I_2 + k_3 I_3 - (\mu + \mu_n + \delta)A\Big) \\
&\leq 5\mu + k_1 + k_2 + k_3 + \alpha_1 + \sigma + \mu_m + \mu_n + \delta + \alpha_2 + \alpha_3 \\
&\quad +c(\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3)S
\end{aligned} \tag{2.3}$$

By Proposition 1, we have $S < \frac{\Lambda}{\mu}$, $I_1 < \frac{\Lambda}{\mu}$, $I_2 < \frac{\Lambda}{\mu}$, and $I_3 < \frac{\Lambda}{\mu}$. Therefore, we obtain the inequality below:

$$\frac{dV_0(t)}{dt} \leq F_0,$$

where

$$F_0 = 5\mu + k_1 + k_2 + k_3 + \alpha_1 + \sigma + \mu_m + \mu_n + \delta + \alpha_2 + \alpha_3 + c\left(\frac{\Lambda}{\mu}\right)^2(\beta_1 + \beta_2 + \beta_3) \text{ is a constant.}$$

Consequently, over the bounded interval $[0, t_1)$, $V_0(t)$ is bounded. Therefore, it is impossible to have that $V_0(X)$ tends to ∞ as $t \to t_1$. Thus, we can conclude that $X(t)$ never exits the set Ω.

3. Equilibria

3.1. Global stability of the disease-free equilibrium

We know that in view of [24], the disease-free equilibrium of model system 2.2 is locally asymptotically stable whenever $\mathcal{R}_0 < 1$. Now, we introduce the following invariant, $\mathcal{R}_G$, which is used to prove a theorem on global asymptotical stability of the disease-free equilibrium:

$$\mathcal{R}_G = \max\Big\{\frac{c\Lambda\beta_1}{\mu^2},\ \frac{c\Lambda\beta_2}{\mu(\mu+k_2)},\ \frac{c\Lambda\beta_3}{\mu(\mu+k_3+\mu_m)}\Big\}. \tag{3.1}$$

Theorem 2 *If $\mathcal{R}_G < 1$, then the disease-free equilibrium Σ_0 of model system 2.2 is globally asymptotically stable.*

Proof. Let us assume that $\mathcal{R}_G < 1$. Then, the following inequalities hold:

$$c\frac{\Lambda}{\mu}\beta_1 - \mu < 0,\ \ c\frac{\Lambda}{\mu}\beta_2 - (\mu+k_2) < 0,\ \ c\frac{\Lambda}{\mu}\beta_3 - (\mu+k_3+\mu_m) < 0. \tag{3.2}$$

For this system of inequalities, there exist $a > 0$ for which

$$(a+1)\frac{\Lambda}{\mu}c\beta_1 - \mu,\ \ (a+1)\frac{\Lambda}{\mu}c\beta_2 - (\mu+k),\ \ (a+1)\frac{\Lambda}{\mu}c\beta_3 - (\mu+\mu_m+k_3) < 0. \tag{3.3}$$

Let us introduce the variable $Z(t) := \frac{\Lambda}{\mu} - S(t)$. We define a function $V_1(Z(t), I_1(t), I_2(t), I_3(t))$ by the following formula:

$$V_1(Z(t), I_1(t), I_2(t), I_3(t)) = aZ(t) + I_1(t) + I_2(t) + I_3(t).$$

Note that V_1 is a positive-definite function. The time derivative of V_1 is

$$\begin{aligned}
\dot{V}_1 &= -a\mu Z + ac(\beta_1 I_1 + \beta_2 I_2 + \beta_3 I_3)S \\
&\quad + I_1[c\beta_1 S - \mu] + I_2[c\beta_2 S - (\mu+k_2)] + I_3[c\beta_3 S - (\mu+\mu_m+k_3)] \\
&\le -a\mu Z + I_1[(1+a)\frac{\Lambda}{\mu}c\beta_1 - \mu] + I_2[(1+a)\frac{\Lambda}{\mu}c\beta_2 - (\mu+k_2)] \\
&\quad + I_3[(1+a)\frac{\Lambda}{\mu}c\beta_3 - (\mu+\mu_m+k_3)]
\end{aligned}$$

Therefore, in view of the inequality 3.3, $\dot{V}_1$ is negative-definite with respect to the disease-free equilibrium point. Thus, V_1 is a Lyapunov function, the existence of which proves global asymptotical stability of the disease-free equilibrium for model system 2.2, and this completes the proof.

Remark 1. *The condition for global asymptotical stability in the latter theorem is quite sharp, as we can deduce from simple calculations such as below.*

Consider Γ_0 to be a function $\Gamma_0(c, \frac{\Lambda}{\mu}, \beta_1, \beta_2, \beta_3)$ of $c, \frac{\Lambda}{\mu}, \beta_1, \beta_2, \beta_3$. Then, in the case that

$$c\frac{\Lambda}{\mu}\beta_1 = \mu,\ \ c\frac{\Lambda}{\mu}\beta_2 = \mu + k_2,\ \ c\frac{\Lambda}{\mu}\beta_3 = \mu + \mu_m + k_3, \tag{3.4}$$

a routine calculation yields:

$$\Gamma_0(c, \frac{\Lambda}{\mu}, \beta_1, \beta_2, \beta_3) = \Gamma_1,$$

and then $\mathcal{R}_G = 1 = \mathcal{R}_0$.
It further follows that whenever $\mathcal{R}_G < 1$, then $\Gamma_0(c, \frac{\Lambda}{\mu}, \beta_1, \beta_2, \beta_3) \leq \Gamma_1$ and consequently $\mathcal{R}_0 < 1$. This statement is, of course, also true because global asymptotical stability always implies local asymptotical stability.

3.2. Existence of the endemic equilibrium

In this section, we show the existence of an endemic equilibrium using a polynomial equation $H(I_1^*)$ if the basic reproduction number $\mathcal{R}_0 > 1$. We first calculate the following.

From Eqs 3 and 4 of the model system 2.2, we have:

$$I_2^* = \frac{k_1(\mu + \mu_m + k_3 + \alpha_2 + \alpha_3)}{(\mu + \mu_m + k_3 + \alpha_2)(\mu + k_2 + \alpha_1 + \sigma) + \alpha_3(\mu + k_2 + \alpha_1)} I_1^*$$

$$I_3^* = \frac{k_1\sigma}{(\mu + \mu_m + k_3 + \alpha_2)(\mu + k_2 + \alpha_1 + \sigma) + \alpha_3(\mu + k_2 + \alpha_1)} I_1^*$$

Taking the sum of the first and second equations of the model system 2.2, we have:

$$\Lambda - \mu S^* - (\mu + k_1)I_1^* + \alpha_1 I_2^* + \alpha_2 I_3^* = 0.$$

We substitute I_2^* and I_3^* above to the expression below $-(\mu + k_1)I_1^* + \alpha I_2^* + \alpha_2 I_3^*$. The latter is simplified by

$$\frac{-\Gamma_1}{\mu[(\mu + \mu_m + k_3 + \alpha_2)(\mu + k_2 + \alpha_1 + \sigma) + \alpha_3(\mu + k_2 + \alpha_1)]} I_1^*$$

Now we can find S^* by

$$\begin{aligned}
\mu S^* - \Lambda &= \frac{-\Gamma_1}{(\mu + \mu_m + k_3 + \alpha_2)(\mu + k_2 + \alpha_1 + \sigma) + \alpha_3(\mu + k_2 + \alpha_1)} I_1^*, \\
\mu S^* &= \Lambda - \frac{\Gamma_1}{\mu[(\mu + \mu_m + k_3 + \alpha_2)(\mu + k_2 + \alpha_1 + \sigma) + \alpha_3(\mu + k_2 + \alpha_1)]} I_1^*, \\
S^* &= \frac{\Lambda\mu[(\mu + \mu_m + k_3 + \alpha_2)(\mu + k_2 + \alpha_1 + \sigma) + \alpha_3(\mu + k_2 + \alpha_1)] - \Gamma_1 I_1^*}{\mu^2[(\mu + \mu_m + k_3 + \alpha_2)(\mu + k_2 + \alpha_1 + \sigma) + \alpha_3(\mu + k_2 + \alpha_1)]}.
\end{aligned}$$

We now search for the expression of I_1^* from

$$\begin{aligned}
H(I_1^*) &= c(\beta_1 I_1^* + \beta_2 I_2^* + \beta_3 I_3^*)S^* - (\mu S^* - \Lambda) \\
H(I_1^*) &= \frac{c\beta_1 I_1^*(\Lambda\mu\Gamma_2 - \Gamma_1 I_1^*)}{\mu^2\Gamma_2} \\
&\quad + \frac{c\beta_2 I_1^* k_1(\mu + \mu_m + k_3 + \alpha_2 + \alpha_3)(\Lambda\mu\Gamma_2 - \Gamma_1 I_1^*)}{\mu^2(\Gamma_2)^2} \\
&\quad + \frac{c\beta_3 I_1^* k_1\sigma(\Lambda\mu\Gamma_2 - \Gamma_1 I_1^*)}{\mu^2(\Gamma_2)^2} \\
&\quad - \frac{\Gamma_1}{\mu\Gamma_2} I_1^*.
\end{aligned}$$

Letting $H(I_1^*) = 0$ leads to

$$\begin{aligned} I_1^* &= \frac{\mu\Gamma_2(\Gamma_0 - \Gamma_1)}{\Gamma_1[c\beta_2 k_1(\mu + k_3 + \alpha_2 + \alpha_3 + \mu_m) + c\beta_1\Gamma_2 + c\sigma\beta_3 k_1]} \\ &= \frac{\mu\Gamma_2\Gamma_1(\mathcal{R}_0 - 1)}{\Gamma_1[c\beta_2 k_1(\mu + k_3 + \alpha_2 + \alpha_3 + \mu_m) + c\beta_1\Gamma_2 + c\sigma\beta_3 k_1]} \\ &= \frac{\mu\Gamma_2(\mathcal{R}_0 - 1)}{[c\beta_2 k_1(\mu + k_3 + \alpha_2 + \alpha_3 + \mu_m) + c\beta_1\Gamma_2 + c\sigma\beta_3 k_1]} \\ &= \frac{\Lambda\mu\Gamma_2(\mathcal{R}_0 - 1)}{\Gamma_0} = \frac{\Lambda\mu\Gamma_2}{\Gamma_1}\left(1 - \frac{1}{\mathcal{R}_0}\right) \end{aligned} \tag{3.5}$$

where

$$\Gamma_2 = [(\mu + \mu_m + k_3 + \alpha_2)(\mu + k_2 + \alpha_1 + \sigma) + \alpha_3(\mu + k_2 + \alpha_1)]$$

Therefore, our model system 2.2 admits a unique endemic equilibrium point $\Sigma_*(S^*, I_2^*, I_3^*)$ with the following coordinates

$$I_2^* = \frac{\Lambda\mu(k_1(\mu + \mu_m + k_3 + \alpha_2 + \alpha_3))}{\Gamma_1}\left(1 - \frac{1}{\mathcal{R}_0}\right)$$

$$I_3^* = \frac{\Lambda\mu k_1\sigma}{\Gamma_1}\left(1 - \frac{1}{\mathcal{R}_0}\right) \tag{3.6}$$

Thus, the expression for S^* emerges as

$$S^* = \frac{\Lambda}{\mu}\frac{\Gamma_1}{\Gamma_0} = \frac{\Lambda}{\mu}\frac{1}{\mathcal{R}_0} = \frac{N}{\mathcal{R}_0} \tag{3.7}$$

noting that $\Lambda = \mu N$.

3.3. Global stability of the endemic equilibrium

We now investigate the global stability of the endemic equilibrium points of the model system 2.2.

Theorem 3. *The endemic equilibrium Σ_* of model system 2.2 is globally asymptotically stable for $\mathcal{R}_0 > 1$.*

Proof. Consider the positive definite function $V_2(t)$ (with respect to Σ_*) defined by the formula:

$$\begin{aligned} V_2(t) &= \left(S - S^* - S^* \ln\frac{S}{S^*}\right) + D_1\left(I_1 - I_1^* - I_1^* \ln\frac{I_1}{I_1^*}\right) \\ &\quad + D_2\left(I_2 - I_2^* - I_2^* \ln\frac{I_2}{I_2^*}\right) + D_3\left(I_3 - I_3^* - I_3^* \ln\frac{I_3}{I_3^*}\right) \end{aligned}$$

where D_1, D_2, and D_3 are positive constants to be determined at a later stage.
Let $x = \frac{S}{S^*}$, $y = \frac{I_1}{I_1^*}$, $z = \frac{I_2}{I_2^*}$, $w = \frac{I_3}{I_3^*}$. The (endemic) equilibrium values of model system 2.2 satisfy the following equations:

$$\Lambda = c(\beta_1 {I_1}^* + \beta_2 {I_2}^* + \beta_3 {I_2}^*)S^* + \mu S^*,$$

$$
\begin{aligned}
(\mu + k_1) &= \frac{c(\beta_1 {I_1}^* + \beta_2 {I_2}^* + \beta_3 {I_2}^*){S}^*}{{I_1}^*} + \alpha_1 \frac{{I_2}^*}{{I_1}^*} + \alpha_2 \frac{{I_3}^*}{{I_1}^*} \\
(\mu + k_2 + \alpha_1 + \sigma) &= k_1 \frac{{I_1}^*}{{I_2}^*} + \alpha_3 \frac{{I_3}^*}{{I_2}^*} \\
(\mu + \mu_m + k_3 + \alpha_2 + \alpha_3) &= \sigma \frac{{I_2}^*}{{I_3}^*}
\end{aligned}
$$

The time derivative of $V_2(t)$ is given by

$$
\begin{aligned}
\dot{V}_2 &= (1 - \frac{1}{x})c\beta_1 {I_1}^* {S}^* (1 - xy) + (1 - \frac{1}{x})c\beta_2 {I_2}^* {S}^* (1 - xz) + (1 - \frac{1}{x})c\beta_3 {I_3}^* {S}^* (1 - xw) \\
&\quad + D_1(1 - \frac{1}{y})c\beta_1 {I_1}^* {S}^* (xy - y) + D_1(1 - \frac{1}{y})c\beta_2 {I_2}^* {S}^* (xz - y) \\
&\quad + D_1(1 - \frac{1}{y})c\beta_3 {I_3}^* {S}^* (xw - y) + D_1(1 - \frac{1}{y})\alpha_1 {I_2}^* (z - y) + D_1(1 - \frac{1}{y})\alpha_2 {I_3}^* (w - y) \\
&\quad + D_2(1 - \frac{1}{z})k_1 {I_1}^* (y - z) + D_2(1 - \frac{1}{z})\alpha_3 {I_3}^* (w - z) \\
&\quad + D_3(1 - \frac{1}{w})\sigma {I_2}^* (z - w) + \mu {S}^* \left(2 - x - \frac{1}{x}\right)
\end{aligned}
$$

When we simplify the latter expression, then we obtain a number of terms which we would hope to vanish. These terms are:

$$
\begin{gathered}
xy(-{S}^* {I_1}^* c\beta_1 + {S}^* {I_1}^* c\beta_1 D_1) \\
xz(-{S}^* {I_2}^* c\beta_2 + {S}^* {I_2}^* c\beta_2 D_1) \\
xw(-{S}^* {I_3}^* c\beta_3 + {S}^* {I_3}^* c\beta_3 D_1) \\
y({S}^* {I_1}^* c\beta_1 - {S}^* {I_1}^* c\beta_1 D_1 - {S}^* {I_2}^* c\beta_2 D_1 - {S}^* {I_3}^* c\beta_3 D_1 + {I_1}^* k_1 D_2 - \alpha_1 {I_2}^* D_1 - \alpha_2 I_3 D_1) \\
w({S}^* {I_3}^* c\beta_3 + {I_3}^* \alpha_2 D_1 + {I_3}^* \alpha_3 D_2 - \sigma {I_2}^* D_3) \\
z({S}^* {I_2}^* c\beta_2 - {I_1}^* k_1 D_2 - {I_3}^* \alpha_3 D_2 + {I_2}^* \alpha_1 D_1 + {I_2}^* \sigma D_3.)
\end{gathered} \tag{3.8}
$$

In fact, each of these expressions becomes zero if we choose the following values for the coefficients D_i:

$$
\begin{gathered}
D_1 = 1, \\
D_2 = \frac{c\beta_2 I_2^* {S}^* + c\beta_3 I_3^* {S}^* + I_3^* \alpha_2 + \alpha_1 I_2^*}{I_1^* k_1}, \\
D_3 = \frac{c\beta_3 I_3^* {S}^* + I_3^* \alpha_2 + I_3^* D_2 \alpha_3}{\sigma I_2^*}.
\end{gathered}
$$

Therefore,

$$
\begin{aligned}
\dot{V}_2 &= (\mu {S}^* + c\beta_1 I_1^* {S}^*)\left(2 - x - \frac{1}{x}\right) + c\beta_2 I_2^* {S}^* \left(3 - \frac{1}{x} - \frac{xz}{y} - \frac{y}{z}\right) \\
&\quad + c\beta_3 I_3^* {S}^* \left(4 - \frac{1}{x} - \frac{xw}{y} - \frac{y}{z} - \frac{z}{w}\right) + \alpha_1 I_2^* \left(2 - \frac{y}{z} - \frac{z}{y}\right)
\end{aligned}
$$

$$+I_3^*\alpha_2\left(3-\frac{w}{y}-\frac{y}{z}-\frac{z}{w}\right)+I_3^*D_2\alpha_3\left(2-\frac{w}{z}-\frac{z}{w}\right).$$

Note that for positive numbers a_i, the arithmetical mean is greater than or equal to the geometric mean, that is

$$\frac{a_1+a_2+...+a_n}{n} \geq \sqrt[n]{a_1a_2...a_n} \text{ for } a_i \geq 0, i = 1,..,n.$$

Thus, it follows that $(2-x-1/x) \leq 0$ for $x > 0$ and $(2-x-1/x) = 0$ if and only if $x = 1$; $\left(2-\frac{z}{y}-\frac{y}{z}\right) \leq 0$ for $y, z > 0$ and $\left(2-\frac{z}{y}-\frac{y}{z}\right) = 0$ if and only if $y = z$; $\left(3-\frac{1}{x}-\frac{xz}{y}-\frac{y}{z}\right) \leq 0$ for $x > 0$, $y > 0$, and $z > 0$ and $\left(3-\frac{1}{x}-\frac{xz}{y}-\frac{y}{z}\right) = 0$ if and only if $x = y = z = 1$; $\left(4-\frac{1}{x}-\frac{xw}{y}-\frac{y}{z}-\frac{z}{w}\right) \leq 0$ for $x > 0, y > 0, z > 0$ and $w > 0$, and $\left(4-\frac{1}{x}-\frac{xw}{y}-\frac{y}{z}-\frac{z}{w}\right) = 0$ if and only if $x = y = z = w = 1$. Therefore, $\dot{V}_2 \leq 0$, and $\dot{V}_2 = 0$ if and only if $x = y = z = w = 1$. Thus, V_2 is a Lyapunov function for system 2.2, and consequently, the endemic equilibrium Σ_* is globally asymptotically stable if $\mathcal{R}_0 > 1$.

4. Parameter analysis and numerical simulations

We perform our numerical simulation in MATLAB with parameter values obtained in Table 1 and do a projection for a period of 50 years from 2024. Some parameters are directly obtained from the literature whereas some have been estimated accordingly. For 2024, Statistics South Africa (Stats SA) estimates the mid-year population at 63.02 million people [1]. The estimated overall HIV prevalence rate is approximately 12.7% among the South African population. The total number of people living with HIV (PLWHIV) is estimated at approximately 8.0 million in 2024, including all stages of HIV and full blown HIV/AIDS. In our sample of simulations, we first technically search the initial values as in [21], and split the total between these classes to find the initial values. This consideration leads us to assign an initial value to S_0 as

$$S(t_0) = 55.02 \text{ million} \tag{4.1}$$

and (also in millions):

$$I_{1,0} = 5.11, \quad I_{2,0} = 1.43, I_{3,0} = 1.12, \quad A_0 = 0.34.$$

Life expectancy is 64.6 years and, therefore, birth and mortality rates by natural causes are taken as the inverse of life expectancy, that is, $\frac{1}{64.6}$. Based on the total population reported in [1], the recruitment rate is estimated as $\Lambda = \frac{1}{64.6} \times 63.02$. The value of c could have been very high, but we find it convenient that c is 2 (see for instance [23]). The β_s values are chosen as $\beta_1 < \beta_2 < \beta_3$ so that the transmission coefficient in the asymptomatic class should not exceed two other two. We present numerical simulations to illustrate the results obtained in Theorems 2 and 3 together with the parameter values given in Table 1.

Table 1. Description of parameters and their estimate values.

Parameters	Numerical and estimate values per year	Reference/comment
δ	0.279	[1]
α_1	0.033	Estimated, cf. [1, 22]
α_2	0.025	Estimated
α_3	0.08	Estimated
k_1	0.0125	Estimated. cf. [25]
k_2	0.01	[25]
k_3	0.0125	Estimated
σ	0.0035	Estimated
c	2	Estimate, cf. [23]
μ	$\frac{1}{64.6}$	[1]
μ_m	0.03	Estimated
μ_n	0.03	Estimated

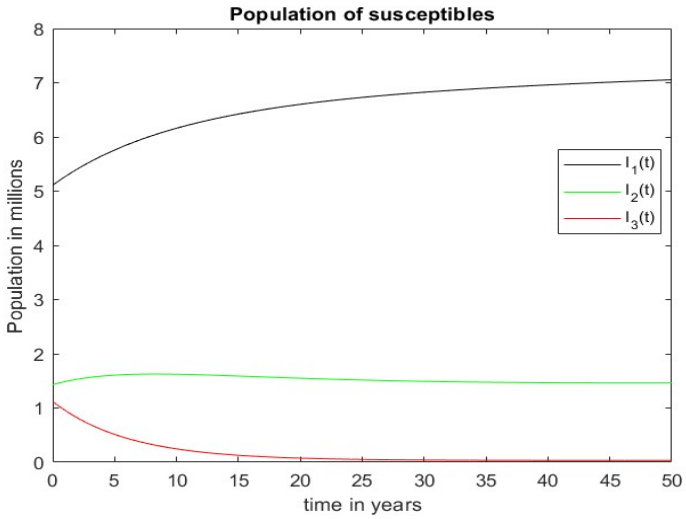

Figure 2. Population dynamics of HIV.

In Figure 2, we choose the β_s values as $\beta_1 = 0.0001, \beta_2 = 0.0005$, and $\beta_3 = 0.0008$ and plot only the classes of I_1, I_2, and I_3. In this case, the basic reproduction number is $\mathcal{R}_0 = 1.24268$ with the following endemic values $I_1^* = 9.06177, I_2^* = 1.87966, I_3^* = 0.0403659$. Thus, the disease remains at the endemic level according to Theorem 3. In Figure 3, we show the susceptible population in a separate graph and $S^* = 50.7131$. The susceptible population is decreasing because the basic reproduction number is greater than the unit. However, if the basic reproduction becomes less than then the unit, then the susceptible population will eventually increase.

In Figure 4, we show the graph of I_3 with a scenario on the values of α_2, α_3. The yellow line in Figure 4 indicates an increase of HIV-cases in the class of I_3 when $\alpha_2, \alpha_3 = 0$, whereas the red line indicates a decrease of HIV-cases when $\alpha_2, \alpha_3 \neq 0$. In other words, the transfer coefficients α_2, α_3 due

to ART or a combination of ART and an appropriate CM treatment can have a significant impact on reducing the number of infectious cases.

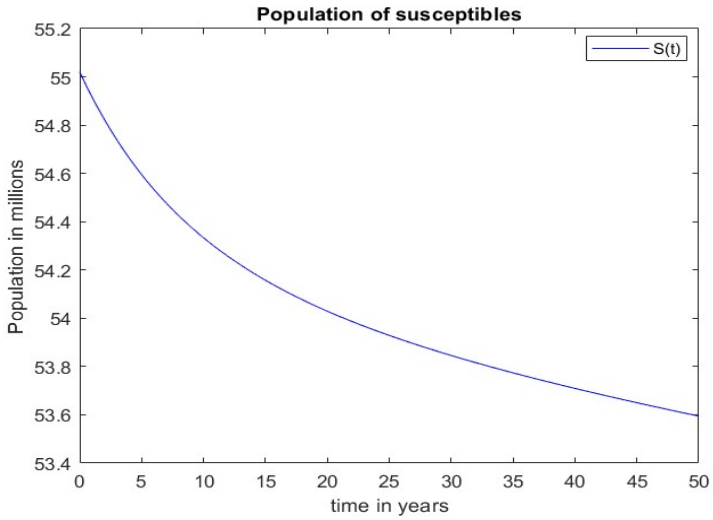

Figure 3. Population of susceptibles.

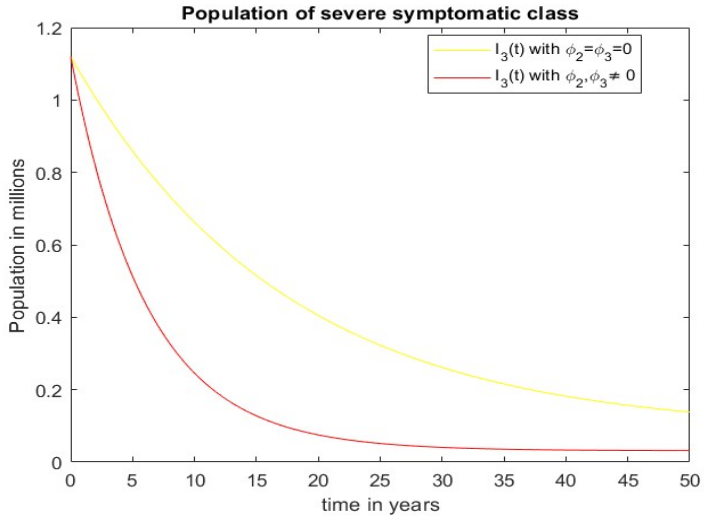

Figure 4. Population of severe symptomatic class.

5. Sensitivity analysis

By the sensitivity of a model parameter (p), we mean its effect on the values of the basic reproduction number, which is measured by the elasticity. This elasticity approximates the fractional change in the estimate of the basic reproduction number $\mathcal{R}_0$ that results from a unit fractional change in parameter (p) while keeping all other parameters constant. A highly sensitive parameter needs careful consideration because a small change might bring about a significant quantitative change. A parameter that is less sensitive may not be catastrophic because a minor change will not significantly impact the

quantity of under consideration. The elasticity index is defined as

$$\eta_p^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial p}\frac{p}{\mathcal{R}_0}.$$

For instance,

$$\eta_{\beta_1}^{\mathcal{R}_0} = \frac{\beta_1\left(\alpha_3\left(\alpha_1+k_2+\mu\right)+\left(\alpha_1+k_2+\mu+\sigma\right)\left(\alpha_2+k_3+\mu+\mu_m\right)\right)}{\beta_3 k_1\sigma+\beta_1\left(\alpha_3\left(\alpha_1+k_2+\mu\right)+\left(\alpha_1+k_2+\mu+\sigma\right)\left(\alpha_2+k_3+\mu+\mu_m\right)\right)+\Gamma_3} > 0$$

$$\eta_{\beta_2}^{\mathcal{R}_0} = \frac{\beta_2 k_1\left(\alpha_2+\alpha_3+k_3+\mu+\mu_m\right)}{\beta_3 k_1\sigma+\beta_1\left(\alpha_3\left(\alpha_1+k_2+\mu\right)+\left(\alpha_1+k_2+\mu+\sigma\right)\left(\alpha_2+k_3+\mu+\mu_m\right)\right)+\Gamma_3} > 0$$

$$\eta_{\beta_3}^{\mathcal{R}_0} = \frac{\beta_3 k_1\sigma}{\beta_3 k_1\sigma+\beta_1\left(\alpha_3\left(\alpha_1+k_2+\mu_1\right)+\left(\alpha_1+k_2+\mu+\sigma\right)\left(\alpha_2+k_3+\mu+\mu_m\right)\right)+\Gamma_3} > 0$$

$$\eta_{\sigma}^{\mathcal{R}_0} = \frac{\sigma\left(\beta_3 k_1+\beta_1\left(\alpha_2+k_3+\mu+\mu_m\right)\right)}{\beta_3 k_1\sigma+\beta_1\left(\alpha_3\left(\alpha_1+k_2+\mu\right)+\left(\alpha_1+k_2+\mu+\sigma\right)\left(\alpha_2+k_3+\mu+\mu_m\right)\right)+\Gamma_3} > 0$$

where

$$\Gamma_3 = \beta_2 k_1\left(\alpha_2+\alpha_3+k_3+\mu+\mu_m\right).$$

For the case of α_1 we have

$$\eta_{\alpha_1}^{\mathcal{R}_0} = c\Lambda\left(\frac{\beta_1\left(\alpha_2+\alpha_3+k_3+\mu+\mu_m\right)\Phi_1-\Phi_2}{\mu{\Phi_1}^2}\right)\frac{\alpha_1}{\mathcal{R}_0} < 0$$

with

$$\Phi_2 > \beta_1\left(\alpha_2+\alpha_3+k_3+\mu+\mu_m\right)\Phi_1$$

noting that

$$\begin{aligned}\Phi_1 &= \alpha_1 k_1\left(k_3+\mu+\mu_m\right)+\alpha_1\mu\left(\alpha_2+k_3+\mu+\mu_m\right)\\ &\quad+\left(\mu\left(\alpha_1+k_2+\mu\right)+k_1\left(k_2+\mu\right)\right)\left(\alpha_2+\alpha_3+k_3+\mu+\mu_m\right)\end{aligned}$$

and

$$\begin{aligned}\Phi_2 &= \left(\mu\left(\alpha_2+k_3+\mu+\mu_m\right)+\mu\left(\alpha_2+\alpha_3+k_3+\mu+\mu_m\right)+k_1\left(k_3+\mu+\mu_m\right)\right)\\ &\quad\times\left(\beta_3 k_1\sigma+\beta_1\left(\alpha_3\left(\alpha_1+k_2+\mu_1\right)+\left(\alpha_1+k_2+\mu+\sigma\right)\left(\alpha_2+k_3+\mu+\mu_m\right)\right)\right.\\ &\quad\left.+\beta_2 k_1\left(\alpha_2+\alpha_3+k_3+\mu+\mu_m\right)\right.\end{aligned}$$

(5.2)

Table 2. Parameters and indices of the basic reproduction number $\mathcal{R}_0$.

Parameters	Sensitivity index
β_1	0.484889
β_2	0.500363
β_3	0.0171925
c	+1
σ	0.0314588
μ	−0.886785
μ_m	−0.0589389
k_1	0.232233
k_2	−0.0915351
k_3	−0.0245579
α_1	−0.298591
α_2	−0.0103111
α_3	0.107028

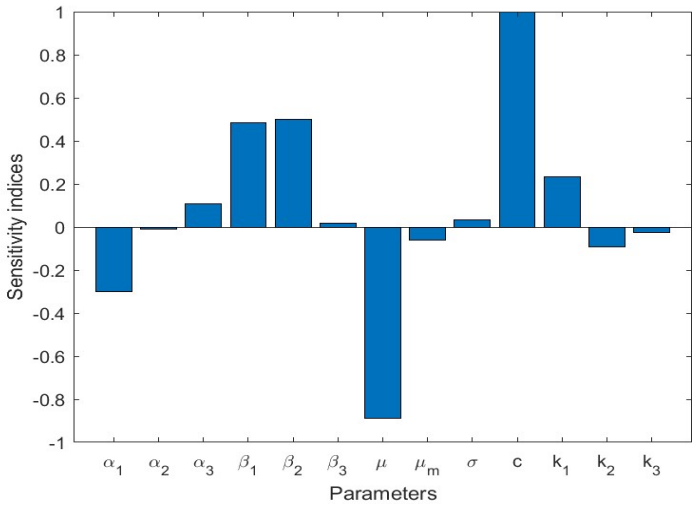

Figure 5. Bar graph of sensitivity indices of the HIV model.

Table 2 shows the sensitivity indices of the model parameters with respect to the basic reproduction number $\mathcal{R}_0$ and shows that the value of $\mathcal{R}_0$ will increase with an increase in the above parameters (or decrease, respectively). Some of the parameters have a direct effect on the value of $\mathcal{R}_0$, while others have an inverse relationship with $\mathcal{R}_0$, which can also be seen in Figure 5. The Sensitivity analysis shows that c is the most sensitive parameter of the model system 2.2 since its sensitivity index is +1 and it is the highest value of all the sensitivity indices. Parameters β_1, β_2, and β_3 also positively impact the basic reproduction number. Increasing (or decreasing) the values of β_s will lead to increasing (or decreasing) the basic reproduction number, as observed in Table 2.

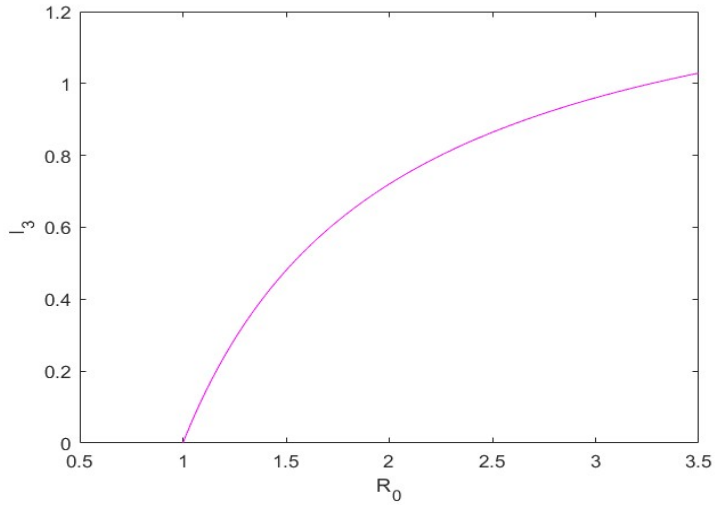

Figure 6. Plot of the basic reproduction number vs I_3.

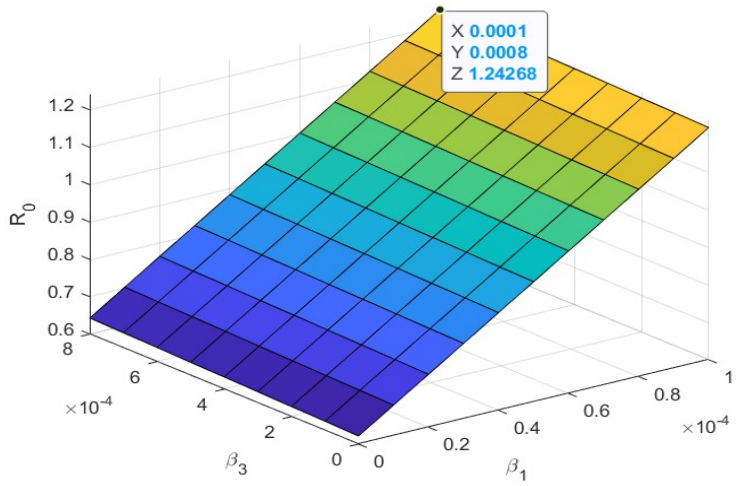

Figure 7. Plot of the basic reproduction number vs β_1 and β_3.

We now show that the class of I_3^* has a direct relationship with $\mathcal{R}_0$ (see for instance Figure 6 below), whereas S^* has an inverse relationship with $\mathcal{R}_0$. Note that from 3.6 and 3.7, we obtain

$$\mathcal{R}_0 = \frac{\Lambda\mu k_1\sigma}{(\Lambda\mu k_1\sigma - \Gamma_1 I_3^*)} \text{ and } \mathcal{R}_0 = \frac{N}{S^*}.$$

Therefore, we have

$$\eta_{I_3^*}^{\mathcal{R}_0} = \frac{\Lambda\mu k_1\sigma\Gamma_1}{(\Lambda k_1\mu\sigma - \Gamma_1 I_3^*)^2}\frac{I_3^*}{\mathcal{R}_0} > 0 \text{ and } \eta_{S^*}^{\mathcal{R}_0} = -\frac{N}{(S^*)^2}\frac{S^*}{\mathcal{R}_0} = -\frac{N}{S^*}\frac{1}{\mathcal{R}_0} < 0.$$

We can gain significant insights from the study of sensitivity analysis. Thus, this study helps identify the input parameters that play an important role in the influence of disease dynamics, understand

uncertainties in model predictions, and in decision making. In Figures 7 and 8, we display the graphs of the basic reproduction versus parameters values such as β_1, β_2, μ, and α_1.

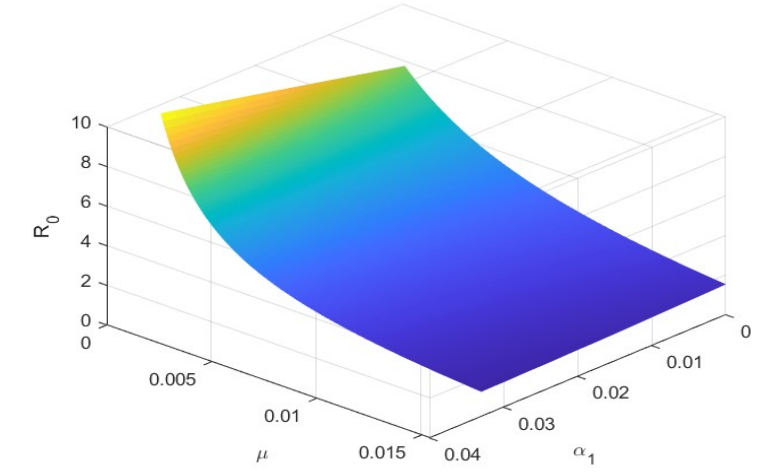

Figure 8. Plot of the basic reproduction number vs μ and α_1.

6. Concluding remarks

In this research, we formulate a mathematical model that explains the population dynamics of HIV/AIDS with mild, moderate, and severe stages of infections. In the model, it is assumed that people in the severe stage of infections would develop OIs such as CM due to lack of adequate treatment or inappropriate care. The model system behaved well, and we proved the existence of positive solutions. Thereafter, we performed stability analysis of the disease-free as well as endemic equilibrium points of the model. In addition, we studied the sensitivity analysis of the model parameters to see the impact of each of these parameters on the basic reproduction number. Moreover, there has been a direct and inverse relationship of parameters of the model with the basic reproduction number, as displayed in Table 2 and Figure 5. We illustrate the theoretical results, especially Theorem 3, by means of numerical simulations. It was noted that many people with HIV can develop opportunistic infections due to not knowing their HIV status or may not be on ART, and that ART may not keep their HIV levels low enough for their immune system to fight off infections. HIV patients need to be aware of common opportunistic infections so that they receive the best advice and necessary treatment recommendations. Therefore, early diagnosis of HIV infection and early initiation of ART before immunosuppression can be beneficial among HIV patients with low CD4 counts. This is also the best strategy to reduce the incidence of opportunistic infections and their associated mortality.

Our primary aim of this paper was to construct a model that addresses the questions mentioned, and to show that the model is mathematically sound. Thereafter, we supplemented it with illustrative simulations. In the literature, we could not find the correct data to sufficiently and accurately determine numerical values for all the parameters. This was a drawback. The utility of the model will be enhanced if this matter of its calibration can be resolved.

Modeling of infectious diseases often requires interdisciplinary work. Therefore, some communication difficulties arise. For instance, estimating the exact number of people who are on HIV-CM

treatment can be very challenging because OIs include many infectious diseases. Although CM is very deadly among these infectious diseases, specific related data on HIV-CM are not easily obtainable. In addition, our model also relies on the population dynamics of HIV than for instance on how HIV attacks a type of immune system cell in the body. Nowadays, modeling with stochastic differential equations has become undeniable because randomness does feature in real world settings. There is currently no vaccine to cure HIV completely, but the implementation of ART and the use of PREP have been very promising worldwide. Therefore, stochastic modeling with viral load suppression of HIV would also yield interesting results.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare there is no conflict of interest regarding the publication of this article.

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