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GLOBAL STABILITY OF HIV-1 AND HIV-2 MODEL WITH DRUG RESISTANCE COMPARTMENT

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Abstract. In this paper we propose a new mathematical model describing the dynamics of the human immunodeficiency virus 1 and 2 with drug resistant compartment. We proved the positivity and boundedness of solutions with non-negative initial conditions. The dynamical system admits four equilibrium states: free equilibrium disease, one endemic equilibrium of each strain and one of the two strains. Two basic reproduction numbers are calculated. The global stability of the four equilibrium points is proved by using suitable Lyapunov functions. Numerical simulations were carried out to illustrate our results and a parameter sensitivity analysis completed this work.

Keywords: HIV-1; HIV-2; drug therapy; basic reproduction number; stability; sensitivity analysis.
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1. INTRODUCTION

Human Immunodeficiency Virus infection remains a major public health problem of global proportions, resulting in nearly 33 million deaths to date [1]. However, with improved access to

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effective prevention, diagnosis, treatment and care, including for opportunistic infections, HIV infection has become a chronic condition that can be managed with the assurance of a long and healthy life, and is classified into two types: HIV-1 and HIV-2. HIV-1 was first discovered and is more prevalent worldwide, while HIV-2 is less pathogenic and is largely housed in West Africa. So when we generally say HIV, we refer to HIV-1. The main differences between HIV-1 and HIV-2 infections lie in the mechanism of retroviral pathogenesis, which is not entirely clear yet, but they have the same symptoms. The advanced stage of HIV infection is the Acquired Immunodeficiency Syndrome (AIDS). There is no vaccine or cure for HIV infection. However, effective antiretroviral drugs (ART) can control the virus, help prevent its transmission to uninfected people and prolong the lives of infected people who receive treatment. Globally 38 million people were living with HIV at the end of 2019 [1]. HIV has great genetic diversity. This genetic diversity of HIV can pose diagnostic and therapeutic problems. Typically HIV mutates and prodiges resistant strains that are no longer sensitive to drug therapy resulting to change drug or the inability to find pharmaceutical that provide effective treatment. HIV drug resistant (HIV-DR) resistance differs between HIV-1 and HIV-2 infection. Therefore, it is recommended to ensure that the differentiation between HIV-1 and HIV-2 is correctly carried out at the time of HIV diagnosis. This is essential in order to use the appropriate and specific virological monitoring tests and to choose an appropriate. Currently World Health Organization (WHO) [1] is developing a new five-tear global action plan for 2017-2021 to support a coordinated emergence of HIV drug resistance, and to strengthen country efforts to achieve the global HIV targets treatment [2].

Mathematical modelling is an important tool for describing and understanding the dynamics of numerous infectious diseases, which allows monitoring. The classical mathematical model for infectious diseases is the compartment model, first proposed by Kermack and McKendric in the year of 1927, in which, individuals are divided into multiple compartments dependent on their epidemiological status [3]. Since then, several mathematical models have been proposed for HIV/ AIDS transmission dynamics to find out the mechanism of HIV transmission and to determine the effective measures in preventing and controlling the spread of HIV/AIDS [4],[5], [6],[7], [8].

In [9] the author's derived HIV therapeutic strategies by formulating and analyzing an optimal control problem using two types of dynamics treatments while [10] investigated the fundamental role

of chemotherapy treatment in controlling the virus reproduction in an HIV patient. Moreover, [11] presented the impact of optimal control on the treatment of HIV/AIDS and screening of unaware infectives on the transmission dynamics of the disease in a homogeneous population with constant immigration of susceptible incorporating use of condom, screening of unaware infectives and treatment of the infected. And the authors in [12] proposed a new epidemiological model for HIV/AIDS transmission including PrEP and study a control problem to determine the PrEP strategy that satisfies the mixed state control constraint and minimizes the number of individuals with pre-AIDS HIV infection balanced against the costs associated with PrEP. Most recently, Gurmu et all. [13] studied the role of passive immunity and drug therapy in reducing the replication and transmission of the disease for a mathematical model of HIV/AIDS transmission dynamics with drug resistance compartment.

In this work, we continue the investigation of this last kind of problems by taking into account two-strain HIV-1 and HIV-2 model with drug resistance compartment. In our paper we will establish the global stability of all our two-strain HIV model equilibria.

The rest of the paper is organized as follows. In the next section, we introduce the HIV-1 and HIV-2 model with drug resistance compartment, and we show the positivity and boundedness of the solutions of our model with positive initial conditions. In section 3, we calculate the basic reproduction number, and we study the global stability of the equilibria. Section 4 presents numerical simulations to assess the dynamics of a HIV-1 and HIV-2 transmission with drug resistance compartment. The sensitivity analysis of the basic reproduction number with respect to the parameters of our model is given in Section 5. Finally, a brief conclusion sums up the paper.

2. Model Formulation and Basic Properties

2.1. Mathematical model. In this section, we will propose a mathematical model describing the transmission dynamics of the HIV-1 and HIV-2 with drug resistance compartment. The total population noted $N(t)$ subdivides into six compartments, namely, susceptible individuals (S), HIV-1 infected individuals (I_1), HIV-2 infected individuals (I_2), drug resistance individuals (D_R), AIDS individuals (A) and removed individuals (R).

The dynamics of the model described by the following nonlinear system of differential equations :

$$
\begin{cases}
S'(t) = \Lambda - \beta_1 S I_1 - \beta_2 S I_2 - \mu S, \\
I_1'(t) = \beta_1 S I_1 - (\theta_1 + \omega_1 + \mu) I_1, \\
I_2'(t) = \beta_2 S I_2 - (\theta_2 + \omega_2 + \mu) I_2, \\
D_R'(t) = \omega_1 I_1 + \omega_2 I_2 - (1-\rho)\eta D_R - (\eta\rho + \mu) D_R, \\
A'(t) = (1-\rho)\eta D_R + \theta_1 I_1 + \theta_2 I_2 - (d+\mu) A, \\
R'(t) = \eta\rho D_R - \mu R,
\end{cases} \tag{2.1}
$$

with :

$$
S(0) \geqslant 0, I_1(0) \geqslant 0, I_2(0) \geqslant 0, D_R(0) \geqslant 0, A(0) \geqslant 0, R(0) \geqslant 0. \tag{2.2}
$$

The corresponding flow chart and description of the parameters for the model (2.1) are given in figure 1 and table 1, respectively.

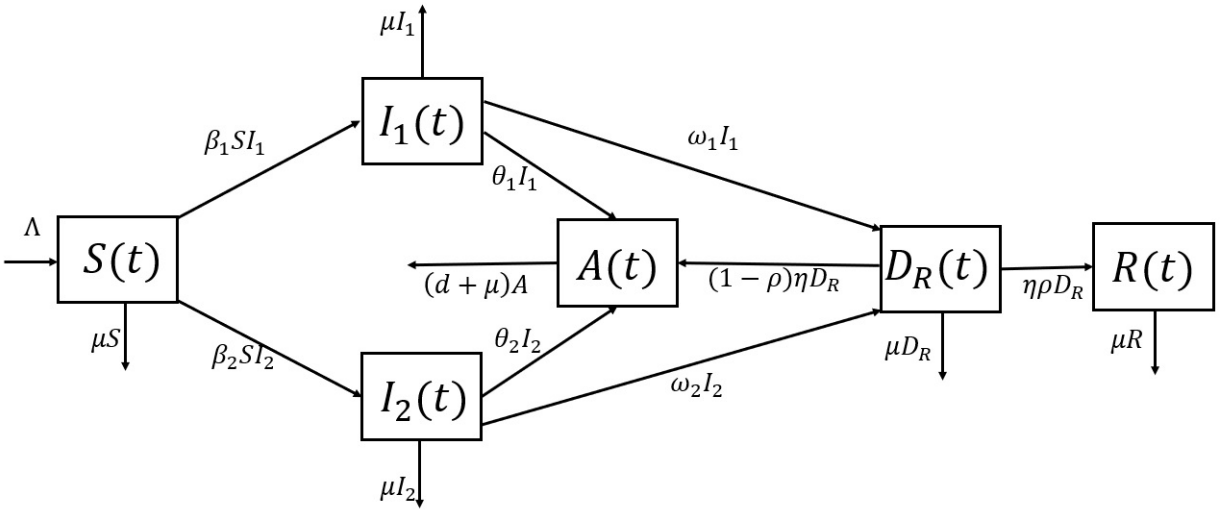

FIGURE 1. Flow diagram of the model (2.1)

Table 1. Model parameters and their interpretations.

Parameter	Description
Λ	Recruitment rate
μ	Natural death rate
β_1	Infection rate of the HIV-1 strain
β_2	Infection rate of the HIV-2 strain
θ_1	Rate at which HIV-1 infected people progress to AIDS stage
θ_2	Rate at which HIV-2 infected people progress to AIDS stage
ω_1	Progression rate from HIV-1 to drug resistance compartment
ω_2	Progression rate from HIV-2 to drug resistance compartment
ρ	Therapy efficacy
η	Removed rate of drug resistance.
d	AIDS induced death rate

2.2. Positivity and boundedness of solutions. All variables of our model represent the populations classes, they can not become negative at any stage. Therefore, it is important to verify the following theorem.

Theorem 1. *The solutions* $(S(t),I_1(t),I_2(t),D_R(t),A(t),R(t))$ *of the model* (2.1) *are positive for all* $t \geqslant 0$ *with non-negative initial conditions* (2.2) *in* $\mathbb{R}^6_+$.

Proof. We have

$$
\begin{cases}
S'(t)\mid_{S(t)=0} = \Lambda \geqslant 0 \\
I_1'(t)\mid_{I_1(t)=0} = 0 \\
I_2'(t)\mid_{I_2(t)=0} = 0 \\
D_R'(t)\mid_{D_R(t)=0} = \omega_1 I_1 + \omega_2 I_2 \geqslant 0 \\
A'(t)\mid_{A(t)=0} = (1-\rho)\eta D_R + \theta_1 I_1 + \theta_2 I_2 \geqslant 0 \\
R'(t)\mid_{R(t)=0} = \eta\rho D_R \geqslant 0
\end{cases} \tag{2.3}
$$

According to Lemma 2 in [14], the positivity of all solutions initiating in $\mathbb{R}^6_+$ under positive initial conditions is guaranteed. □

Theorem 2. *The biologically region*

$$\Omega = \{(S, I_1, I_2, D_R, A, R) \in \mathbb{R}^6_+ : N \leqslant \frac{\Lambda}{\mu}\}$$

is positively invariant for the model (2.1) *in* $\mathbb{R}^6_+$.

Proof. Let $N(t) = S(t) + I_1(t) + I_2(t) + D_R(t) + A(t) + R(t)$, we have

$$\begin{aligned} \frac{dN}{dt} &= \Lambda - \mu N - dA \leqslant \Lambda - \mu N \\ &\Rightarrow \frac{dN}{dt} + \mu N \leq \Lambda \\ &\Rightarrow 0 \leq N \leq \frac{\Lambda}{\mu} + N(0)e^{-\mu t} \end{aligned}$$

For $t \to \infty$, $0 \leq N \leq \frac{\Lambda}{\mu}$. Therefore, $N(t)$ is bounded, and all the solutions of the model (2.1) starting in Ω confined within the region. This completes the proof. □

3. Model Analysis

3.1. Basic Reproduction Number R_0. The basic reproduction number, denoted R_0, is one of the most important concepts about the dynamics of epidemic models, which represents the expected number of secondary cases caused by a typical infected individual in a completely susceptible population [15].

Mathematically the basic reproduction number is defined as a spectral radius of the next generation matrix FV^{-1} [16]: $R_0 = \rho(FV^{-1})$, where F is the non-negative matrix of the new infection terms, and V is the matrix of the transition infections associated.

In our model, the infected compartments are I_1, I_2 and A, then the matrices F and V are :

$$F = \begin{pmatrix} \beta_1 \frac{\Lambda}{\mu} & 0 & 0 \\ 0 & \beta_2 \frac{\Lambda}{\mu} & 0 \\ 0 & 0 & 0 \end{pmatrix} \text{ and } V = \begin{pmatrix} \theta_1 + \omega_1 + \mu & 0 & 0 \\ 0 & \theta_2 + \omega_2 + \mu & 0 \\ -\theta_1 & -\theta_2 & d + \mu \end{pmatrix}$$

The dominant eigenvalues of FV^{-1} are :

$$R_0^1 = \frac{\beta_1 \Lambda}{\mu(\theta_1 + \omega_1 + \mu)} \text{ and } R_0^2 = \frac{\beta_2 \Lambda}{\mu(\theta_2 + \omega_2 + \mu)}$$

Consequently, the basic reproduction number of model (2.1) is : $R_0 = \max\{R_0^1, R_0^2\}$.

3.2. Model steady states. The model (2.1) admits four equilibrium points, whose one disease-free equilibrium (DFE) and three endemic equilibrium as follows :

- The disease-free equilibrium $\mathscr{E}_f = (S^*, I_1^*, I_2^*, D_R^*, A^*, R^*) = (\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0)$
- The HIV-1 only endemic equilibrium exist when $R_0^1 > 1$, and is given by $\mathscr{E}_{S_1} = (S_1^*, I_{1,1}^*, 0, D_{R,1}^*, A_1^*, R_1^*)$ where :
  $S_1^* = \frac{\theta_1+\omega_1+\mu}{\beta_1}$; $I_{1,1}^* = \frac{\mu}{\beta_1}(R_0^1 - 1)$; $D_{R,1}^* = \frac{\omega_1}{\eta+\mu} I_{1,1}^*$; $A_1^* = \frac{1}{d+\mu}\left[(1-\rho)\eta\frac{\omega_1}{\eta+\mu} + \theta_1\right] I_{1,1}^*$
  and $R_1^* = \frac{\eta\rho\omega_1}{\mu(\eta+\mu)} I_{1,1}^*$
- The HIV-2 only endemic equilibrium exists when $R_0^2 > 1$, and is given by $\mathscr{E}_{S_2} = (S_2^*, 0, I_{2,2}^*, D_{R,2}^*, A_2^*, R_2^*)$ where :
  $S_2^* = \frac{\theta_2+\omega_2+\mu}{\beta_2}$; $I_{2,2}^* = \frac{\mu}{\beta_2}(R_0^2 - 1)$; $D_{R,2}^* = \frac{\omega_2}{\eta+\mu} I_{2,2}^*$; $A_2^* = \frac{1}{d+\mu}\left[(1-\rho)\eta\frac{\omega_2}{\eta+\mu} + \theta_2\right] I_{2,2}^*$
  and $R_2^* = \frac{\eta\rho\omega_2}{\mu(\eta+\mu)} I_{2,2}^*$
- The interior endemic equilibrium point for the model (2.1) is given by $\mathscr{E}_{S_t} = (S_t^*, I_{1,t}^*, I_{2,t}^*, D_{R,t}^*, A_t^*, R_t^*)$ where :
  $S_t^* = \frac{1}{\mu}\left(\Lambda - (\theta_1+\omega_1+\mu) I_{1,t}^* - (\theta_2+\omega_2+\mu) I_{2,t}^*\right) = \frac{1}{\mu}\left(\Lambda - \frac{\beta_1 \frac{\Lambda}{\mu}}{R_0^1} I_{1,t}^* - \frac{\beta_2 \frac{\Lambda}{\mu}}{R_0^2} I_{2,t}^*\right)$;
  $D_{R,t}^* = \frac{\omega_1 I_{1,t}^* + \omega_2 I_{2,t}^*}{\eta+\mu}$;
  $A_t^* = \left(\frac{(1-\rho)\eta}{\eta+\mu} + \theta_1\right) I_{1,t}^* + \left(\frac{(1-\rho)\eta}{\eta+\mu} + \theta_2\right) I_{2,t}^*$;
  $R_t^* = (\frac{\eta\rho}{\mu})\frac{\omega_1 I_{1,t}^* + \omega_2 I_{2,t}^*}{\eta+\mu}$
  with $\Lambda \geq \frac{\beta_1 \frac{\Lambda}{\mu}}{R_0^1} I_{1,t}^* + \frac{\beta_2 \frac{\Lambda}{\mu}}{R_0^2} I_{2,t}^*$.

3.3. Global stability. In this section, we will prove the global stability of the equilibrium points.

Theorem 3. *If $R_0 \leq 1$, the disease-free equilibrium point $\mathscr{E}_f$ is globally asymptotically stable.*

Proof. We define a Lyapunov Function V_0 as follows : $V_0 = \frac{1}{\theta_1+\omega_1+\mu} I_1 + \frac{1}{\theta_2+\omega_2+\mu} I_2$

The derivative of V_0 is given by :

$\dot{V}_0 = \frac{1}{\theta_1+\omega_1+\mu}\dot{I}_1 + \frac{1}{\theta_2+\omega_2+\mu}\dot{I}_2 = (R_0^1 - 1) I_1 + (R_0^2 - 1) I_2$

If $R_0 \leq 1$, we obtain $\dot{V}_0 \leq 0$, thus the disease-free equilibrium $\mathscr{E}_f$ is globally asymptotically stable.

□

Theorem 4. *The HIV-1 only endemic equilibrium $\mathscr{E}_{S_1}$ is globally asymptotically stable if $R_0^2 \leqslant 1 < R_0^1$.*

Proof. Consider the following Lyapunov function :

$$\begin{aligned} V_1 &= (S-S_1^*-S_1^*\ln S)+(I_1-I_{1,1}^*-I_{1,1}^*\ln I_1)+(D_R-D_{R,1}^*-D_{R,1}^*\ln D_R)+(A-A_1^*-A_1^*\ln A) \\ &+ (R-R_1^*-R_1^*\ln R) \end{aligned}$$

Differentiating V_1 with respect to time gives :

$$\dot{V}_1 = (1-\frac{S_1^*}{S})\dot{S}+(1-\frac{I_{1,1}^*}{I_1})\dot{I}_1+(1-\frac{D_{R,1}^*}{D_R})\dot{D}_R+(1-\frac{A_1^*}{A})\dot{A}+(1-\frac{R_1^*}{R})\dot{R}$$

Substituting the expressions for the derivatives in $\dot{V}_1$, it follows from 2.1 that

$$\begin{aligned} \dot{V}_1 &= (1-\frac{S_1^*}{S})\Big[\Lambda-\beta_1 SI_1-\mu S\Big]+(1-\frac{I_{1,1}^*}{I_1})\Big[\beta_1 SI_1-(\theta_1+\omega_1+\mu)I_1\Big] \\ &+(1-\frac{D_{R,1}^*}{D_R})\Big[\omega_1 I_1-(1-\rho)\eta D_R-(\eta\rho+\mu)D_R\Big] \\ &+(1-\frac{A_1^*}{A})\Big[(1-\rho)\eta D_R+\theta_1 I_1-(d+\mu)A)\Big]+(1-\frac{R_1^*}{R})\Big[\eta\rho D_R-\mu R\Big] \end{aligned}$$

We have $\Lambda=\beta_1 S_1^* I_{1,1}^*+\mu S_1^*$ from the first equation of 2.1 at steady-state $\mathscr{E}_{S_1}$, therefore, $\dot{V}_1$ can be written as

$$\begin{aligned} \dot{V}_1 &= (1-\frac{S_1^*}{S})\Big[\beta_1 S_1^* I_{1,1}^*+\mu S_1^*-\beta_1 SI_1-\mu S\Big]+(1-\frac{I_{1,1}^*}{I_1})\Big[\beta_1 SI_1-(\theta_1+\omega_1+\mu)I_1\Big] \\ &+(1-\frac{D_{R,1}^*}{D_R})\Big[\omega_1 I_1-(1-\rho)\eta D_R-(\eta\rho+\mu)D_R\Big] \\ &+(1-\frac{A_1^*}{A})\Big[(1-\rho)\eta D_R+\theta_1 I_1-(d+\mu)A)\Big]+(1-\frac{R_1^*}{R})\Big[\eta\rho D_R-\mu R\Big] \end{aligned}$$

then, $\dot{V}_1$ can be simplified to :

$$\begin{aligned} \dot{V}_1 &= \beta_1 S_1^* I_{1,1}^*\Big(1-\frac{I_1}{I_{1,1}^*}\frac{S_1^*}{S}\Big)+\beta_1 S_1^* I_1\Big(1-\frac{S}{S_1^*}\frac{I_{1,1}^*}{I_1}\Big)+\mu S_1^*\Big(2-\frac{S_1^*}{S}-\frac{S}{S_1^*}\Big) \\ &+\theta_1 I_{1,1}^*\Big(1-\frac{I_1}{I_{1,1}^*}\frac{A_1^*}{A}\Big)+\omega_1 I_{1,1}^*\Big(1-\frac{I_1}{I_{1,1}^*}\frac{D_{R,1}^*}{D_R}\Big)+\mu I_{1,1}^*\Big(1-\frac{I_1}{I_{1,1}^*}\Big) \\ &+(1-\rho)\eta D_{R,1}^*\Big(1-\frac{D_R}{D_{R,1}^*}\frac{A_1^*}{A}\Big)+\eta\rho D_{R,1}^*\Big(1-\frac{R_1^*}{R}\frac{D_R}{D_{R,1}^*}\Big)+\mu D_{R,1}^*\Big(1-\frac{D_R}{D_{R,1}^*}\Big) \\ &+(d+\mu)A_1^*\Big(1-\frac{A}{A_1^*}\Big)+\mu R_1^*\Big(1-\frac{R}{R_1^*}\Big) \end{aligned}$$

This implies $\dot{V}_1 < 0$, by the relation between geometric and arithmetic means. The equality $\dot{V}_1 = 0$ holds if and only if (S, I_1, I_2, D_R, A, R) take the equilibrium values $(S_1^*, I_{1,1}^*, 0, D_{R,1}^*, A_1^*, R_1^*)$. Therefore, by LaSalle's Invariance Principle [18], the endemic equilibrium $\mathscr{E}_{S_1}$ is globally asymptotically stable. □

Theorem 5. *The HIV-2 only endemic equilibrium $\mathscr{E}_{S_2}$ is globally asymptotically stable if $R_0^1 \leqslant 1 < R_0^2$.*

Proof. Consider the following Lyapunov function :

$$\begin{aligned} V_2 &= (S - S_2^* - S_2^* \ln S) + (I_2 - I_{2,2}^* - I_{2,2}^* \ln I_2) + (D_R - D_{R,2}^* - D_{R,2}^* \ln D_R) + (A - A_2^* - A_2^* \ln A) \\ &+ (R - R_2^* - R_2^* \ln R) \end{aligned}$$

Differentiating V_2 with respect to time gives :

$$\dot{V}_2 = (1 - \frac{S_2^*}{S})\dot{S} + (1 - \frac{I_{2,2}^*}{I_2})\dot{I}_2 + (1 - \frac{D_{R,2}^*}{D_R})\dot{D}_R + (1 - \frac{A_2^*}{A})\dot{A} + (1 - \frac{R_2^*}{R})\dot{R}$$

Substituting the expressions for the derivatives in $\dot{V}_2$, it follows from 2.1 that

$$\begin{aligned} \dot{V}_2 &= (1 - \frac{S_2^*}{S})\Big[\Lambda - \beta_2 S I_2 - \mu S\Big] + (1 - \frac{I_{2,2}^*}{I_2})\Big[\beta_2 S I_2 - (\theta_2 + \omega_2 + \mu) I_2\Big] \\ &+ (1 - \frac{D_{R,2}^*}{D_R})\Big[\omega_2 I_2 - (1-\rho)\eta D_R - (\eta\rho + \mu) D_R\Big] \\ &+ (1 - \frac{A_2^*}{A})\Big[(1-\rho)\eta D_R + \theta_2 I_2 - (d+\mu)A)\Big] + (1 - \frac{R_2^*}{R})\Big[\eta\rho D_R - \mu R\Big] \end{aligned}$$

We have $\Lambda = \beta_2 S_2^* I_{2,2}^* + \mu S_2^*$ from the first equation of 2.1 at steady-state $\mathscr{E}_{S_2}$, therefore, $\dot{V}_2$ can be written as

$$\begin{aligned} \dot{V}_2 &= (1 - \frac{S_2^*}{S})\Big[\beta_2 S_2^* I_{2,2}^* + \mu S_2^* - \beta_2 S I_2 - \mu S\Big] + (1 - \frac{I_{2,2}^*}{I_2})\Big[\beta_2 S I_2 - (\theta_2 + \omega_2 + \mu) I_2\Big] \\ &+ (1 - \frac{D_{R,2}^*}{D_R})\Big[\omega_2 I_2 - (1-\rho)\eta D_R - (\eta\rho + \mu) D_R\Big] \\ &+ (1 - \frac{A_2^*}{A})\Big[(1-\rho)\eta D_R + \theta_2 I_2 - (d+\mu)A)\Big] + (1 - \frac{R_2^*}{R})\Big[\eta\rho D_R - \mu R\Big] \end{aligned}$$

then, $\dot{V}_2$ can be simplified to :

$$\begin{aligned}\dot{V}_2 &= \beta_2 S_2^* I_{2,2}^* \Big(1-\frac{I_2}{I_{2,2}^*}\frac{S_2^*}{S}\Big)+\beta_2 S_2^* I_2\Big(1-\frac{S}{S_2^*}\frac{I_{2,2}^*}{I_2}\Big)+\mu S_2^*\Big(2-\frac{S_2^*}{S}-\frac{S}{S_2^*}\Big)\\ &+\theta_2 I_{2,2}^*\Big(1-\frac{I_2}{I_{2,2}^*}\frac{A_2^*}{A}\Big)+\omega_2 I_{2,2}^*\Big(1-\frac{I_2}{I_{2,2}^*}\frac{D_{R,2}^*}{D_R}\Big)+\mu I_{2,2}^*\Big(1-\frac{I_2}{I_{2,2}^*}\Big)\\ &+(1-\rho)\eta D_{R,2}^*\Big(1-\frac{D_R}{D_{R,2}^*}\frac{A_2^*}{A}\Big)+\eta\rho D_{R,2}^*\Big(1-\frac{R_2^*}{R}\frac{D_R}{D_{R,2}^*}\Big)+\mu D_{R,2}^*\Big(1-\frac{D_R}{D_{R,2}^*}\Big)\\ &+(d+\mu)A_2^*\Big(1-\frac{A}{A_2^*}\Big)+\mu R_2^*\Big(1-\frac{R}{R_2^*}\Big)\end{aligned}$$

This implies $\dot{V}_2 < 0$, by the relation between geometric and arithmetic means. The equality $\dot{V}_2 = 0$ holds if and only if (S, I_1, I_2, D_R, A, R) take the equilibrium values $(S_2^*, I_{2,2}^*, 0, D_{R,2}^*, A_2^*, R_2^*)$. Therefore, by LaSalle's Invariance Principle [18], the endemic equilibrium $\mathscr{E}_{S_2}$ is globally asymptotically stable. □

Theorem 6. *The interior endemic equilibrium $\mathscr{E}_{S_t}$ is globally asymptotically stable if $R_0 > 1$.*

Proof. Consider the following Lyapunov function :

$$\begin{aligned}V_t &= (S-S_t^*-S_t^*\ln S)+(I_1-I_{1,t}^*-I_{1,t}^*\ln I_1)+(I_2-I_{2,t}^*-I_{2,t}^*\ln I_2)\\ &+(D_R-D_{R,t}^*-D_{R,t}^*\ln D_R)+(A-A_t^*-A_t^*\ln A)+(R-R_t^*-R_t^*\ln R)\end{aligned}$$

Differentiating V_t with respect to time gives :

$$\dot{V}_t = (1-\frac{S_t^*}{S})\dot{S}+(1-\frac{I_{1,t}^*}{I_1})\dot{I}_1+(1-\frac{I_{2,t}^*}{I_2})\dot{I}_2+(1-\frac{D_{R,t}^*}{D_R})\dot{D}_R+(1-\frac{A_t^*}{A})\dot{A}+(1-\frac{R_t^*}{R})\dot{R}$$

Substituting the expressions for the derivatives in $\dot{V}_t$, it follows from 2.1 that

$$\begin{aligned}\dot{V}_t &= (1-\frac{S_t^*}{S})\Big[\Lambda-\beta_1 S I_1-\beta_2 S I_2-\mu S\Big]+(1-\frac{I_{1,t}^*}{I_1})\Big[\beta_1 S I_1-(\theta_1+\omega_1+\mu)I_1\Big]\\ &+(1-\frac{I_{2,t}^*}{I_2})\Big[\beta_2 S I_2-(\theta_2+\omega_2+\mu)I_2\Big]+(1-\frac{D_{R,1}^*}{D_R})\Big[\omega_1 I_1+\omega_2 I_2-(1-\rho)\eta D_R-(\eta\rho+\mu)D_R\Big]\\ &+(1-\frac{A_t^*}{A})\Big[(1-\rho)\eta D_R+\theta_1 I_1+\theta_2 I_2-(d+\mu)A\Big]+(1-\frac{R_t^*}{R})\Big[\eta\rho D_R-\mu R\Big]\end{aligned}$$

We have $\Lambda = \beta_1 S_t^* I_{1,t}^* + \beta_1 S_t^* I_{2,t}^* + \mu S_t^*$ from the first equation of 2.1 at steady-state $\mathscr{E}_{S_t}$, therefore, $\dot{V}_t$ can be written as

$$\begin{aligned}
\dot{V}_t &= (1-\frac{S_t^*}{S})\Big[\beta_1 S_t^* I_{1,t}^* + \beta_1 S_t^* I_{2,t}^* + \mu S_t^* - \beta_1 S I_1 - \beta_2 S I_2 - \mu S\Big] + (1-\frac{I_{1,t}^*}{I_1})\Big[\beta_1 S I_1 - (\theta_1+\omega_1+\mu) I_1\Big] \\
&+(1-\frac{I_{2,t}^*}{I_2})\Big[\beta_2 S I_2 - (\theta_2+\omega_2+\mu) I_2\Big] + (1-\frac{D_{R,t}^*}{D_R})\Big[\omega_1 I_1 + \omega_2 I_2 - (1-\rho)\eta D_R - (\eta\rho+\mu) D_R\Big] \\
&+(1-\frac{A_t^*}{A})\Big[(1-\rho)\eta D_R + \theta_1 I_1 + \theta_2 I_2 - (d+\mu) A\Big] + (1-\frac{R_t^*}{R})\Big[\eta\rho D_R - \mu R\Big]
\end{aligned}$$

which can then be simplified to

$$\begin{aligned}
\dot{V}_t &= \beta_1 S_t^* I_1\Big(1-\frac{S}{S_t^*}\frac{I_{1,t}^*}{I_1}\Big) + \beta_2 S_t^* I_2\Big(1-\frac{S}{S_t^*}\frac{I_{2,t}^*}{I_2}\Big) + \Big(\beta_1 S_t^* I_{1,t}^* + \beta_2 S_t^* I_{2,t}^*\Big)\Big(1-\frac{S_t^*}{S}\Big) \\
&+\mu S_t^*\Big(2-\frac{S_t^*}{S}-\frac{S}{S_t^*}\Big) + \theta_1 I_{1,t}^*\Big(1-\frac{I_1}{I_{1,t}^*}\frac{A_t^*}{A}\Big) + \theta_2 I_{2,t}^*\Big(1-\frac{I_2}{I_{2,t}^*}\frac{A_t^*}{A}\Big) \\
&+\omega_1 I_{1,t}^*\Big(1-\frac{I_1}{I_{1,t}^*}\frac{D_{R,t}^*}{D_R}\Big) + \omega_2 I_{2,t}^*\Big(1-\frac{I_2}{I_{2,t}^*}\frac{D_{R,t}^*}{D_R}\Big) + \mu I_{1,t}^*\Big(1-\frac{I_1}{I_{1,t}^*}\Big) + \mu I_{2,t}^*\Big(1-\frac{I_2}{I_{2,t}^*}\Big) \\
&+(1-\rho)\eta D_{R,t}^*\Big(1-\frac{D_R}{D_{R,t}^*}\frac{A_t^*}{A}\Big) + \eta\rho D_{R,t}^*\Big(1-\frac{R_t^*}{R}\frac{D_R}{D_{R,t}^*}\Big) + \mu D_{R,t}^*\Big(1-\frac{D_R}{D_{R,t}^*}\Big) \\
&+(d+\mu) A_t^*\Big(1-\frac{A}{A_t^*}\Big) + \mu R_t^*\Big(1-\frac{R}{R_t^*}\Big)
\end{aligned}$$

This implies $\dot{V}_t < 0$, by the relation between geometric and arithmetic means. The equality $\dot{V}_t = 0$ holds if and only if (S, I_1, I_2, D_R, A, R) take the equilibrium values $(S_t^*, I_{t,1}^*, I_{t,2}^*, D_{R,t}^*, A_t^*, R_t^*)$. Therefore, by LaSalle's Invariance Principle [18], the interior endemic equilibrium $\mathscr{E}_{S_t}$ is globally asymptotically stable.

□

4. NUMERICAL SIMULATIONS

In this section, we give some numerical simulations of the model 2.1 to verify the validity of our theoretical results. The parameter values for each numerical simulation are displayed in table 2.

From figure 2, we show that all curves are decreases to zero, unless the susceptible individuals, this is because both the basic reproduction numbers are less than one ($R_0^1 = 0.47$ and $R_0^2 = 0.37$). This shows that the disease persists and thus agrees with Theorem 3 which says that the disease-free equilibrium is globally asymptotically stable.

Next, from Figure 3, we show that HIV-1 infected individuals persists while the HIV-2 infected

individuals dies out, this is because the basic reproduction number for I_2 is less than unity while the other is great than 1 ($R_0^1 = 2.39$ and $R_0^2 = 0.37$). Thus result agrees with Theorem 4.

From Figure 4, we observe the persistence of the HIV-1 infected individuals and HIV-2 infected individuals, we can also remark that the persistence of I_1 is higher than the one of I_2, this is because ($R_0^1 = 7,09 > 1$ and $R_0^2 = 6.67 > 1$). Thus result agrees the global stability of the interior endemic equilibrium.

Table 2. Model parameters and their interpretations.

Parameter	Figure 2	Figure 3	Figure 4
Λ	1	1	1
μ	0.2	0.2	0.2
β_1	0.17	0.86	0.95
β_2	0.12	0.12	0.9
θ_1	0.7	0.7	0.27
θ_2	0.6	0.6	0.25
ω_1	0.9	0.9	0.2
ω_2	0.8	0.8	0.15
ρ	0.48	0.48	0.48
η	0.05	0.05	0.05
d	0.3	0.3	0.3

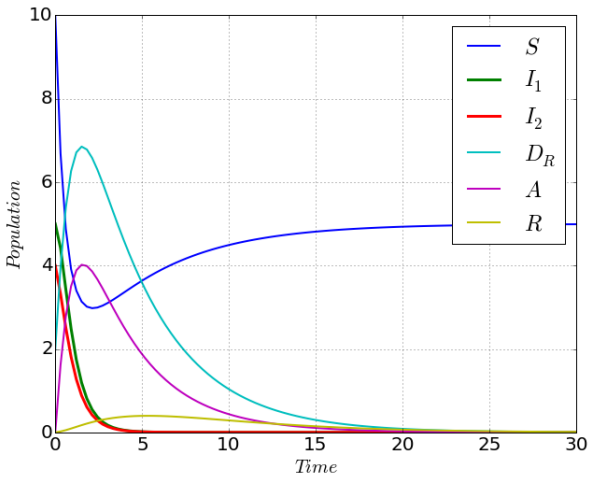

FIGURE 2. Simulation of the model 2.1 with $R_0^1 = 0.47$ and $R_0^2 = 0.37$

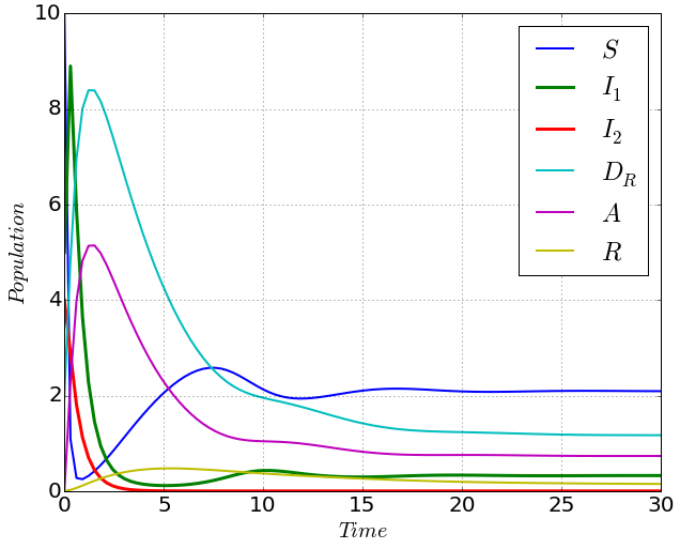

FIGURE 3. Simulation of the model 2.1 with $R_0^1 = 2.39$ and $R_0^2 = 0.37$

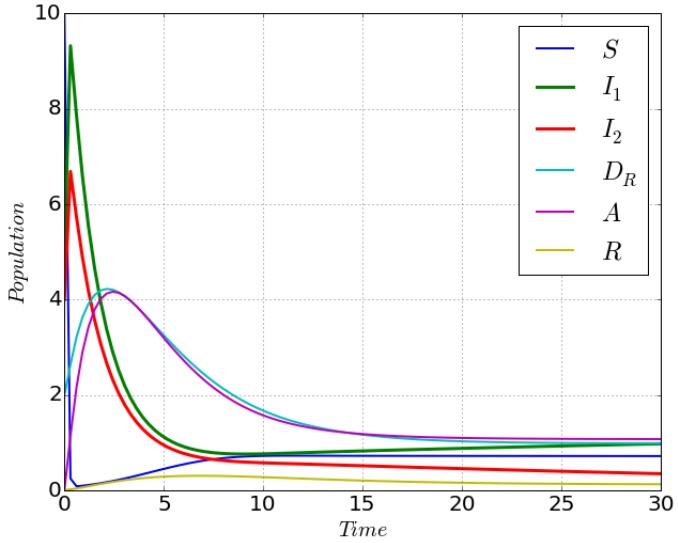

FIGURE 4. Simulation of the model 2.1 with $R_0^1 = 7,09$ and $R_0^2 = 6.67$

5. SENSITIVITY OF THE BASIC REPRODUCTION NUMBER

The sensitivity analysis of the basic reproduction numbers aims to determine the influence of some parameters on dynamic of the model 2.1, using the normalized forward sensitivity index follows.

Definition 7. [19]; [20] *The normalized forward sensitivity index of R_0 that depends differentiability on a parameter p is defined by*

$$\Upsilon_p^{R_0} := \frac{\partial R_0}{\partial p} \times \frac{p}{R_0}.$$

We examine the sensitivity index firstly for the basic reproduction number R_0^1 with respect to Λ and β_1.

Proposition 8. *The normalized forward sensitivity index of R_0^1 with respect to Λ and β_1 is 1 : $\Upsilon_\Lambda^{R_0^1} = 1$ and $\Upsilon_{\beta_1}^{R_0^1} = 1$.*

Proof. It is a simple application of definition 7. □

The sensitivity index of R_0^1 with respect to θ_1, ω_1 and μ is given, respectively, by :
$\Upsilon_{\theta_1}^{R_0^1} = \frac{-\theta_1}{\theta_1+\omega_1+\mu} = -0.389$, $\Upsilon_{\omega_1}^{R_0^1} = \frac{-\omega_1}{\theta_1+\omega_1+\mu} = -0.5$, $\Upsilon_{\mu}^{R_0^1} = \frac{-\mu}{\theta_1+\omega_1+\mu} = -0.111$.
Secondly, we compute the sensitivity index for the basic reproduction number R_0^2 with respect to Λ, β_2 , θ_2, ω_2 and μ.
$\Upsilon_\Lambda^{R_0^2} = 1$, $\Upsilon_{\beta_2}^{R_0^2} = 1$, $\Upsilon_{\theta_2}^{R_0^2} = \frac{-\theta_2}{\theta_2+\omega_2+\mu} = -0.375$, $\Upsilon_{\omega_2}^{R_0^2} = \frac{-\omega_2}{\theta_2+\omega_2+\mu} = -0.5$, $\Upsilon_{\mu}^{R_0^2} = \frac{-\mu}{\theta_2+\omega_2+\mu} = -0.125$.

Table 3. Sensitivity index of R_0^1 and R_0^2 for parameter values given in Table 2, Figure 2 .

Parameter	Sensitivity indices for R_0^1	Parameter	Sensitivity index for R_0^2
Λ	1	Λ	1
β_1	1	β_2	1
θ_1	-0.389	θ_2	-0.375
ω_1	-0.5	ω_2	-0.5
μ	-0.111	μ	-0.125

The parameters that they have a positive sensitivity indices means that they have a great impact on persistence of the disease in the population if their values are increasing, will lead to an increase in the basic reproduction number. Furthermore, the parameters that they have a negative sensitivity indices means that they have an influence to minimizing the burden of the disease in the population as their values increasing while the others are left constant, will lead to a decreases in the basic reproduction number, which leads to minimizing the rate of infection in the population [21].

6. Conclusion

In this work, we have formulated a mathematical model for the transmission dynamics of HIV-1 and HIV-2 with drug resistance compartment. Moreover, existence, positivity and boundedness are verified. We have computed the basic reproduction numbers, then, we found two basic reproduction numbers, we have proved the global stability of both the disease-free and endemic equilibrium by using Lyapunov's direct method and LaSalle's invariance principle. Furthermore, we have introduced a numerical simulations illustrate and extend the obtained theoretical results. Sensitivity analysis of the model is analyzed to establish which parameter has high effect on the transmission of the disease.

Conflict of Interests

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

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