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Sensitivity Analysis of a HIV Superinfection Model

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Abstract. In this work, a HIV superinfection model with two unique viral strains was presented. The next generation method was adopted to compute the reproduction number of the model. The model was analyzed for the parameters responsible for the spread of the strains in the population of CD4 T-cells. This is to help us find the most sensitive parameters out of all. Using the normalized sensitivity index, the most sensitive parameter of the model is the rate of infection of the primary strain *(β)*. Hence *β* should be minimized so that the population of the primary strains in the CD4 T cells population does not lead to an endemic state.

Keywords: Endemic, Parameters, Reproduction number, Sensitivity, Superinfection

Introduction

Infectious diseases are obviously one of the threats to the human race (UNICEF, 2023). Several infectious diseases have been documented. One of the prominent among them is Acquired Immune Deficiency Syndrome (AIDS). AIDS is caused by a virus called Human Immunodeficiency Virus (HIV). This virus, on infesting the system, binds itself to its target cells, which is the CD4 T-cells (Ahmad, Khan, Akbar, & Al-Moneef, 2023). It then hijacked the system and proliferate itself within the cells. It gradually destroys the ability of the immune system to fight against other infections and diseases such as Tuberculosis, Hepatitis B, Hepatitis C and Cancer (National Institutes of Health, 2023). A blood count of CD4 T-cells less than $200\ cells/mm^3$ shows that HIV has engulfed the system (WHO, 2007).

HIV has emerged into a disease that begged for global attention. In 2022, about 39 million persons are living with the virus, while new infection stands at 1.5 million. It is also on record that about 630 000 people died from AIDS-related illnesses in 2021 (UNAIDS, 2023a). While the world of science is still in search for a possible total curative measure or a complete eradication of this deadly virus, HIV has metamorphosized into types and sub-types so that this effort is further faced with set backs upon the discovery of superinfection of HIV.

The likelihood of reinfection of a 2nd unique HIV viral strain in a mono-infected patient has been reported in literatures, kicking off theories that an infected individual cannot be reinfected with a different strain. The first case of HIV superinfection was reported in 1987 (Smith, Richman & Little, 2005), and fifteen years after this, Blackard, Cohen and Mayer (2002) reported a case in human.

HIV superinfection is a situation where an already infected person with a viral strain is reinfected with a unique strain at another time after the establishment of the primary infection Sun and Xiao (2016). Research has shown that the new strain can replace the original strain or co-exist with the original strain or in some cases recombine to form another generation of viral strain. Superinfection may cause some people to get sicker faster because the new strain of the virus is resistant to the antiretroviral therapy (ART). The use of HART to treat HIV could help to hinder progression to superinfection (Blackard, Cohen & Mayer, 2002; Moreh, Szilagyi, & Scheuring, 2018). HIV superinfection has been reported among men who have sex with men (Sun & Xiao, 2016). Woodson, Basu, Olszewski, Gilmour, Brill, Kilembe, Allen & Hunter (2019), conducted a pilot on the reduction of HIV superinfection in a high-risk cohort in

Zambia. Superinfection of seropositive wives was also reported by Dieckhaus, Ha, Schensul and Sarna (2020).

Model Assumptions, Description and Development

The target population, which are the CD4 T cells proliferate at the rate Λ, and are also produced from the thymus at the rate π. The model comprises five classes dealing with cellular and viral populations. The uninfected CD4 T cells are denoted *U(t)*, and it has a natural death rate μ. The two forms of viral strains are denoted by $V_p(t)$ and $V_s(t)$, which are the population of the primary and superinfection viral strains respectively. The two viral strains are distinct, they co-exist and co-circulate in their host but do not recombine in their life time. Their corresponding infected classes are the primarily infected class and super-infected class, represented by $I_p(t)$ and $I_s(t)$ respectively. The natural death rate of the viral strain is δ.

Upon infection of the system by the primary viral strain, uninfected CD4 T cells population are primarily infected at the rate β. Primarily infected cells are super-infected at the rate α. Upon the death of the primarily infected cells, new virions are produced at the rate ρ, thereby contributing $\rho N_p I_p$ to the population of primarily infected cells. Also, upon the death of the secondarily infected cells, new virions are produced at the rate γ, so that a portion $(1-\gamma)N_s I_s$ progresses into the primarily infected cell class while $\gamma N_s I_s$ progressed into into the super-infected class. Super-infected cells are not re-infected. Relying on these assumptions and description, the formulated model is presented as equations (1) – (5).

$$\frac{dU(t)}{dt} = s - \beta V_p(t)U(t) - \mu U(t) \quad (1)$$

$$\frac{dI_p(t)}{dt} = \beta V_p(t)U(t) - \alpha V_s(t)I_p(t) - \mu I_p(t) \quad (2)$$

$$\frac{dI_s(t)}{dt} = \alpha V_s(t)I_p(t) - \mu I_s(t) \quad (3)$$

$$\frac{dV_p(t)}{dt} = \rho N_p I_p(t) + (1-\gamma)N_s I_s(t) - \beta V_p(t)U(t) - \delta V_p(t) \quad (4)$$

$$\frac{dV_s(t)}{dt} = \gamma N_s I_s(t) - \alpha V_s(t)I_p(t) - \delta V_s(t) \quad (5)$$

Equations (1) – (5) are subject to the following inequalities initial conditions: $U(0) > 0$, $I_p(0) \geq 0$, $I_s(0) \geq 0$, $V_p(0) \geq 0$ and $V_s(0) \geq 0$, where $s = \pi + \Lambda$.

The Dynamics of the Model

The total population of the CD4 T cells in the system is denoted by $N(t)$, and it is given as

$$N(t) = U(t) + I_p(t) + I_s(t) \quad (6)$$

Taking the derivative of (6) with respect to time, t, the expression in (7) was obtained.

$$\frac{dN}{dt} = s - \mu U(t) - \mu I_p(t) - \mu I_s(t) \quad (7)$$

Equation (7) is the population dynamics of the model. It represents the state where changes take place in the population of CD4 T cells.

Existence and Uniqueness of the Solution of the Model

Theorem 1: Assume ϕ denote the region $0 \leq N(t) \leq \frac{s}{\mu}$, then the equations (1) – (5) have unique solution.

Proof: We have to show that the partial derivatives of equations (1) – (5) are continuous and bounded. Let

$$f_1 = s - \beta V_p U(t) - \mu U(t) \quad (8)$$

$$f_2 = \beta V_p(t)U(t) - \alpha V_s(t)I_p(t) - \mu I_p(t) \quad (9)$$

$$f_3 = \alpha V_s(t)I_p(t) - \mu I_s(t) \quad (9)$$

$$f_4 = \rho N_p I_p(t) + (1-\gamma)N_s I_s(t) - \beta V_p(t)U(t) - \delta V_p(t) \quad (10)$$

$$f_5 = \gamma N_s I_s(t) - \alpha V_s(t) I_p(t) - \delta V_s(t) \quad (11)$$

Differentiating each of the equations of equations (8) – (11) partially with respect to $U(t)$, $I_p(t)$, $I_s(t)$, $V_p(t)$ and $V_s(t)$ gives the following:

$$\left|\frac{\partial f_1}{\partial U(t)}\right| = \left|-\beta V_p(t) - \mu\right| = \left(\beta V_p(t) + \mu\right) < \infty \quad (12)$$

$$\left|\frac{\partial f_1}{\partial I_p(t)}\right| = |0| = 0 < \infty \quad (13)$$

$$\left|\frac{\partial f_1}{\partial I_s(t)}\right| = |0| = 0 < \infty \quad (14)$$

$$\left|\frac{\partial f_1}{\partial V_p(t)}\right| = |-\beta U(t)| = \beta U(t) < \infty \quad (15)$$

$$\left|\frac{\partial f_1}{\partial V_s(t)}\right| = |0| = 0 < \infty \quad (16)$$

Similarly, it can be shown that $\left|\frac{\partial f_i}{\partial x_i(t)}\right| < \infty$, for $i = 2, 3, 4, 5$ where $x_i(t) = \{U(t), I_p(t), I_s(t), V_p(t), V_s(t)\}$. Since all the partial derivatives exist, and are finite bounded, then the system has a unique solution. This completes the proof.

Positivity of Solution

Theorem 2: Assume that the initial conditions satisfy $U(0) > 0$, $I_p(0) \geq 0$, $I_s(0) \geq 0$, $V_p(0) \geq 0$ and $V_s(0) \geq 0$, then the solution $\{U(t), I_p(t), I_s(t), I_p(t), V_p(t), V_s(t)\}$ of the system is non-negative for all $t > 0$.

Proof: Recall that the first equation of the model is given $\frac{dU(t)}{dt} = s - \beta V_p U(t) - \mu U(t)$. This can be written as

$$\frac{dU(t)}{dt} = \left(\beta V_p(t) + \mu\right)U(t) \geq 0, (\because s > 0) \quad (17)$$

By using integrating factor method to solve for $U(t)$ in equation (17), the relation becomes

$$\frac{d}{dx}\left\{U(t)\, exp\left(\int_0^t \beta V_p(x)dx + \mu t\right)\right\} \geq 0. \quad (18)$$

Integrating over the time interval $[0, t]$ yields

$$U(t)\, exp\left\{\left(\int_0^t \beta V_p(x)dx + \mu t\right)\right\} - U(0) \geq 0. \quad (19)$$

This leads to

$$U(t) \geq U(0)\, exp\left\{-\left(\int_0^t \beta V_p(x)dx + \mu t\right)\right\} > 0 \text{ for all } t > 0. \quad (20)$$

Using similar procedures, it can be also be shown that $I_p(t) > 0$, $I_s(t) > 0$, $V_p(t) > 0$ and $V_s(t) > 0$ for all $t > 0$. Since the solution of the system continuously depends on the respective initial conditions in the neighbourhood of zero, then the system is non-negative for all $t > 0$.

Derivation of Basic Reproduction Number (R_0)

Epidemiologists are usually concerned with the ability of the disease to spread in a system. Basic reproduction number provides a gauge of the ability of a disease to infect and spread in a population (Van de Driessche & Watmough, 2002). In this work, R_0 is the number of post-primary occurrence that HIV superinfection will result into in the population of healthy CD4 T cells that has no immunity to HIV and at the same time, has no strategy to control the infection. We derived the Jacobian matrix corresponding to the equilibrium state, $J(E)$, of the model equations as follows:

$$J(E) = \begin{pmatrix} -\mu & 0 & 0 & -\frac{\beta s}{\mu} & 0 \\ 0 & -\mu & 0 & \frac{\beta s}{\mu} & 0 \\ 0 & 0 & -\mu & 0 & 0 \\ 0 & \rho N_p & k_1 & k_2 & 0 \\ 0 & 0 & \mu N_s & 0 & \delta \end{pmatrix} \quad (21)$$

where $k_1 = (1-\gamma)N_s$ and $-\left(\frac{\beta s}{\mu} + \delta\right)$. R_0 is the largest eigenvalue of the Jacobian matrix in equation (21). R_0 was obtained using the Jacobian stability approach (Martcheva, 2015). It is given as

$$R_0 = \sqrt{\frac{\beta(\pi+\Lambda)N_p}{\beta(\pi+\Lambda)+\mu\delta}} \quad (22)$$

Sensitivity Analysis

Sensitivity analysis is the study of how uncertainty in the output of a model can be aassigned to different sources of uncertainty in the model input. It is concerned with the uncertainty inherent in mathematical models where the values for the inputs used in the model can vary (Wachira, Lawi & Omondi, 2022). Hence, it is a tool used to identify how much variations in the input values for a given variable will impact the results for a mathematical model (Adewale, Olopade, Adeniran & Ajao, 2015). Its use has found application in several fields including mathematical modeling. Adamu and Ibrahim (2020), adopted this approach in determining sensitive parameters in a terrorism model. In this work, the normalized forward sensitivity indices, as discussed by Diekmann, Heesterbeek and Metz (1990), was used to determine sensitive parameters in R_0. For the purpose of investigating the sensitivity of the parameters, data from related studies was used to compute sensitivity index. The data are presented in Table 1.

Table 1: Parameter Values

Parameters	Values	Sources
β	$0.000024mm^3day^{-1}$	Ngina (2018)
N_p	$100day^{-1}$	Mbogo et al., (2018)
π	$100mm^{-3}$	Ngina (2018)
Λ	$0.03day^{-1}$	Roy and Chartterjee (2010)
μ	$0.02day^{-1}$	Roy and Chartterjee (2010)
δ	$0.02day^{-1}$	Culshaw and Ruan (2000)

Table 2: Results of Numerical Sensitivity of Parameters in R_0

Parameters	Values
β	+04483
N_p	+0.0161
π	-0.0001

Results and Discussion

From the results of sensitivity analysis presented in Tables 2, it is observed that β is the most sensitive parameter. This shows that the rate of infection of the primary strain has the greatest effect on the spread of infection in the system. Increasing β would lead to an increase in the rate at which cells are primarily-infected. This will result in a higher value of R_0. The converse is true. By epidemiological interpretation, a larger value of R_0 implies that

the system will become endemic. This is corroborated by Figure 3, where it is observed that the population of virions in the system is on increase. This obviously led to a drastic decline in the population of healthy CD4 T cells as seen in Figure 1.

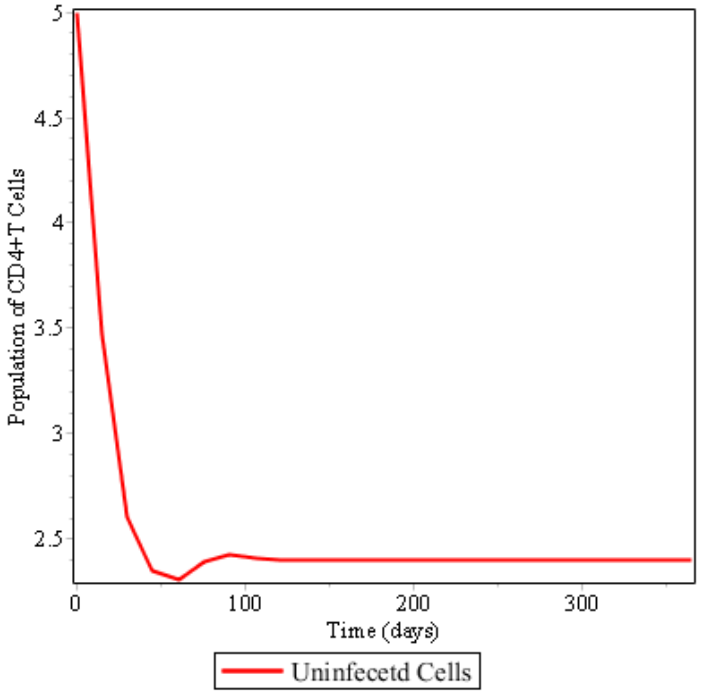

Figure 1: Population of uninfected CD4 T cells

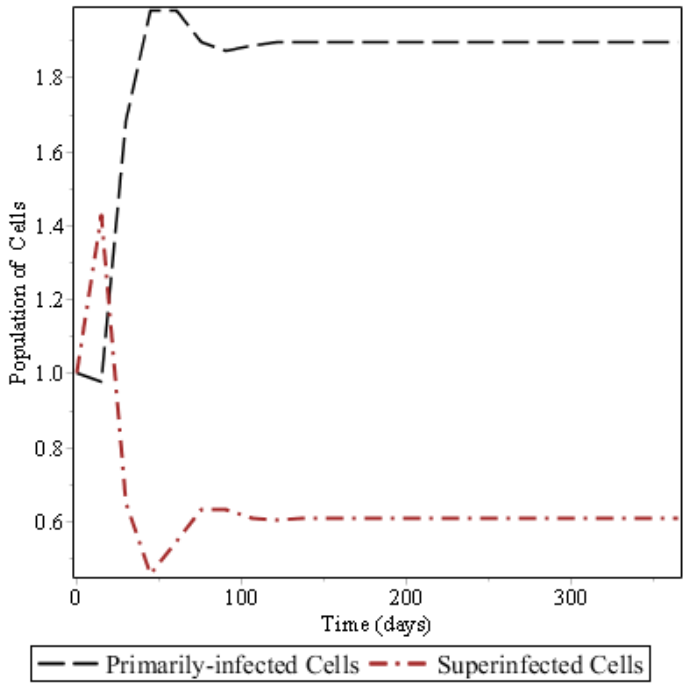

Figure 2: Population of infected CD4 T cells

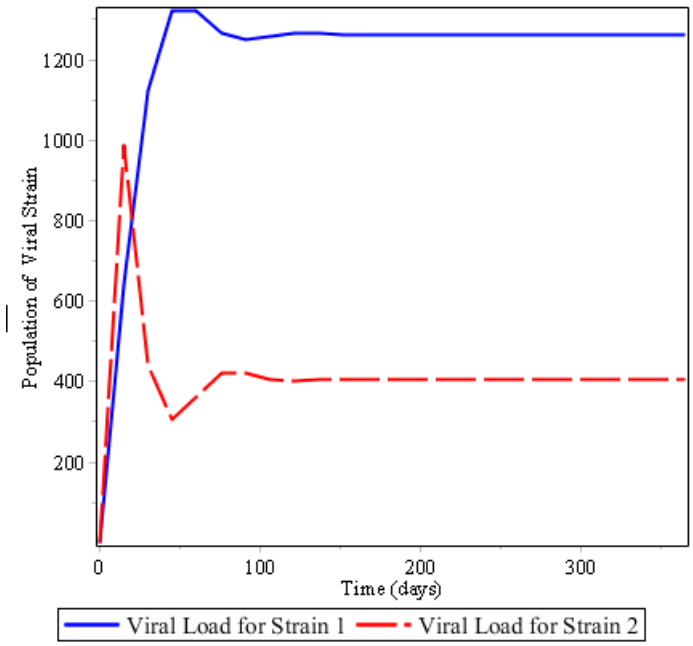

Figure 3: Viral loads for viral strains 1 and 2

The parameter, N_p, which is the amount of viral strain 1 produced upon successful lysing of infected CD4 T cells is also positive. Infection rate of the first viral strain is higher than of the second (see Figure 3). This agrees with the clinical findings of Vidya Vijayan (2017). The source term, π, for the production of uninfected cells triggered by the invasion of viral strain 1 is negative. This reveals that π does not contribute to the endemicity of the system as it will reduce the value of R_0. Thus, the population of new uninfected CD4 T cells that are produced as infection triggers the system has no significant effect in combating viruses in the system. Sensitivity Analysis was not carried out on naturally occurring parameters. We assume that their values are independent of the activities of the viral strains in the system. Hence, these parameters are fixed.

Intervention and control strategies should therefore be targeted on the most sensitive parameter as follows: Infection rates for viral strain 1 should be minimized so that the rate at which virions are reproduced by infected cells is reduced. It is known that upon successful infection of the host, viral strains can reproduce as high as 10^9 *virions per day*, whereas the clearance rate of virus is estimated to be between *0.01* and *0.02 virions per day* (Vidya Vijayan, 2017). It is logical to say that, if other factors remain constant, the number of virions produced will always be greater than the number of virions cleared. Obviously, the system will remain in an endemic state.

Conclusion

In this work, we presented a mathematical model of HIV superinfection and carried out sensitivity analysis on the parameters of the model using the normalized forward sensitivity indices. The most sensitive parameter was found to be the rate of infection of viral strain 1. Intervention and control measures should therefore be targeted at reducing the effect of (β) in the system.

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