MATHEMATICAL MODELLING OF HIV SUPERINFECTION OF TWO UNIQUE VIRAL STRAINS

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Background

HIV superinfection, the acquisition of a second distinct viral strain in an individual already infected, presents challenges to HIV management and vaccine development. Understanding the dynamics and implications of superinfection is crucial for advancing HIV research and developing more effective prevention and treatment strategies. While HIV superinfection is recognized, the mechanisms, factors influencing its occurrence, and its impact on disease progression remain inadequately understood. This study addresses the gaps in knowledge regarding HIV superinfection by employing mathematical modeling to analyze the dynamics of coexistence and competition between two unique viral strains within the same host.

What we set out to do

The aim of this study was to propose a mathematical model as a tool to prevent HIV superinfection. The objectives were to:

- develop a new mathematical model of HIV superinfection;
- obtain and analyze the equilibrium states of the model for stability;
- obtain the basic reproduction number of the model;
- identify the sensitive parameters of the model; and
- investigate the effects of the control measures on HIV superinfection.

INTRODUCTION: HIV and HIV SUPERINFECTION

- Acquired Immune Deficiency Syndrome (AIDS) is one of the leading causes of death in the world.
- AIDS is caused by a virus called Human Immunodeficiency Virus (HIV).
- Its target cells are the Cluster of Differentiation 4 (CD4) cells.
- Destroys CD4 cells and weakens the body immunity against opportunistic diseases such as hepatitis B virus, tuberculosis and fungi infections (Ahmad et. al, 2023).

Two Prominent School of thoughts on the Origin of HIV

- HIV/AIDS was discovered in 1959 in Africa, in a man living in the Democratic Republic of Congo. His blood sample tested positive for the virus. Further investigations carried out on his blood sample revealed that HIV was likely to have originated in the late 1940s or early 1950s (The American Association for the Advancement of Science, 2004).

- HIV/AIDS was discovered in 1981 among gays and drug users in the United States in New York and California (Centers for Disease Control and Prevention, 2024; Shabani and Okebukola, 2006).

HIV SUPERINFECTION

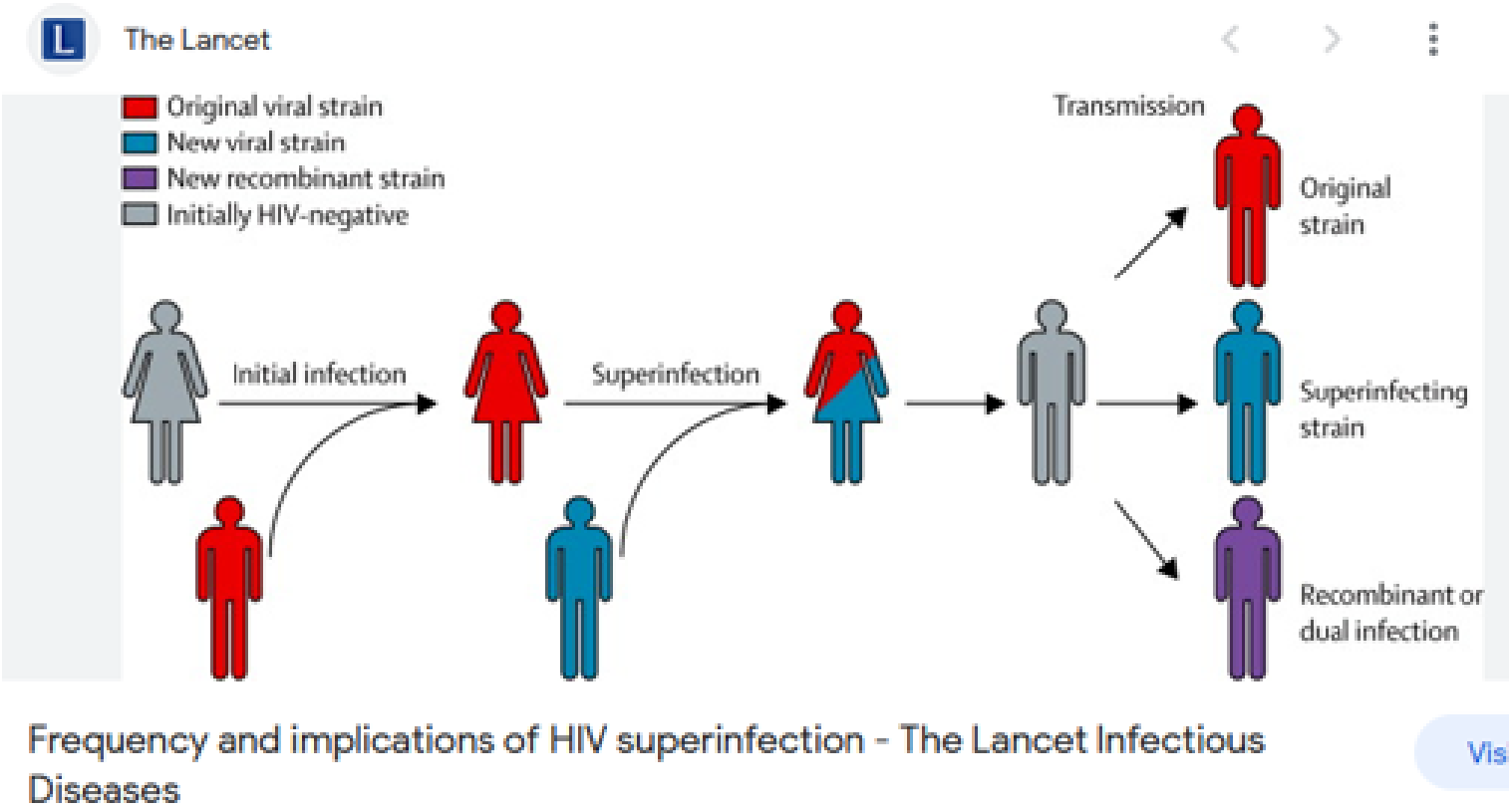

Figure 1: HIV Superinfection Pattern

HIV STATISTICS (UNAIDS, 2023a; UNAIDS, 2023b)

- About 39 million persons were living with the virus globally.
- New infection stands at 1.3 million.
- Nigeria has a figure of 1.8 million HIV positive individuals.
- About 630 000 people died globally from AIDS-related illnesses.
- About 49 000 deaths were recorded due to HIV in Nigeria.
- The first case of HIV superinfection was reported in 2002 (Smith, Richman and Little, 2005).

HIV STATISTICS (UNAIDS, 2023a; UNAIDS, 2023b)

- About 16 cases of HIV-1 superinfection was reported in 2022.
- The region of African is the most severely affected area.
- About 1 in every 25 adults in Africa are living with HIV.
- That is about 66.7 percent of persons living with HIV globally are Africans.
- Nigeria is ranked 4th in the world most-hit countries by HIV.
- South Africa (7.5 million), Mozambique (2.2 million), India (2.1 million) and Nigeria (1.8 million).

REVIEW OF LITERATURE: Preamble

- HIV superinfection is the re-infection of an already infected person with a unique strain of HIV (Jost, Kaiser, Bernard and Yerly, 2002).
- Basically, there are 2 types of HIV, namely HIV-1 and HIV-2 (Blackard *et al.*, 2002).
- Two important clinical tests for HIV patients are **CD4 cell count** and **viral load** tests: to access immune status and to monitor the level of viral replication and effectiveness of Antiretroviral therapy (ART) (WHO, 2023a).
- The goals of the tests are to reduce viral load to $< 50 copies/ml$ and keep CD4 cell count below $200 cells/mm^3$ (WHO, 2023b).

What has been done and the gaps

Shingo, Shinji and Yashuhiro (2008): Mathematical Analysis of HIV Model with Frequency Dependence and Viral Diversity

- **Focus:** Effects of HIV strains on the immune system
- **Findings:** The process of viral diversity continues over disease progression; a high proliferation rate of CTLs and decrease in its death rate induces efficiency of the immune response; viral diversity depends much on the density of the available healthy CD4+T cells.
- **The gaps:** Superinfection of a unique strain; the role of drug

What has been done and the gaps

Roy and Chatterjee (2010): T-cell proliferation in a mathematical model of CTL activity through HIV-1 infection

- **Focus:** Drugs (combination) regime and HIV-1 infection
- **Findings:** Decline in virus relication whenever an HIV-1 infecetd person is treated with the combination; the proliferation rate is always greater than the death rate of uninfected cells; when this rate increases, the density of uninfected cells increases fast while that od the CTL population increases slowly; when the force of infection increases, the numerical vlaue of infected cell and CTL decreases.
- **The gaps:** Viral particles not considered as a class; the possibility of superinfection was neglected

What has been done and the gaps

Srivastava, Banerjee, and Chandra (2009): Modeling the Drug Therapy for HIV Infection

- **Focus:** Effects of Reverse Transcriptase inhibitor on HIV infection
- **Findings:** Reverse transcription begins prior to the replication of virus by the infected cells; un-integrated virus may die-off with time; and some portion of infected cells will return to the uninfected class due to the effect of drugs before complete transcription takes place.
- **The gaps:**The effects of CTL immune response and that of a a second strain were not considered.

What has been done and the gaps

Woodson, Basu, Olszewski, Gilmour, Brill, Kilembe, Allen and Hunter (2019): Reduced Frequency of HIV superinfection in a high-risk cohort in Zambia

- **Focus:** Investigate the possibility of HIV superinfection among 3 serodiscondant couples
- **Findings:** The 3 were superinfected with HIV subtype C from non-spousal partners
- **The gaps:** It did not study activities of viral strains and CTL immune response

What has been done and the gaps

Moreh, Szilagyi and Scheuring (2018): Variable Effect of HIV Superinfection on Clinical Status: Insights from Mathematical Modeling

- **Focus:** Viral recombination and co-existence cannot be disputed
- **Findings:** Superinfection might have effect on the evolution of virulent strains
- **The gaps:** The CTL immune response was not considered

Why the study on HIV superinfection?

- Not many models have been developed to study HIV superinfection.
- The few models in literature either do not consider CTL immune response and HIV treatment in a single model or omit both controls.
- Similarly, most of these models do not consider viral particles as a class.
- HIV treatment gulps *US*\$ 134 per patient per annum. Nigeria will need approximately $134 \times 1800000 \times 1200 \approx 290$ billion naira to manage People Living with HIV per year. This is a substantial amount that could have been channeled into the economy. Hence, any study that will mitigate the effect of HIV on the budget of the country is one in a good direction.

Basic HIV Model

The flow chart of Model 1 is given in Figure 2

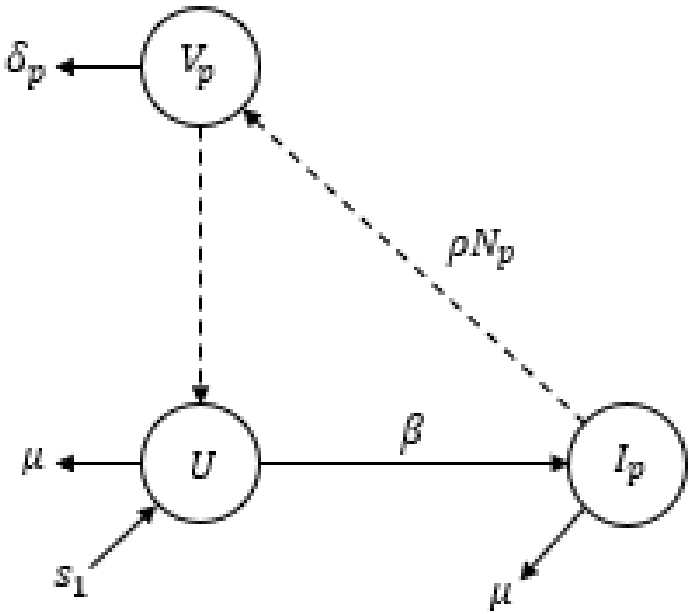

Figure 2: The Flow Diagram of the Model

The HIV Superinfection Model

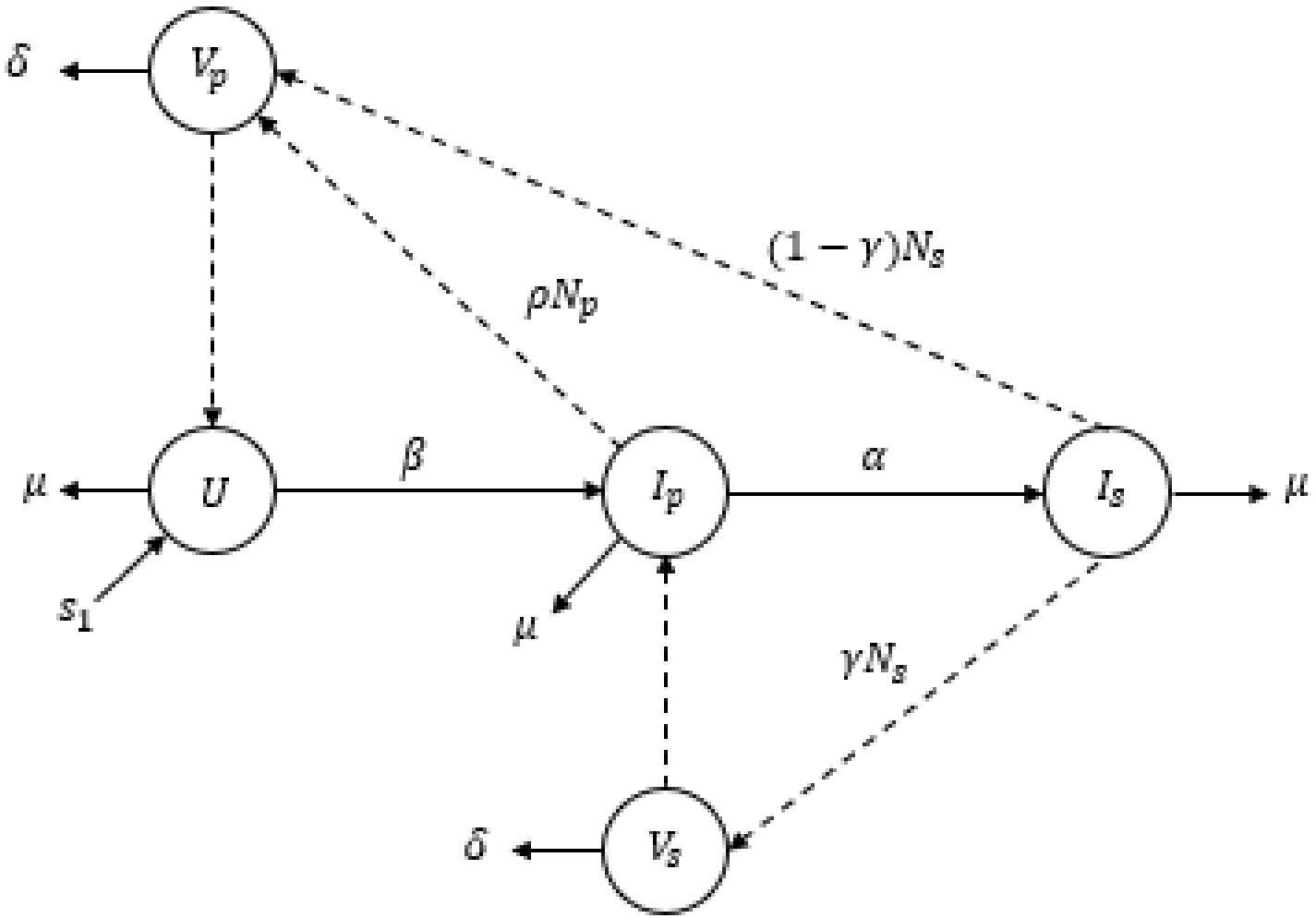

Figure 3: The Flow Diagram of HIV Superinfection Model

HIV Superinfection Model Equation

$$\frac{dU}{dt} = s_1 - \beta V_p U - \mu U \tag{1}$$

$$\frac{dI_p}{dt} = \beta V_p U - \alpha V_s I_p - \mu I_p \tag{2}$$

$$\frac{dI_s}{dt} = \alpha V_s I_p - \mu I_s \tag{3}$$

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

$$\frac{dV_s}{dt} = \gamma N_s I_s - \alpha V_s I_p - \delta V_s \tag{5}$$

s.t. $U(0) > 0$, $I_p(0) \geq 0$, $I_s(0) \geq 0$, $V_p(0) \geq 0$ and $V_s(0) \geq 0$.

Properties of HIV Superinfection Model (III)

The total population of CD4+T cells is given as $N(t) = U(t) + I_p(t) + I_s(t)$. Taking the derivative gives

$$\frac{dN}{dt} = s_1 - \mu U - \mu I_p - \mu I_s = s_1 - \mu N(t) \tag{6}$$

Region of Feasibility

The feasible solution which is the invariant set of the model is given as

$$\Psi = \left\{ (U, I_p, I_s, V_p, V_s) \in \ R_+^5 : N(t) \leq \frac{s_1}{\mu} \right\} \tag{7}$$

so that as $t \to \infty$, then every solution of the model in R_+^5 approaches and stays in Ψ.

Properties of HIV Superinfection Model (III)

Existence and Uniqueness of Solution: It is necessary to show that $\frac{\partial f_i}{\partial x_i}, i = 1, 2, ..., 5$ are continuous and bounded in ψ.

$$\left|\frac{\partial f_1}{\partial U}\right| = \mu < \infty; \left|\frac{\partial f_1}{\partial I_p}\right| = 0 < \infty; \left|\frac{\partial f_1}{\partial I_s}\right| = 0 < \infty \tag{8}$$

$$\left|\frac{\partial f_1}{\partial V_p}\right| = \beta U < \infty; \left|\frac{\partial f_1}{\partial V_s}\right| = 0 < \infty \tag{9}$$

$$\tag{10}$$

where f_i, represents the equations (12) - (16) respectively. Since all the partial derivatives exist, they are finite bounded, hence the system has a unique solution.

Equilibrium Points

Viral Strain-free Equilibrium, E_1

$$E_1 = \left(U^*, I_p^*, V_P^*, I_s^*, V_s^*\right) = \left(\frac{s_1}{\mu}, 0, 0, 0, 0\right) \tag{11}$$

Primary Viral Strain-only Equilibrium, E_2

$$E_2 = \left(U^{**}, I_p^{**}, V_P^{**}, I_s^{**}, V_s^{**}\right) = \left(\frac{\mu_p \delta}{\beta(\mu - \rho N_p)}, c_1, c_2, 0, 0\right) \tag{12}$$

Superinfection Viral Strain Equilibrium, E_3

$$E_3 = \left(U^{***}, I_p^{***}, V_P^{***}, I_s^{***}, V_s^{***}\right) = \left(\frac{s_1}{\beta k + \mu}, d_1, d_2, d_3, d_4\right) \tag{13}$$

Stability Analysis and Basic Reproduction Number

Local Stability

Theorem 1: The viral strains-free equilibrium is locally stable whenever the Basic Reproduction Number (R_0) is less than 1.

Proof: We derive the Jacobian of the model equations (12) - (16), and compute the eigenvalues as:

$$\lambda = \left(-\mu, -\mu, -\mu, -\delta, \frac{k_1 \beta U^* - \mu(\beta U^* + \delta)}{\mu} \right). \tag{14}$$

For λ_5 to be negative,

$$\frac{k_1 \beta U^* - \mu(\beta U^* + \delta)}{\mu} < 0. \tag{15}$$

On solving equation (26), we obtain

$$\sqrt{\frac{\beta N_p U^*}{\beta U^* + \delta}} < 1, \tag{16}$$

which implies,

$$R_0 < 1. \tag{17}$$

Interpretation: $R_0 < 1$ implies that the system is locally stable. Epidemiologically, viral strains will becomes extinct in the CD4+T cells population because on the average, an infected cell will cause less than one new infection throughout the life span of the viral strain so that in the long run, infection will die off.

Sensitivity Analysis

The Normalized Forward Sensitivity Index approach as discussed by Wachira, Lawi and Omondi (2022) and Byamukama, Kajunguri and Karuhanga (2023), was used to identify parameters in R_0. It is defined

$$X_M^{R_0} = \frac{\partial R_0}{\partial M} \times \frac{M}{R_0} \tag{18}$$

Table 1: Results of Numerical Sensitivity of Parameters in R_0

Parameters	Values
β	$+0.4483$
N_p	$+0.0161$
δ	-0.0001

Plots of CD4+T cells and Viral Strains without control

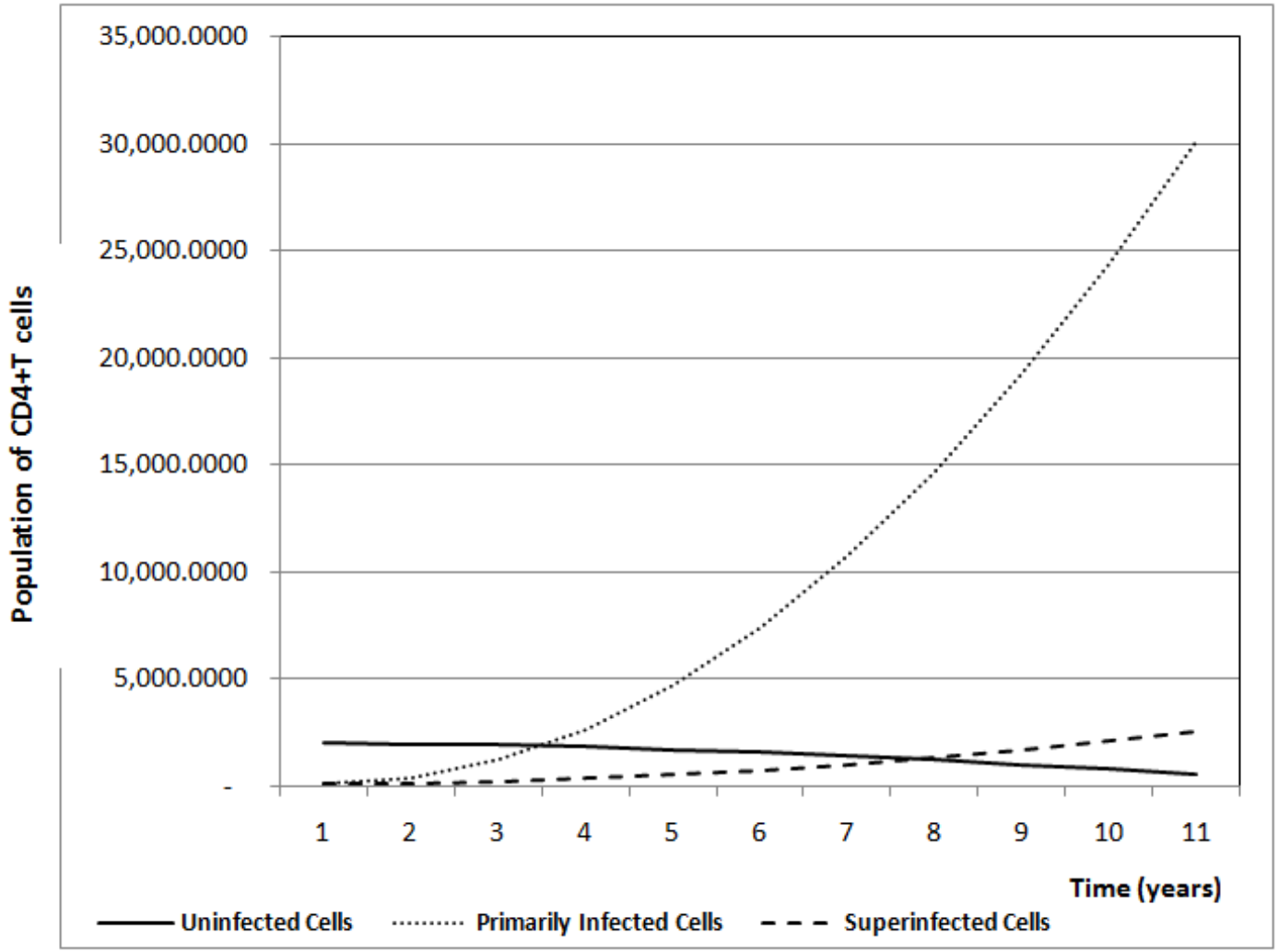

Figure 4: Plot of CD4+T cells

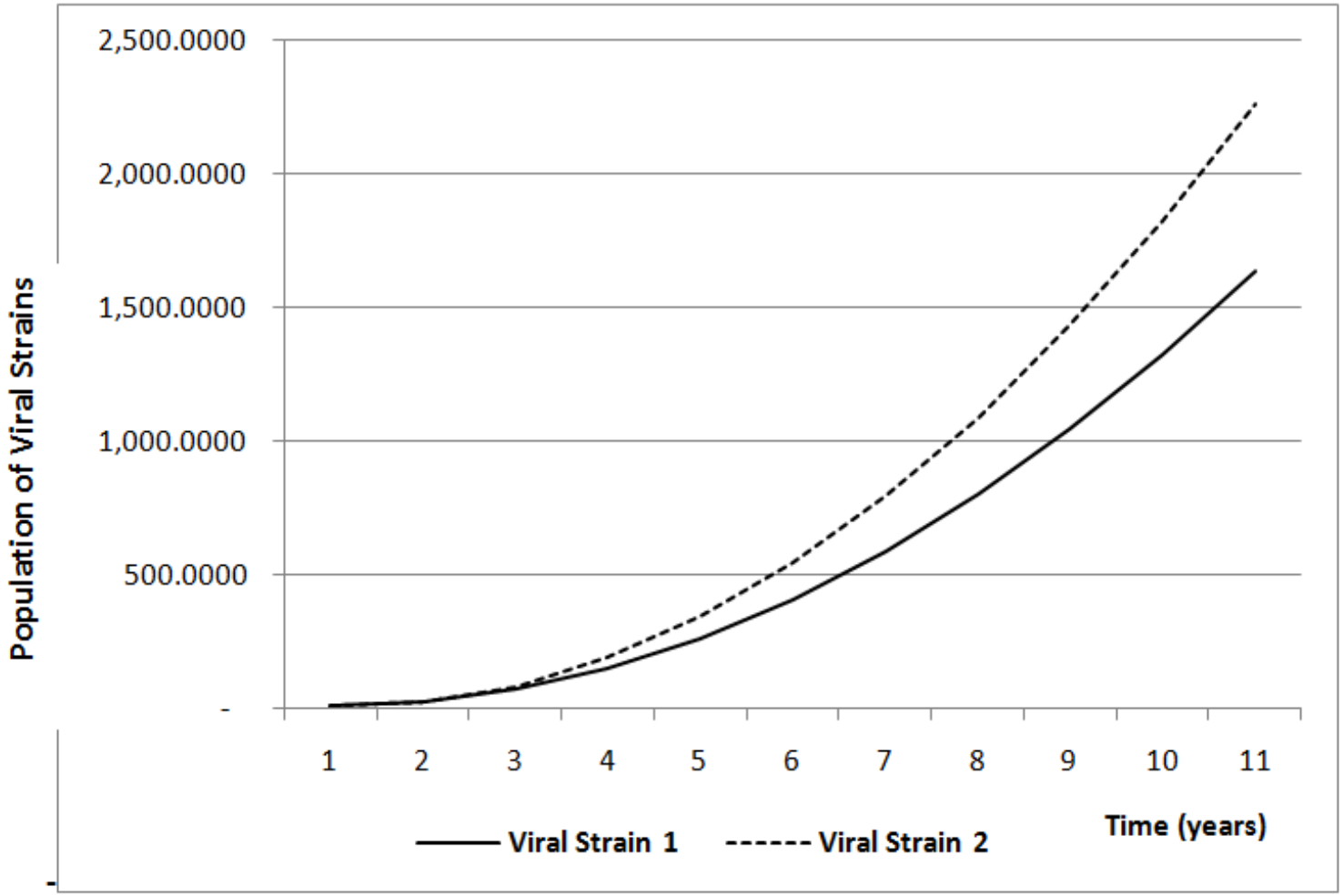

Figure 5: Primary and superinfection viral strains with no control

- From Table 1 and Figure 4, we observe that infection rate is the most sensitive parameter. N_p is also observed to be positive, while δ (natural death rate of virus) is the least sensitive parameter.

- The rate of viral infections has the greatest effect on R_0.

- By epidemiological interpretation, a larger value of R_0 (> 1) implies that the infection will persist and spread within the system.

- This is corroborated by Figure 5, where it is observed that the population of virions is on a sharp increase leading to a drastic decline in the population of healthy CD4+T cells.

What Next? Addressing the Effects of HIV Superinfection

- Control strategies were included in the model to target sensitive parameters.
- HIV drug therapy, that is, u_1 and u_2, were included in the model to reduce the number of virions produced by the two viral strains by $(1 - u_1)$ and $(1 - u_2)$ respectively.
- Similarly, the infection rates of te two strains were reduced by $(1 - u_1)$ and $(1 - u_2)$ respectively.
- From literature, CTL immune response cells are known for slowing down the activities of free viruses. The model was extended to include CTL immune response cells.

The Control Model for HIV Superinfection

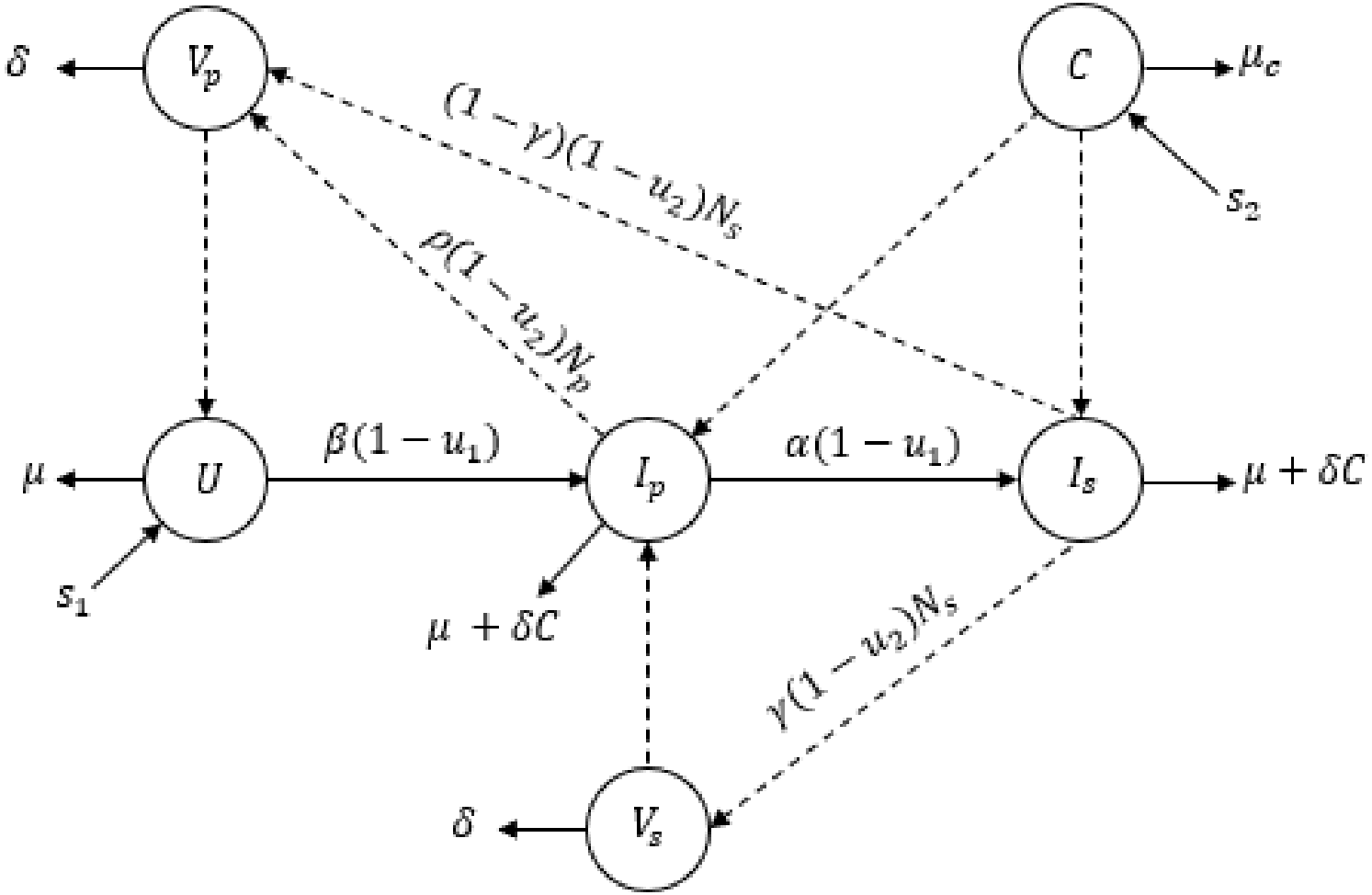

Figure 6: The Flow Diagram of the HIV Superinfection Control Model

Numerical Simulations and Discussion of Results

Case I: When the numbers of viruses produced by viral strains 1 and 2 are considered to be small with control strategy

Here, we set $N_p = 500$ *copies*/*ml* and $N_s = 500$ *copies*/*ml*. Since there is control, we set $u_1^* = 0.95$ and $u_2^* = 0.95$.

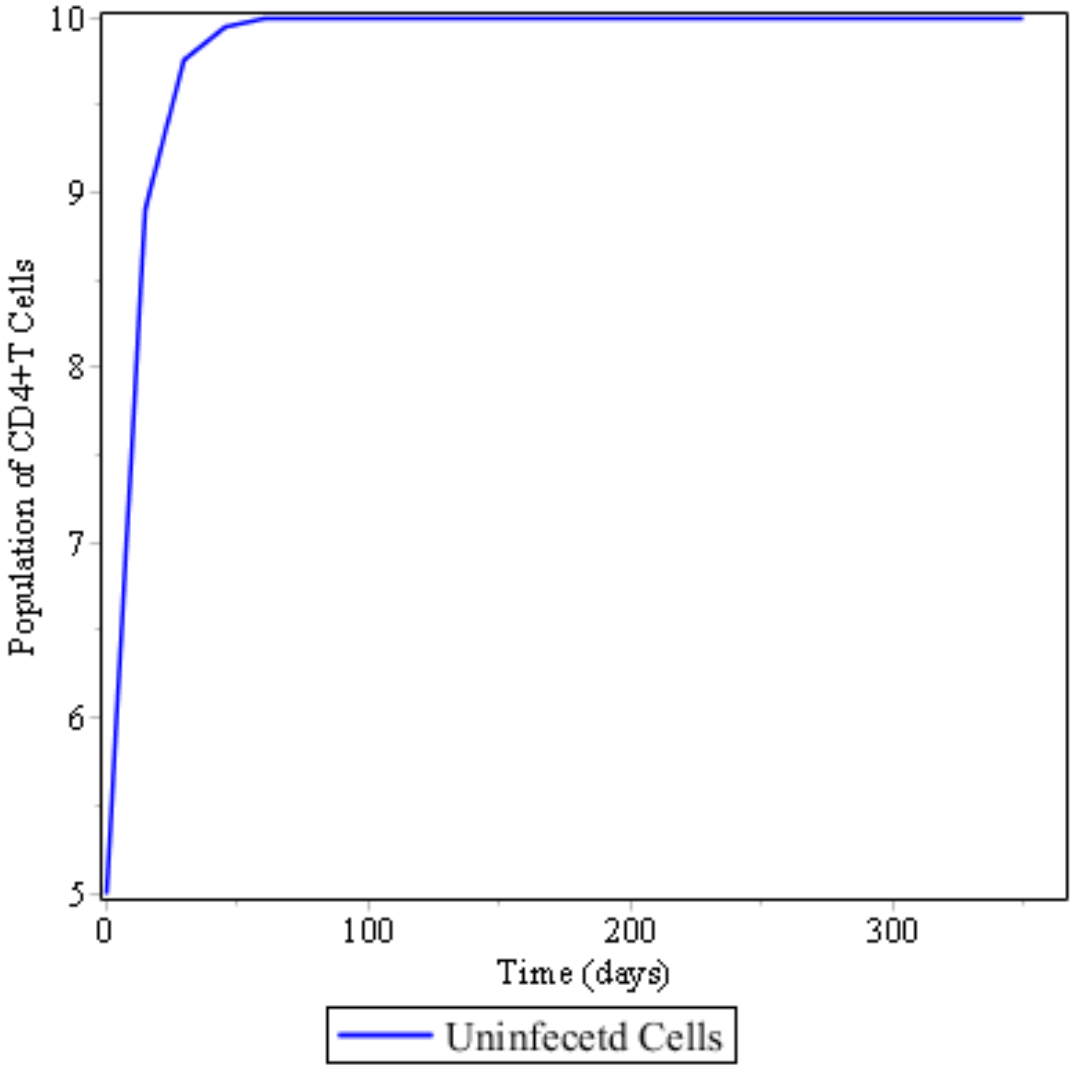

Figure 7: Uninfected CD4+T Cells with control strategy when number of viruses produced by the two viral strains are small

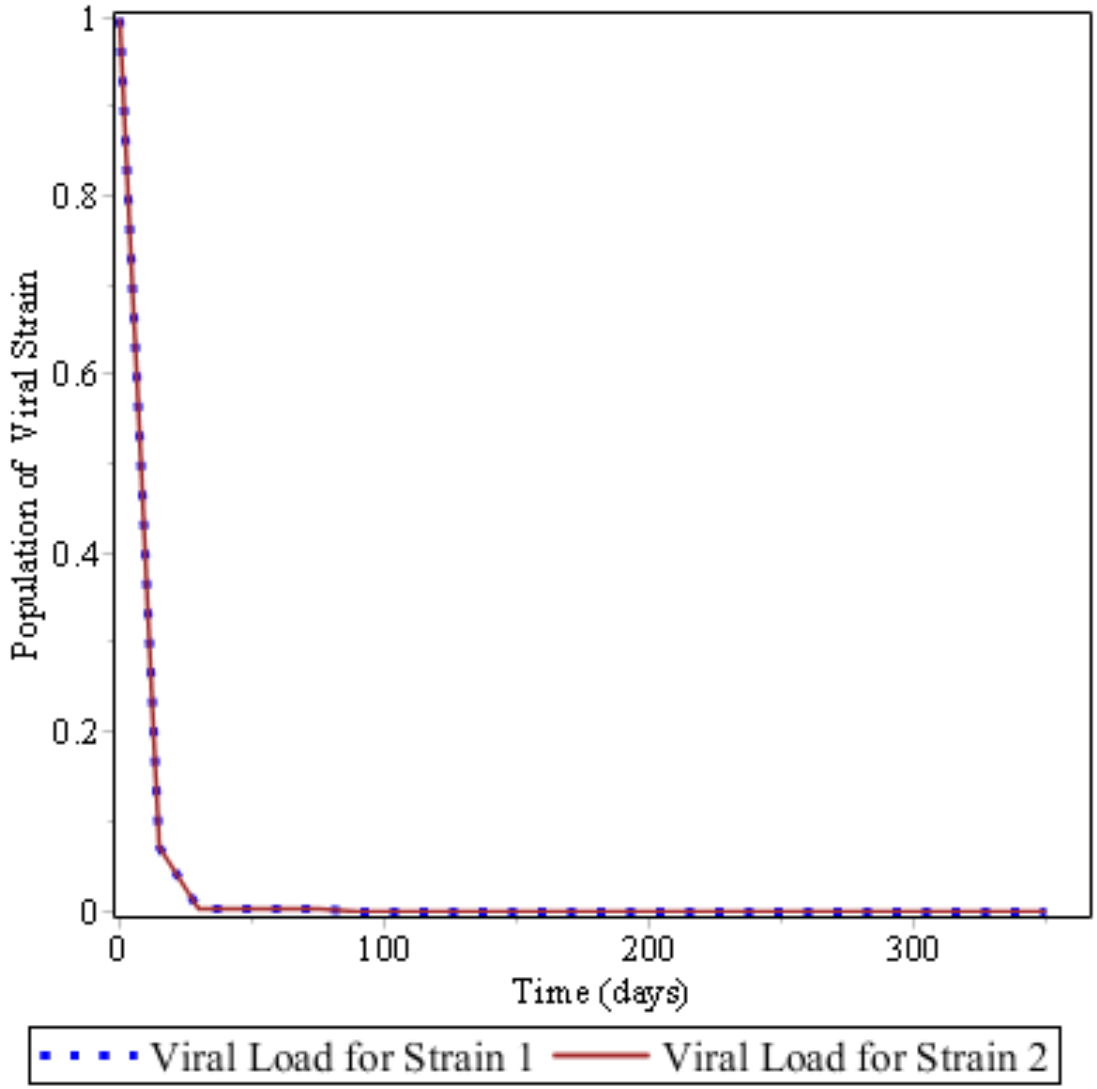

Figure 8: Viral Loads for Viral Strains 1 and 2 with control strategy when number of viruses produced by the two viral strains are small

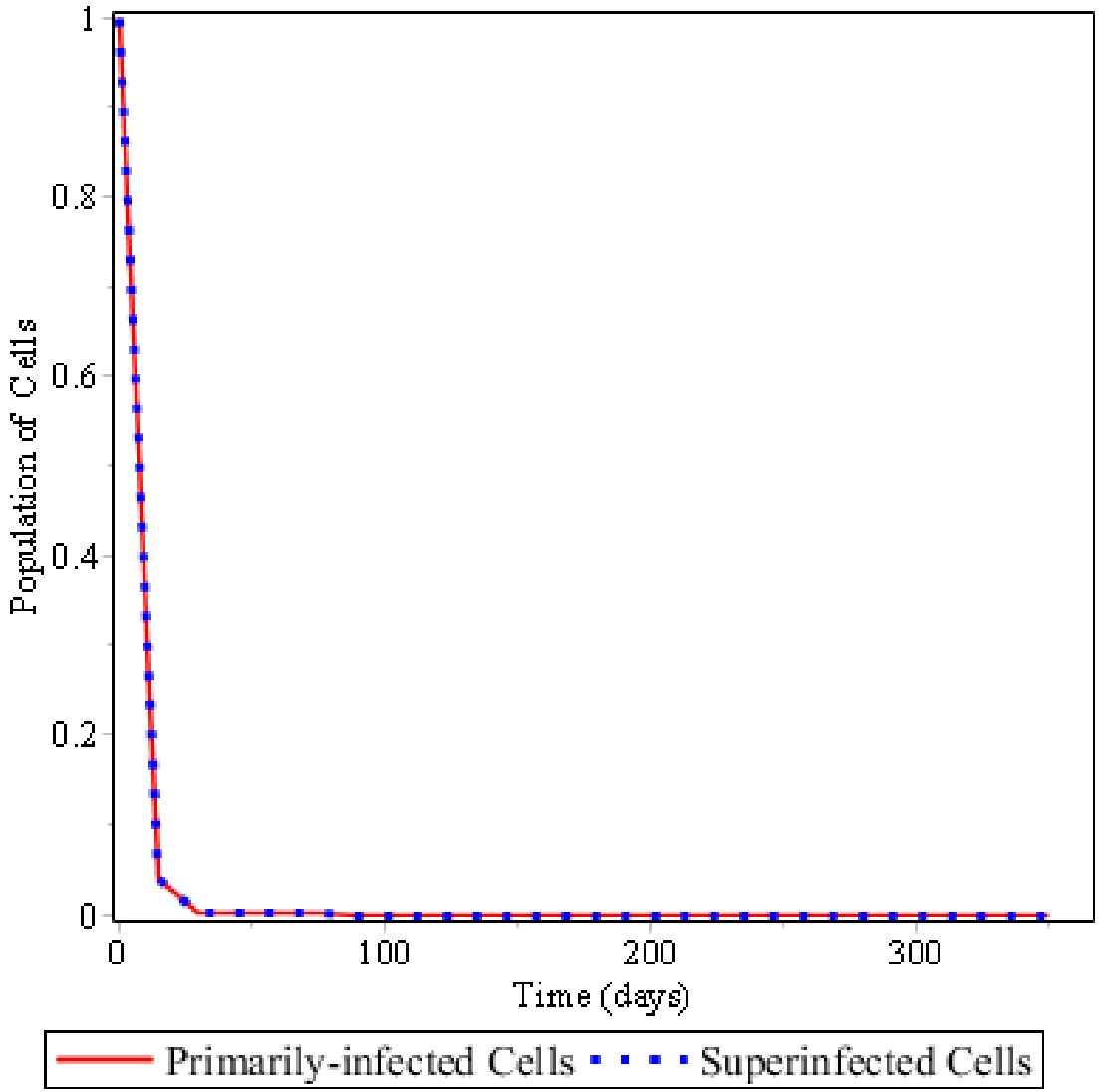

Figure 9: Infected CD4+T Cells with control strategy when number of viruses produced by the two viral strains are small

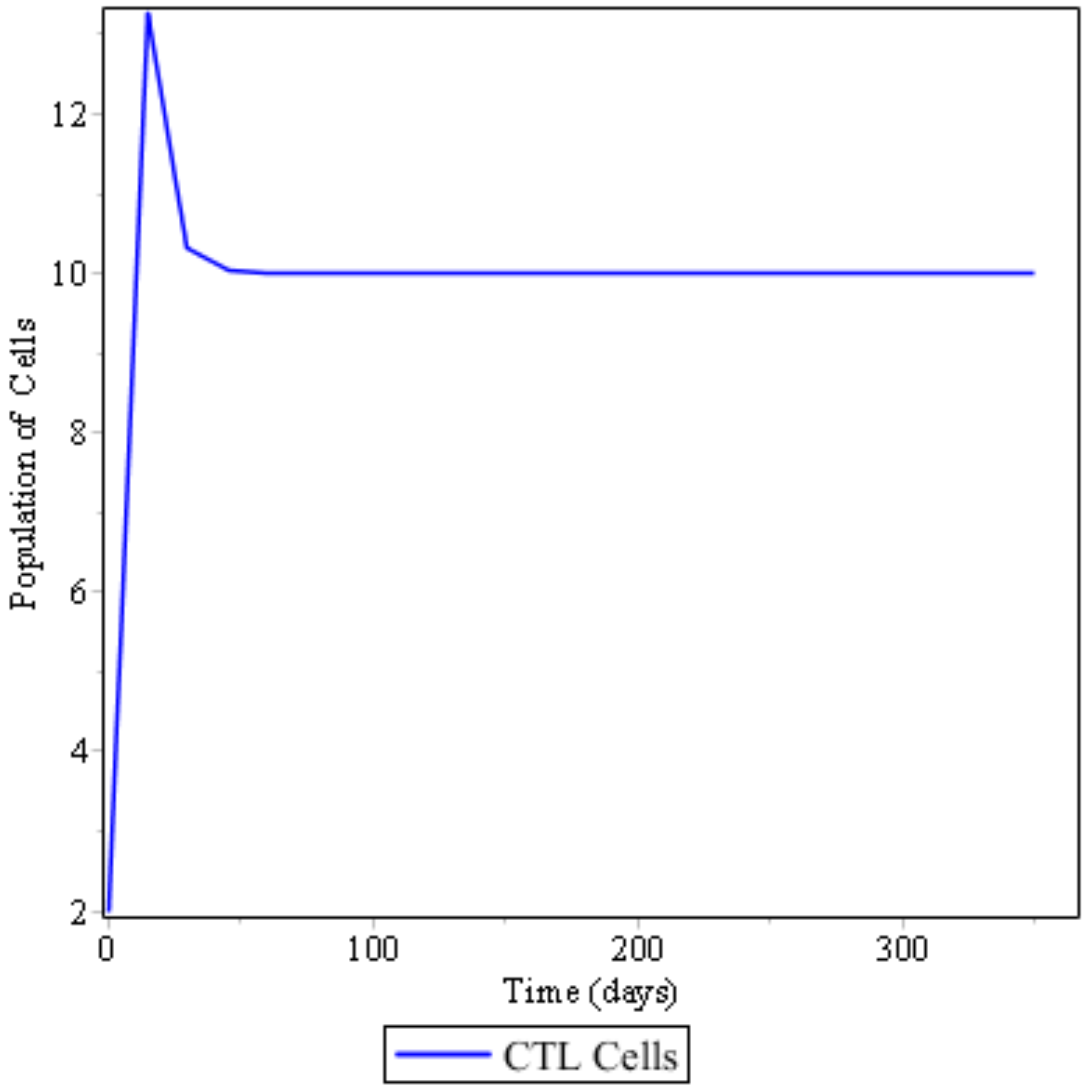

Figure 10: CTL Cells with control strategy when number of viruses produced by the two viral strains are small

Case 2: When the numbers of viruses produced by viral strains 1 and 2 are considered to be large with control strategy

Here, we set $N_p = 10,000$ *copies*/*ml* and $N_s = 10,000$ *copies*/*ml*. Since there is control, we set $u_1^* = 0.95$ and $u_2^* = 0.95$.

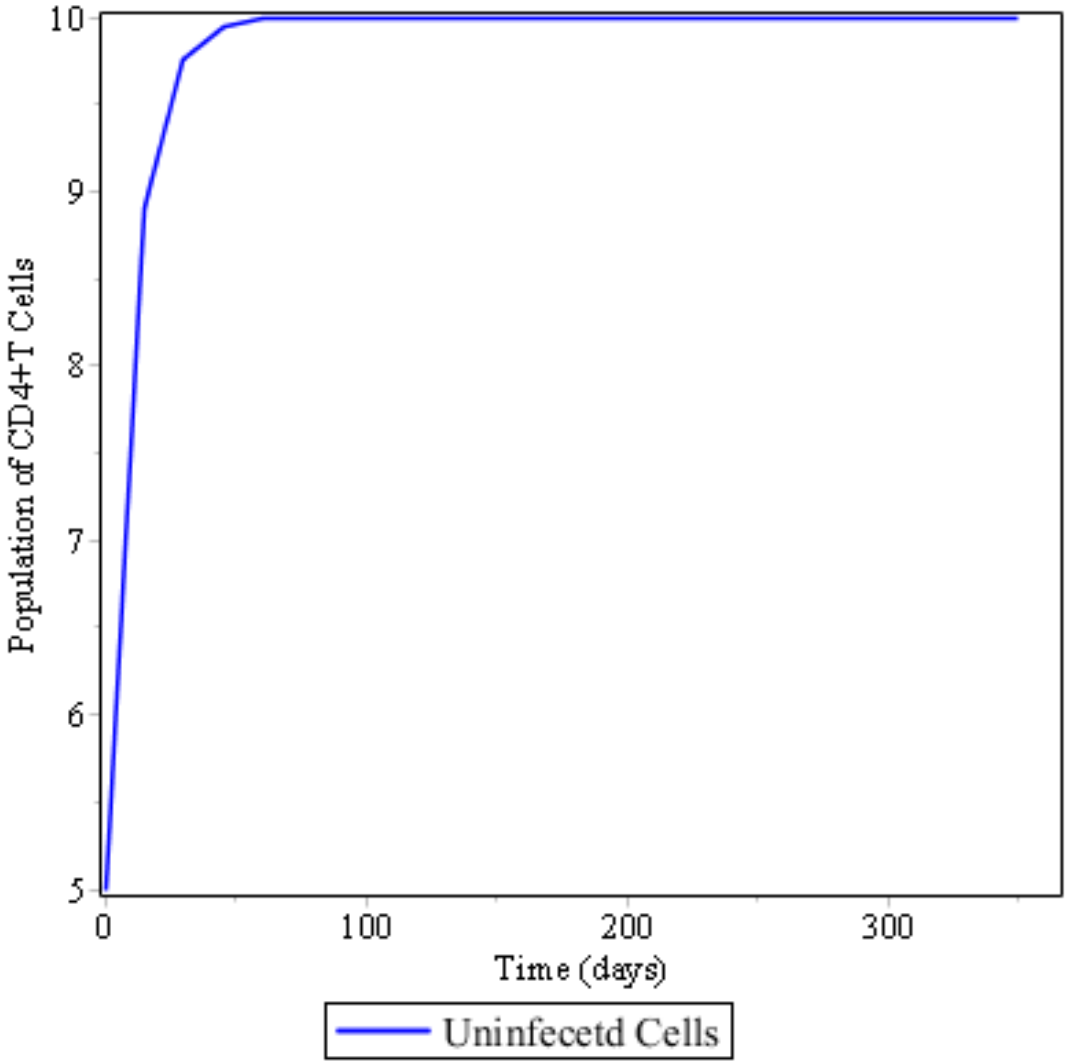

Figure 11: Infected CD4+T Cells with control strategy when number of viruses produced by the two viral strains are large

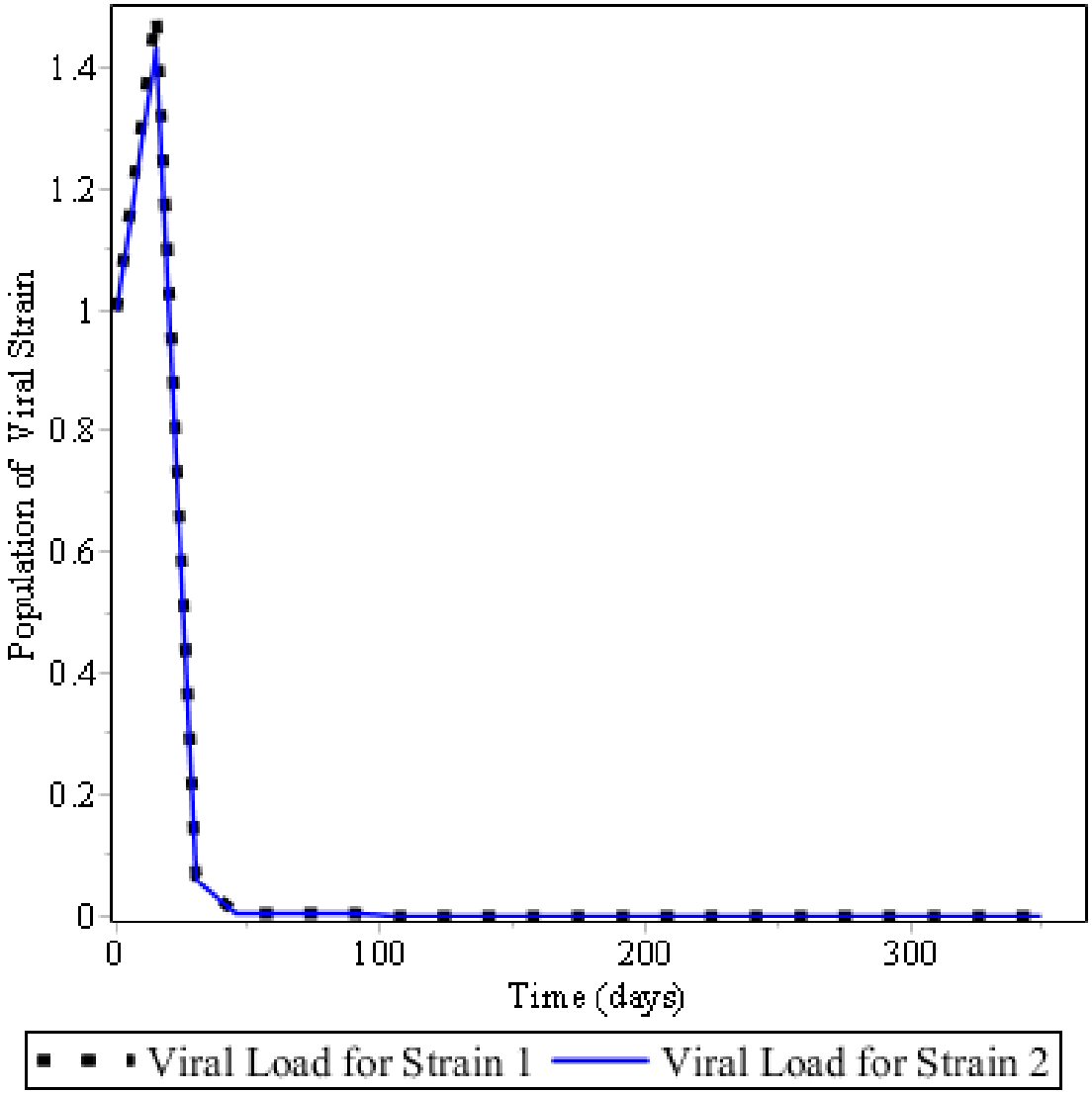

Figure 12: Infected CD4+T Cells with control strategy when number of viruses produced by the two viral strains are large

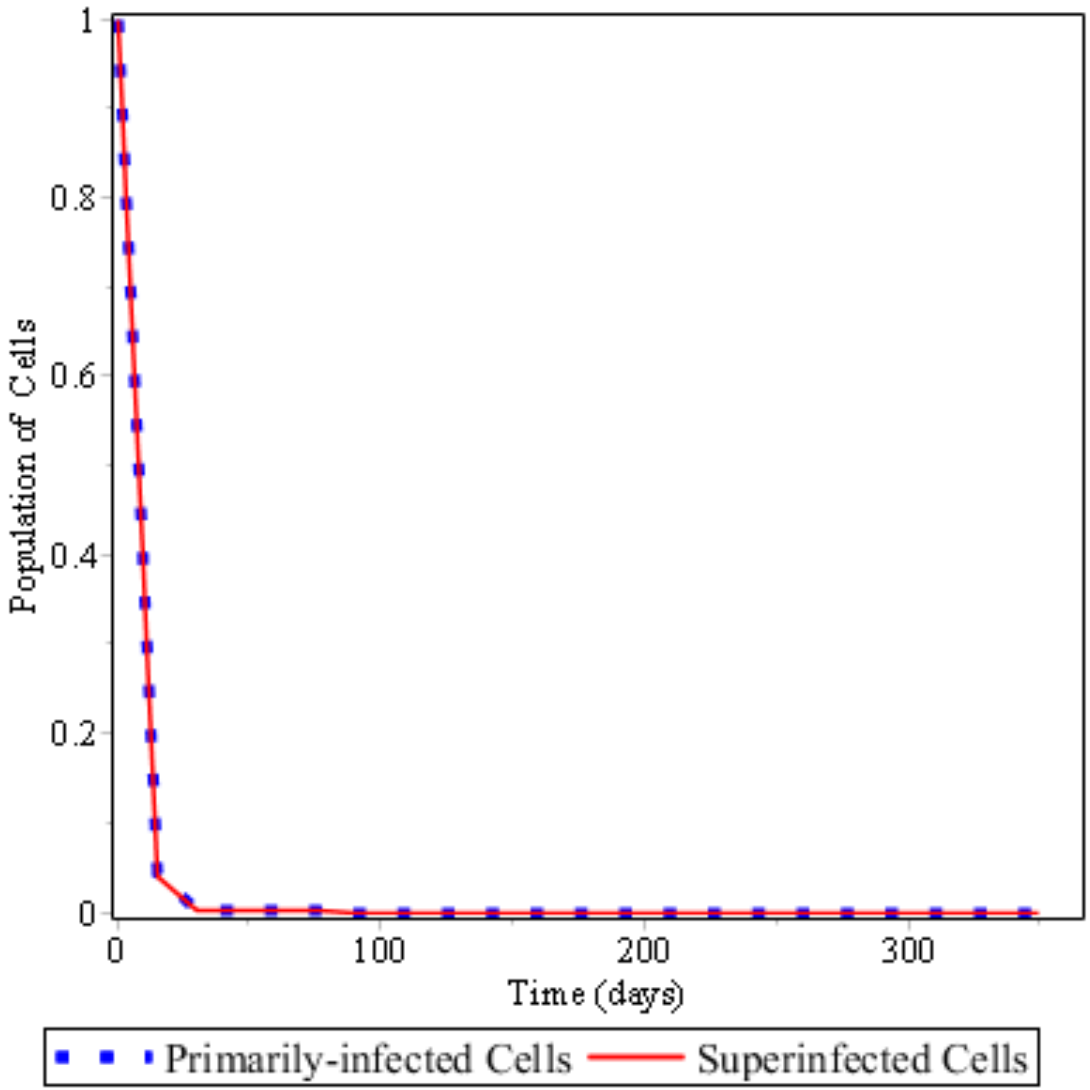

Figure 13: Infected CD4+T Cells with control strategy when number of viruses produced by the two viral strains are large

Large amount of second strain, $N_p = 500$, $N_s = 10000$

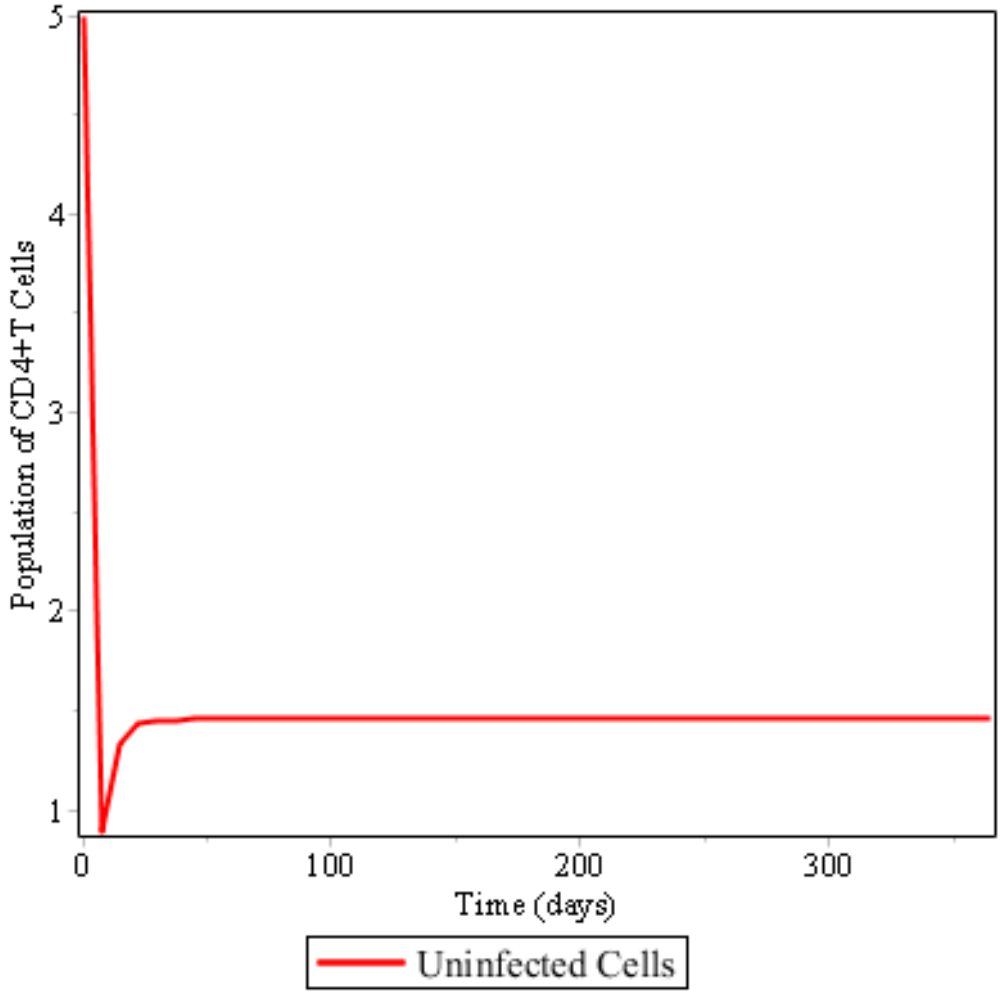

Figure 14: Uninfected CD4+T Cells when number of viruses produced by the second viral strain is large

Small amount of second strain, $N_p = 10,000$, $N_s = 500$

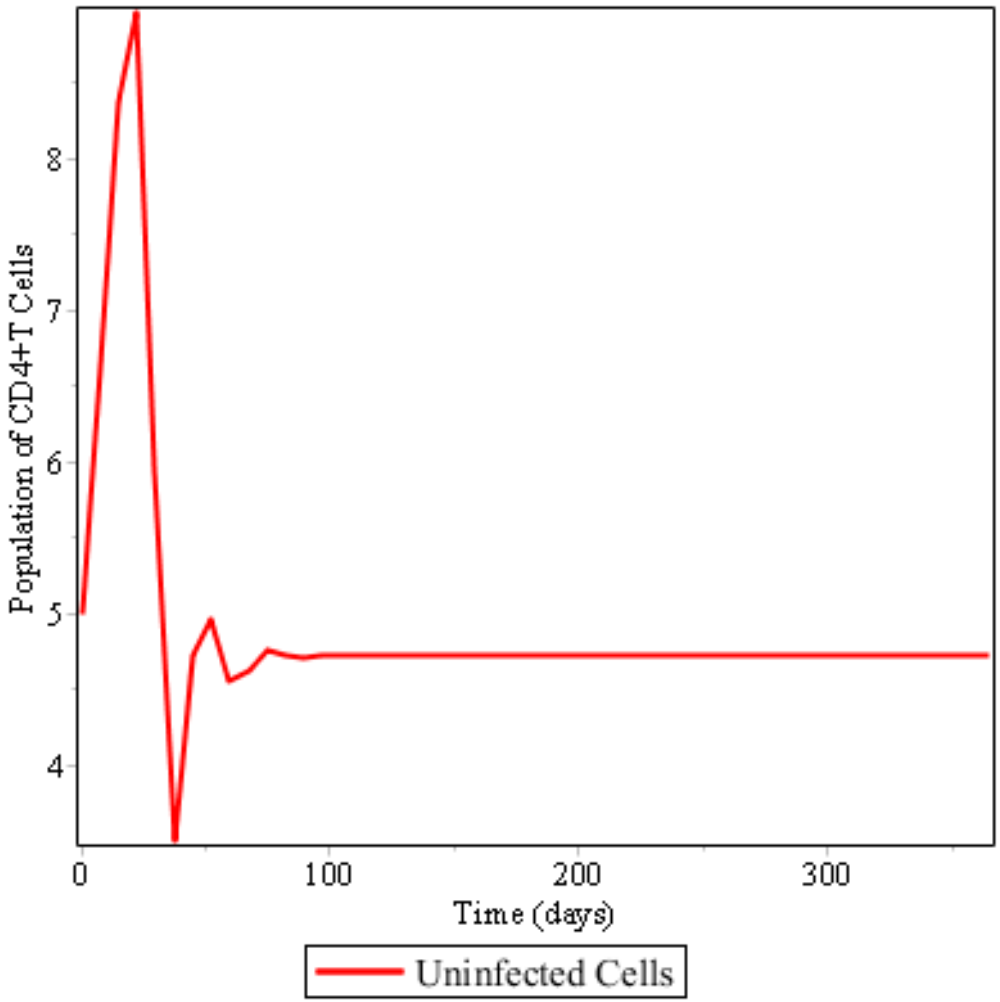

Figure 15: Uninfected CD4+ T Cells when number of viruses produced by the second strain is small

Findings-1

- The new HIV superinfection model that was developed is well-posed;
- The viral strains-free and viral strains equilibria states were obtained and found to be stable;
- The analysis of the reproduction number (R_0) showed that, HIV superinfection will be prevented when $R_0 < 1$;
- The most sensitive parameters are the rate of infection and rate at which new viruses are produced; and

Findings-2

- HIV viral strains can co-exist and co-circulate in their host, CD4+T cells.
- Small amount of viruses, that is when $N_p = 500$ *copies*/*ml*, produced by the second viral strain do not only increase the viral load of the first strain, but also increased the production of infected CD4+T cells and caused a significant decline in the population of healthy CD4+T cells.
- Hence, when a larger amount of virions (when $N_s = 10,000$ *copies*/*ml*), are produced by the second viral strains, the effects on healthy cells is more.

Findings-3

- The study reveals that that the new HIV superinfection model proposed minimizes the rate of infection and the rate at which new viruses are produced by the second strain of HIV.

- The models also show that the second strain of HIV contributes to the persistence of HIV in the system, increases viral load, orchestrates the multiplication of infected cells and results in the decline of the population of healthy cells.

Conclusion and Recommendations

- Prevent HIV Superinfection by blocking and preventing new infections of HIV in persons already diagnosed with HIV of a unique strain since there are currently no sufficient and documented information on the types of HIV strains that HIV-infected persons are carrying.

- Where HIV superinfection has occurred and discovered early, treatment must be targeted at the second strain also. Hence, the drug regime has to be remodeled to combat not only the first strain but also the second strain. Drug should be administered to keep the population of viruses produced by the second strain to a minimal level at a time not exceeding 50 days after infection.

- The study, therefore, concluded that the new HIV superinfection models developed in this study should be adopted to prevent HIV superinfection in persons already infected with one strain of HIV.

Contributions to Knowledge

- HIV superinfection is a reality though very scanty literature and works are available on this subject. This current work provided more facts about HIV superinfection and presented some results on epidemiological analysis that could be useful to other modelers and clinicians in developing and improving on HIV superinfection drug therapy.

- Most of the works that have been done on HIV superinfection focuses on effect of HIV superinfection on human population. This work however is an in-vivo study where the internal workings and interactions among CD4+T cells, HIV strains and CTL immune response cells were the focus.

- The different scenarios showing the behaviours of the second strain were illustrated in this work.

Suggestions for Further Studies

- This study covers HIV superinfection without viral strains recombination. Other researchers could extend this work to incorporate recombination of viral strains.

- Co-infection of HIV superinfection with other infectious diseases such as Hepatitis B Virus can also be considered in another study.

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