

Journal of Biological Systems, Vol. 26, No. 4 (2018) 1–23
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DOI: 10.1142/S0218339018500262



MODELING MONOCYTE-DERIVED DENDRITIC CELLS AS A THERAPEUTIC VACCINE AGAINST HIV

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Received 28 May 2018

Accepted 15 November 2018

Published

Successful immunologic control of HIV infection can be achieved in long-term non-progressors or HIV-1 controllers. Dendritic cells (DCs) are required for specific antigen presentation to naïve T lymphocytes and for antiviral, type I interferon secretion. To understand this mechanism, we develop a mathematical model that describes the role of direct presentation (replicating virus-infected DCs or other CD4⁺ T cells directly) and cross presentation (DCs obtain antigen processed in other infected cells such as CD4⁺ T lymphocytes) during HIV-1 infection. We find equilibria and determine stability in the case of no vaccination, and then, when vaccination is taken, we determine analytical thresholds for the strength and frequency of the vaccine to ensure the disease-free equilibrium remains stable. Our theoretical results suggest that the restoration of DC numbers may be predictive of immune restoration and may be a goal for immunotherapy to enhance viral control in a larger proportion of patients.

Keywords: HIV; Mathematical Model; Vaccination; Monocyte-Derived Dendritic Cells.

1. Introduction

In the last few decades, the advent of antiretroviral therapy (ART) has changed the course of HIV-1 infection by reducing the AIDS-related morbidity and mortality of patients.¹ This clinical benefit is clearly related to the limitation of the immunological damage that is caused by HIV-1 replication as well as to the specific responses against pathogens.^{2,3} However, ART induces a large range of toxicities, raising the concern of long-term use over decades. Therefore, the development of therapeutic strategies that may help to control viral replication and to limit drug exposure is essential.

The rationale for therapeutic immunization in HIV-1 infection is based on several lines of evidence suggesting that the immune system contributes to the long-term control of HIV-1 replication.⁴⁻⁹ Remarkably, a state of durable evolution of HIV-1 infection without a significant decrease of CD4⁺ T-cell counts and/or detectable viral replication does occur in a limited number of untreated patients called long-term non-progressors⁶ or HIV-1 controllers (reviewed in Ref. 8). These clinical observations provide clear evidence that durable containment of HIV-1 replication and/or prevention of disease progression without ART are possible. Additionally, mathematical models provide an alternative way to study the effects of different drugs. These studies also provide clinicians with almost instant results that would have required several months or even years when conducted on patients. Recently, impulsive differential equations have been used to describe the effects of adherence to antiretroviral drugs.¹⁰⁻¹⁵ Here we consider a mathematical model incorporating *in vitro* Dendritic cell (DC) vaccination via monocyte-derived dendritic cells (moDCs) against HIV-1 infection.

DCs are potent antigen-presenting cells (APCs) capable of inducing cytotoxic T-lymphocyte and helper T-cell responses that are essential in the process of vaccination.¹⁶⁻²¹ In designing a therapeutic vaccine for treating HIV/AIDS, an important aim is to increase the number and efficacy of the polyfunctional HIV-1 antigen-specific cytotoxic CD8⁺ T cells, CD4⁺ T cells and natural killer lysing.³ Several groups have demonstrated the efficacy of DC vaccines in the therapeutic treatment of viral infections including HIV-1.^{16,22-24} Here, we report the few studies on the use of DC-based vaccines in HIV-infected patients. Lu *et al.* studied 18 untreated infected subjects who were vaccinated with DCs.²⁵ It was observed that, after immunization, the median plasma viral load decreased by 80%; eight individuals showed a decrease of more than 90% over the period of the study (one year), while the reduction was weaker and transient for the other 10.²⁶ The CD4⁺ T cell count in those 10 subjects was increased significantly for a short period of time (three months), while no significant changes were observed in the CD8⁺ T cell count.²⁶ The total HIV antibodies remained unchanged after the vaccination and neutralizing antibodies were detected at low levels (1/10 titers).²⁷ We carried out the study on 18 patients with chronic HIV infection undergoing ART, who were randomized either to be vaccinated with autologous monocyte-derived DCs loaded with autologous heat-inactivated HIV (12 subjects) or to represent a control group (six subjects). After treatment (five immunizations at six-week intervals), ART was interrupted and the patients were observed for at least 24 weeks to monitor safety and both the immune and clinical responses. The DC-based vaccine was well tolerated, and there were no significant side effects, except for two patients who experienced mild flu-like symptoms 24h after immunization. In both cases, the DC-based vaccine was used in the form of live DCs. So it is to be assumed that *in vitro* antigen-loaded DCs have similar function as the *in vivo* antigen-loaded DCs when this vaccine is given to the infected individual.

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to model the mechanism of infection. The model explains how immune dysfunction can be a result of both an impaired DC function as well as CD4⁺ T cell infection. It contains eight compartments: uninfected CD4⁺ T helper cells (C_{D4}), infected CD4⁺ T helper cells (C_{D4}^I), free virus (V), DCs (D_C), antigen-loaded DCs (D_C^A), CD8 memory cells (W), CD8 effector cells (E) and interferon- γ (I). We assume that uninfected CD4⁺ T helper cells are produced at a rate λ , die at a rate d_1 and become infected by free virus at a rate β_1 . The interaction between uninfected CD4⁺ T helper cells and activated DCs may result in infection of the former at a rate β_2 . This infection is mediated via DC-sign which allows DCs to transport HIV from peripheral regions of the body to CD4⁺ T lymphocytes without themselves being infected. The fraction of activated DCs carrying the virus is $(1 - x)$. The infected cells die at a rate d_2 or are killed through lysis by CD8 effectors at a rate p . In the third equation, n represents the number of virus particles that are produced by one infected CD4⁺ T cell, and d_V is the clearance rate.

$$\begin{aligned}
 \frac{dC_{D4}}{dt} &= \lambda - d_1 C_{D4} - \beta_1 C_{D4} V - \beta_2 D_C^A C_{D4} \eta R, \\
 \frac{dC_{D4}^I}{dt} &= \beta_1 C_{D4} V + \beta_2 (1 - x) D_C^A C_{D4} \eta R - d_2 C_{D4}^I - p E C_{D4}^I, \\
 \frac{dV}{dt} &= n d_2 C_{D4}^I - d_V V, \\
 \frac{dD_C}{dt} &= \varphi - \mu_1 D_C - \epsilon D_C C_{D4}^I - \beta_3 D_C I, \\
 \frac{dD_C^A}{dt} &= \epsilon D_C C_{D4}^I + \beta_3 D_C I - \mu_2 D_C^A, \\
 \frac{dW}{dt} &= k C_{D4} D_C^A \eta R - q C_{D4}^I W - d_W W, \\
 \frac{dE}{dt} &= q C_{D4}^I W - d_E E, \\
 \frac{dI}{dt} &= \gamma C_{D4}^I - d_I I, \\
 \frac{dR}{dt} &= -gR \quad t \neq t_k, \\
 \Delta R &= R^i \quad t = t_k.
 \end{aligned} \tag{2.1}$$

DCs are produced at a rate φ and die at a rate μ_1 . It is assumed that they cross present the antigen from infected cells at a rate ϵ . This process does not require apoptosis or necrosis of infected cells. Interferon- γ (INF- γ) helps in the maturation of antigen-loaded DCs from immature DCs at a rate β_3 . The antigen-loaded DCs die at a rate μ_2 . We also include CD8 memory cells whose proliferation is a result of the interaction between antigen-loaded DCs and T helper cells at a rate k . Subsequently, antigen-loaded DCs (in the presence of Interleukin-2) enhance

their proliferation and mature into upregulated DCs, which in turn multiply the release of IFN- γ to induce the CD8 cells for further processing. The CD8 memory cells die at a rate d_W or differentiate into CD8 effector cells as a result of direct presentation of antigen by infected CD4⁺ T helper cells at a rate q . CD8 effectors

Table 1. List of parameters used for system (2.1).

Parameter	Definition	Value	Unit	Reference
C_{D4}	Uninfected CD4 ⁺ T population	Variable	mm ⁻³	—
C_{D4}^I	Infected CD4 ⁺ T helper cells population	Variable	mm ⁻³	—
V	Free virus	Variable	mm ⁻³	—
D_C	Dendritic cells population	Variable	mm ⁻³	—
D_C^*	Infected dendritic cells population	Variable	mm ⁻³	—
W	CD8 memory cells	Variable	mm ⁻³	—
E	CD8 effector cells	Variable	mm ⁻³	—
I	Interferon- γ concentration	Variable	mm ⁻³	—
R	moDC vaccine	Variable	mm ⁻³	—
λ	Influx rate of uninfected C_{D4} cells	14.3	mm ⁻¹ day ⁻¹	28
d_1	Death rate of C_{D4} cells	0.045	day ⁻¹	15
β_1	Bonding force between C_{D4} and V of each molecule in complex	1.09×10^{-6}	mm ³ day ⁻¹	29
β_2	Bonding force between C_{D4} and D_C^* of each molecule in complex	0.05	mm ⁻¹ day ⁻¹	21
x	The fraction of activated DCs carrying the virus	0–1	—	Assumed
d_2	Death rate of C_{D4}^I cells	0.2	day ⁻¹	29
p	Killing rate of C_{D4}^I cells by CD8 effectors	50	mm ³ day ⁻¹	31
n	Rate of production of virions per infected cell	540		32
d_V	Clearance rate of virus	2.1	day ⁻¹	33
φ	Influx rate of DCs	0.182	mm ⁻¹ day ⁻¹	34
μ_1	Death rate of DCs	0.008	day ⁻¹	21
ϵ	Rate of cross presentation of antigen by DC from infected cells	0.4	day ⁻¹	35
β_3	Maturation rate of DC	0.0025	day ⁻¹	Assumed
μ_2	Death rate of antigen loaded DCs	0.09	day ⁻¹	21
k	Bonding force between C_{D4} and D_C^* of each molecule in complex	0.5985	mm ³ day ⁻¹	34
q	Rate of direct presentation of antigen by infected CD4 ⁺ T helper cells	0.07	day ⁻¹	35
d_W	Death rate of CD8 memory cells	0.9	mm ⁻³ day ⁻¹	21
d_E	Death rate of CD8 effector cells	0.85	day ⁻¹	21
γ	Production rate of IFN- γ	0.06	mm ⁻³ day ⁻¹	36
d_I	Decay rate of IFN- γ	0.08	day ⁻¹	Assumed
g	Rate that the vaccine is cleared <i>in vivo</i>	1	day ⁻¹	30
η	Efficacy rate of the vaccine	0.28	μ mm ⁻³	Assumed

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decay at a rate d_E , which is higher than the death rate of CD8 memory cells. The production of interferon is assumed to be proportional to the influx of the infected CD4⁺ T cells at a rate γ .

$R(t)$ denotes the moDC concentration and η is its efficacy rate. Parameter g represents the rate at which moDC is cleared. R^i is the vaccine strength (a constant) that is taken at each impulse time t_k , ($k = 1, 2, 3, \dots$). Note that the impulse times t_k may not be fixed, since vaccination may occur at either regular or irregular intervals. Parameters are listed in Table 1.

3. The System Without Vaccination

First, we analyze the (continuous) model in the absence of treatment. In this section, we discuss the existence of the equilibria and their stability for model (2.1) when the last two equations are absent and $R = 0$.

3.1. The disease-free equilibrium (DFE)

In the absence of infection, we have $C_{D4}^{I0} = D_C^{A0} = V^0 = W^0 = E^0 = I^0 = 0$ and $C_{D4}^0 = \frac{\lambda}{d_1}$, $D_C^0 = \frac{\varphi}{\mu_1}$. Therefore, the DFE always exists and is in the form $E_0(C_{D4}^0, C_{D4}^{I0}, V^0, D_C^0, D_C^{A0}, W^0, E^0, I^0) = (\frac{\lambda}{d_1}, 0, 0, \frac{\varphi}{\mu_1}, 0, 0, 0, 0)$. The infected compartments are C_{D4}^I, V and D_C^A . Thus the linearization of the second, third and sixth equations of model (2.1) at the disease-free state E_0 can be rewritten in the following form:

$$\frac{dX}{dt} = (Y_{E_0} - Z_{E_0})X,$$

where $X = (C_{D4}^I, V, D_C^A)$. The new infection terms, Y_{E_0} , and the remaining transfer terms, Z_{E_0} , are given by

$$Y_{E_0} = \begin{pmatrix} 0 & \beta_1 C_{D4}^0 & \beta_2(1-x)C_{D4}^0 \\ nd_2 & 0 & 0 \\ \epsilon D_C^0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad Z_{E_0} = \begin{pmatrix} d_2 & 0 & 0 \\ 0 & d_V & 0 \\ 0 & 0 & \mu_2 \end{pmatrix}.$$

A threshold criteria, R_0 , can be derived using the spectral radius of the next-generation matrix.^{37,38} Thus

$$R_0 = \rho(Y_{E_0} Z_{E_0}^{-1}) = \max_{|\xi|} \det \begin{pmatrix} \xi & -\frac{\beta_1 C_{D4}^0}{d_V} & -\frac{\beta_2(1-x)C_{D4}^0}{\mu_2} \\ -n & \xi & 0 \\ -\frac{\epsilon D_C^0}{d_2} & 0 & \xi \end{pmatrix}$$

$$= \max_{|\xi|} \det \begin{pmatrix} \xi & -\frac{\beta_1 \lambda}{d_1 d_V} & -\frac{\beta_2(1-x)\lambda}{d_1 \mu_2} \\ -n & \xi & 0 \\ -\frac{\epsilon \varphi}{\mu_1 d_2} & 0 & \xi \end{pmatrix}.$$

The characteristic equation of $Y_{E_0} Z_{E_0}^{-1}$ is

$$\xi \left[\xi^2 - \left(\frac{n\beta_1 \lambda}{d_V d_1} + \frac{\beta_2(1-x)\lambda \epsilon \varphi}{d_1 d_2 \mu_1 \mu_2} \right) \right] = 0.$$

Then

$$R_0 = \sqrt{\frac{\lambda}{d_1} \left(\frac{n\beta_1}{d_V} + \frac{\beta_2(1-x)\epsilon \varphi}{d_2 \mu_1 \mu_2} \right)}.$$

Thus, E_0 always exists, is locally stable if $R_0 < 1$ and is unstable if $R_0 > 1$.³⁸ We use the threshold, R_0 , to answer the question of whether the infection can be established. When $R_0 > 1$, HIV infection can take hold. Otherwise, the virus will be eliminated.

3.2. Endemic equilibrium

The endemic equilibrium (if it exists) can be expressed in the form $\bar{E} = (\bar{C}_{D4}, \bar{C}_{D4}^I, \bar{V}, \bar{D}_C, \bar{D}_C^A, \bar{W}, \bar{E}, \bar{I})$, where

$$\begin{aligned} \bar{C}_{D4} &= \frac{\lambda d_V \mu_2 (\mu_1 d_1 + (\epsilon d_I + \beta_3 \gamma) \bar{C}_{D4}^I)}{\bar{v}}, \\ \bar{V} &= \frac{n d_2 \bar{C}_{D4}^I}{d_V}, \\ \bar{D}_C &= \frac{\varphi d_I}{\mu_1 d_I + (\epsilon d_I + \beta_3 \gamma) \bar{C}_{D4}^I}, \\ \bar{D}_C^A &= \frac{\varphi (\epsilon d_I + \beta_3 \gamma) \bar{C}_{D4}^I}{\mu_2 (\mu_1 d_I + (\epsilon d_I + \beta_3 \gamma) \bar{C}_{D4}^I)}, \\ \bar{W} &= \frac{k \varphi (\epsilon d_I + \beta_3 \gamma) \bar{C}_{D4} \bar{C}_{D4}^I}{\mu_2 (q \bar{C}_{D4}^I + d_W) (\mu_1 d_I + (\epsilon d_I + \beta_3 \gamma) \bar{C}_{D4}^I)}, \\ \bar{E} &= \frac{k q \varphi (\epsilon d_I + \beta_3 \gamma) \bar{C}_{D4} (\bar{C}_{D4}^I)^2}{\mu_2 d_E (q \bar{C}_{D4}^I + d_W) (\mu_1 d_I + (\epsilon d_I + \beta_3 \gamma) \bar{C}_{D4}^I)}, \\ \bar{I} &= \frac{\gamma \bar{C}_{D4}^I}{d_I}, \end{aligned} \tag{3.1}$$

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with the denominator in the first term given by

$$\bar{v} = d_1 d_V d_I \mu_1 \mu_2 + (d_V (d_1 \mu_2 + \beta_2 \varphi) (\epsilon d_I + \beta_3 \gamma) + \beta_1 n d_2 d_I \mu_1 \mu_2) \bar{C}_{D4}^I + \beta_1 n \mu_2 d_2 (\epsilon d_I + \beta_3 \gamma) (\bar{C}_{D4}^I)^2.$$

Here \bar{C}_{D4}^I (if it exists) is a positive, real root of the quartic equation

$$f(\bar{C}_{D4}^I) = \Theta_1 (\bar{C}_{D4}^I)^4 + \Theta_2 (\bar{C}_{D4}^I)^3 + \Theta_3 (\bar{C}_{D4}^I)^2 + \Theta_4 \bar{C}_{D4}^I + \Theta_5 = 0, \quad (3.2)$$

with

$$\begin{aligned} \Theta_1 &= \beta_1 n q \mu_2^2 d_2^2 d_V d_E (\epsilon d_I + \beta_3 \gamma)^2, \\ \Theta_2 &= \beta_1 n q \mu_1 \mu_2^2 d_2^2 d_V d_E d_I (\epsilon d_I + \beta_3 \gamma) + \beta_1 n \mu_2^2 d_2^2 d_V d_E d_W (\epsilon d_I + \beta_3 \gamma)^2 \\ &\quad + q \mu_2 d_V^2 d_E d_2 (d_1 \mu_2 + \beta_2 \varphi) (\epsilon d_I + \beta_3 \gamma)^2 + \beta_1 q n d_2^2 d_I \mu_1 \mu_2^2 d_V d_E (\epsilon d_I + \beta_3 \gamma) \\ &\quad + \lambda p q k \varphi \mu_2 d_V^2 (\epsilon d_I + \beta_3 \gamma)^2 - \beta_1 q \lambda n \mu_2^2 d_2 d_V d_E (\epsilon d_I + \beta_3 \gamma)^2, \\ \Theta_3 &= (\epsilon d_I + \beta_3 \gamma) [(\beta_1 n \mu_1 \mu_2^2 d_2^2 d_V d_I d_E d_W + q \mu_1 \mu_2^2 d_1 d_2 d_I d_V^2 d_E + \lambda p q k \varphi d_V^2 d_I \mu_1 \mu_2) \\ &\quad - (\beta_1 n \lambda q \mu_1 \mu_2^2 d_2 d_V d_I d_E + \lambda d_V \mu_2 d_E (\epsilon d_I + \beta_3 \gamma) (\beta_1 n d_2 d_W \mu_2 \\ &\quad + \beta_2 (1-x) \varphi q d_V) + q \lambda \beta_1 n \mu_1 \mu_2^2 d_2 d_I d_E d_V)], \\ \Theta_4 &= d_2 d_V d_E \mu_2 (\beta_1 n d_2 d_I \mu_1 \mu_2 + (d_2 \mu_2 + \beta_2 \varphi) (\epsilon d_I + \beta_3 \gamma)) (\mu_1 d_I (d_W + q) \\ &\quad + d_W (\epsilon d_I + \beta_3 \gamma)) - \lambda d_V \mu_2 (d_I \mu_1 (\beta_1 n d_I d_2 d_E \mu_1 \mu_2 q \\ &\quad + d_E (\epsilon d_I + \beta_3 \gamma) (\beta_1 n \mu_2 d_2 d_W + \beta_2 (1-x) \varphi q d_V)) \\ &\quad + d_E d_W (\epsilon d_I + \beta_3 \gamma) (\beta_1 n \mu_1 \mu_2 d_2 d_I + \beta_2 (1-x) \varphi d_V (\epsilon d_I + \beta_3 \gamma))), \\ \Theta_5 &= \mu_1 \mu_2 d_V d_I d_E d_W (\mu_1 \mu_2 d_1 d_2 d_V d_I - \lambda (\beta_1 n d_2 d_I \mu_1 \mu_2 \\ &\quad + \beta_2 (1-x) \varphi d_V (\epsilon d_I + \beta_3 \gamma))). \end{aligned} \quad (3.3)$$

Now, to show the existence of a positive endemic equilibrium E^* of system (2.1), we use Descartes' rule of signs. Following this rule, we concluded that Eq. (3.2) will have a unique positive root either if (i) $\Theta_i < 0$, for $(i = 2, 3, 4, 5)$ or (ii) $\Theta_2, \Theta_3, \Theta_4 > 0$ and $\Theta_5 < 0$. Numerically, we plotted the graph of $f(\bar{C}_{D4}^I)$ against \bar{C}_{D4}^I in Fig. 2 for values given in Table 1. We can see from the figure that the graph cuts the negative vertical axis at P_1 and the positive horizontal axis at P_2 . P_1 indicates the negativity of Θ_5 , which satisfies the Descartes condition and P_2 indicates the existence of a positive root of $f(\bar{C}_{D4}^I) = 0$. No other positive root exists, as the graph is increasing in the interval from P_2 to infinity. Hence, E^* is unique for these parameter choices.

Remark. When infection does not exist (i.e., $\bar{C}_{D4}^I = 0$), then $f(\bar{C}_{D4}^I) = \Theta_5$. $\Theta_5 > 0$ implies $R_0 < (1 - \frac{\gamma \beta_2 \beta_3 (1-x) \lambda \varphi}{\mu_1 \mu_1 d_1 d_2 d_I}) < 1$. That means when $R_0 < 1$, then the DFE is the only equilibrium that exists and E^* does not exist.

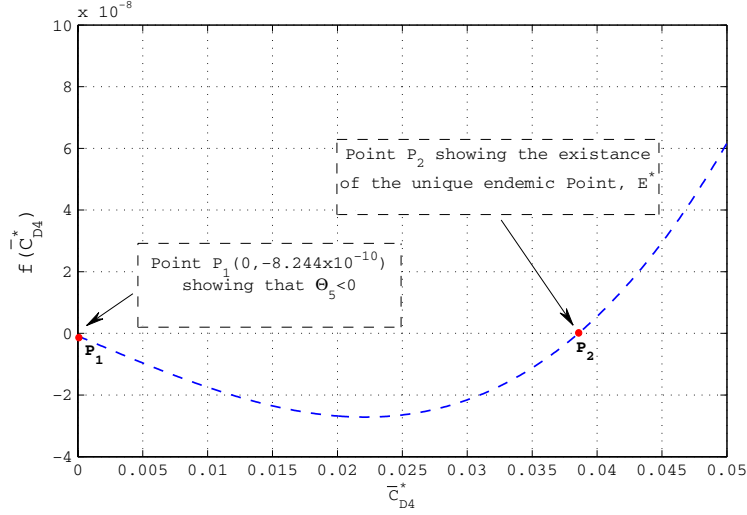


Fig. 2. Existence of a unique positive root of $f(\bar{C}_{D4}^I) = 0$ satisfying $\Theta_5 < 0$. Values are given in Table 1.

3.3. The global stability of E_0

In the absence of HIV, the concentration of the $CD4^+$ T cells, C_{D4} , and the concentration of the *in vivo* dendritic cells, D_C , should satisfy

$$\frac{dC_{D4}}{dt} = \lambda - d_1 C_{D4}, \quad (3.4)$$

$$\frac{dD_C}{dt} = \varphi - \mu_1 D_C. \quad (3.5)$$

For example, the solution of the first equation of system (3.5) is

$$C_{D4}(t) = \frac{\lambda}{d_1} - \left(\frac{\lambda}{d_1} - C_{D4}(0) \right) e^{-d_1 t}.$$

It follows that $C_{D4}(t) \rightarrow \lambda/d_1$ when $t \rightarrow \infty$. If the initial value satisfies $C_{D4}(0) < \lambda/d_1$, then all trajectories remain below λ/d_1 . Conversely, if the initial value satisfies $C_{D4}(0) > \lambda/d_1$, then all trajectories remain above λ/d_1 .

Suppose the initial values of the immune system are at or below its steady state. Then the inequalities $C_{D4} \leq \lambda/d_1$ and $D_C \leq \varphi/\mu_1$ can be used in our proof below. To prove the global stability of the disease-free equilibrium, we take a Liapunov function of the form:

$$L = C_{D4}^I + \psi_1 V + \psi_2 D_C^* + \psi_3 W + \psi_4 E + \psi_5 I, \quad (3.6)$$

where the coefficients $\psi_1, \psi_2, \psi_3, \psi_4$ and ψ_5 are positive constants to be chosen later. On differentiating (3.6) with respect to t , the value of L along the solutions of the

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continuous model is obtained as

$$\begin{aligned} \frac{dL}{dt} \leq & C_{D4}^I \left[-d_2 + \psi_1 n d_2 + \psi_2 \frac{\epsilon \varphi}{\mu_1} + \gamma \psi_5 \right] + V \left[\frac{\beta_1 \lambda}{d_1} - \psi_1 d_V \right] \\ & + D_C^A \left[\frac{\beta_2 (1-x) \lambda}{d_1} - \psi_2 \mu_2 + \psi_3 \frac{k \lambda}{d_1} \right] - \psi_3 d_W W \\ & - p E C_{D4}^I - \psi_4 d_E E + I \left[\psi_2 \frac{\beta_2 \varphi}{\mu_1} - \psi_5 d_I \right] + (\psi_4 - \psi_3) q C_{D4}^I W. \end{aligned} \quad (3.7)$$

Thus, we can choose positive numbers $\psi_1, \psi_2, \psi_3, \psi_4$ and ψ_5 as follows:

$$\begin{aligned} \psi_1 &= \frac{\beta_1 \varphi}{d_1 d_V}, \\ \psi_2 &= \frac{\mu_1 d_I d_2 (d_1 d_V - n \beta_1 \lambda)}{d_1 d_V \varphi (\epsilon d_I + \gamma \beta_3)}, \\ \psi_3 = \psi_4 &= \frac{\mu_1 \mu_2 d_2 d_I (d_1 d_V - n \beta_1 \lambda) - \beta_2 (1-x) \lambda \varphi d_V (\epsilon d_I + \gamma \beta_3)}{k \lambda \varphi d_V (\epsilon d_I + \gamma \beta_3)}, \\ \psi_5 &= \frac{\beta_3 d_2 (d_1 d_V - n \beta_1 \lambda)}{d_1 d_V (\epsilon d_I + \gamma \beta_3)}. \end{aligned}$$

Note that $\psi_1, \psi_2, \psi_5 > 0$, provided $d_1 d_V > n \beta_1 \lambda$, and $\psi_3 = \psi_4 > 0$ if $R_0 < (1 - \frac{\gamma \beta_2 \beta_3 (1-x) \lambda \varphi}{\mu_1 \mu_2 d_1 d_2 d_I}) < 1$.

Hence, we have $dL/dt \leq 0$ when $R_0 < 1$, and, when $C_{D4}^I = 0$, we get that $V \rightarrow 0, D_C^* \rightarrow 0, W \rightarrow 0, E \rightarrow 0, I \rightarrow 0$ as $t \rightarrow \infty$. Then the disease-free equilibrium is globally asymptotically stable when $R_0 \leq 1$ by the Liapunov–Lasalle theorem.³⁹

Remark. Although \bar{E} exists for $R_0 > 1$, we have not proven that it is locally stable. However, numerical simulations converged to this equilibrium and did not reveal any other phenomena.

4. The System with Vaccination

Consider the impulsive subsystem

$$\begin{aligned} \frac{dR}{dt} &= -gR, \quad t \neq t_k, \\ \Delta R &= R^i, \quad t = t_k. \end{aligned}$$

There is an impulsive periodic orbit if the time between doses is constant; i.e., $\tau \equiv t_{k+1} - t_k$. We shall fix R^* constant such that

$$\frac{R^i e^{-g\tau}}{1 - e^{-g\tau}} \leq R^* \leq \frac{R^i}{1 - e^{-g\tau}}. \quad (4.1)$$

Note that we are choosing a fixed constant as representative of the impulsive periodic orbit in order to perform a stability analysis; see Ref. 40.

The disease-free equilibrium is in the form

$$\tilde{E}_0(C_{D4}^0, C_{D4}^{I0}, V^0, D_C^0, D_C^{A0}, W^0, E^0, I^0, R^0) = \left(\frac{\lambda}{d_1}, 0, 0, \frac{\varphi}{\mu_1}, 0, 0, 0, 0, R^* \right).$$

Thus, similar to Sec. 3.1, the threshold for system (2.1) is

$$\tilde{R}_0 = \sqrt{\frac{\lambda}{d_1} \left(\frac{n\beta_1}{d_V} + \frac{\beta_2(1-x)\epsilon\varphi\eta R^*}{d_2\mu_1\mu_2} \right)}.$$

The endemic equilibrium is in the form $\tilde{E}(\tilde{C}_{D4}, \tilde{C}_{D4}^I, \tilde{V}, \tilde{D}_C, \tilde{D}_C^A, \tilde{W}, \tilde{E}, \tilde{I}, R^*)$, where

$$\begin{aligned} \tilde{C}_{D4} &= \frac{\lambda d_V \mu_2 (\mu_1 d_1 + (\epsilon d_I + \beta_3 \gamma) \tilde{C}_{D4}^I)}{\bar{v}}, \\ \tilde{V} &= \frac{n d_2 \tilde{C}_{D4}^I}{d_V}, \\ \tilde{D}_C &= \frac{\varphi d_I}{\mu_1 d_I + (\epsilon d_I + \beta_3 \gamma) \tilde{C}_{D4}^I}, \\ \tilde{D}_C^A &= \frac{\varphi (\epsilon d_I + \beta_3 \gamma) \tilde{C}_{D4}^I}{\mu_2 (\mu_1 d_I + (\epsilon d_I + \beta_3 \gamma) \tilde{C}_{D4}^I)}, \\ \tilde{W} &= \frac{k \varphi (\epsilon d_I + \beta_3 \gamma) \tilde{C}_{D4} \tilde{C}_{D4}^I}{\mu_2 (q \tilde{C}_{D4}^I + d_W) (\mu_1 d_I + (\epsilon d_I + \beta_3 \gamma) \tilde{C}_{D4}^I)}, \\ \tilde{E} &= \frac{k q \varphi (\epsilon d_I + \beta_3 \gamma) \tilde{C}_{D4} (\tilde{C}_{D4}^I)^2}{\mu_2 d_E (q \tilde{C}_{D4}^I + d_W) (\mu_1 d_I + (\epsilon d_I + \beta_3 \gamma) \tilde{C}_{D4}^I)}, \\ \tilde{I} &= \frac{\gamma \tilde{C}_{D4}^I}{d_I}, \end{aligned} \tag{4.2}$$

where

$$\begin{aligned} \bar{v} &= d_1 d_V d_I \mu_1 \mu_2 + (d_V (d_1 \mu_2 + \beta_2 \varphi \eta R^*) (\epsilon d_I + \beta_3 \gamma) + \beta_1 n d_2 d_I \mu_1 \mu_2) \tilde{C}_{D4}^I \\ &\quad + \beta_1 n \mu_2 d_2 (\epsilon d_I + \beta_3 \gamma) (\tilde{C}_{D4}^I)^2. \end{aligned}$$

Here \tilde{C}_{D4}^I (if it exists) is a positive, real root of the quartic equation

$$f(\tilde{C}_{D4}^I) = \tilde{\Theta}_1 (\tilde{C}_{D4}^I)^4 + \tilde{\Theta}_2 (\tilde{C}_{D4}^I)^3 + \tilde{\Theta}_3 (\tilde{C}_{D4}^I)^2 + \tilde{\Theta}_4 \tilde{C}_{D4}^I + \tilde{\Theta}_5 = 0, \tag{4.3}$$

where

$$\begin{aligned} \tilde{\Theta}_1 &= \beta_1 n q \mu_2^2 d_2^2 d_V d_E (\epsilon d_I + \beta_3 \gamma)^2, \\ \tilde{\Theta}_2 &= \beta_1 n q \mu_1 \mu_2^2 d_2^2 d_V d_E d_I (\epsilon d_I + \beta_3 \gamma) + \beta_1 n \mu_2^2 d_2^2 d_V d_E d_W (\epsilon d_I + \beta_3 \gamma)^2 \end{aligned}$$

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$$\begin{aligned}
 & + q\mu_2 d_V^2 d_E d_2 (d_1 \mu_+ \beta_2 \varphi) (\epsilon d_I + \beta_3 \gamma)^2 + \beta_1 q n d_2^2 d_I \mu_1 \mu_2^2 d_V d_E (\epsilon d_I + \beta_3 \gamma) \\
 & + \lambda p q k \varphi \mu_2 d_V^2 (\epsilon d_I + \beta_3 \gamma)^2 - \beta_1 q \lambda n \mu_2^2 d_2 d_V d_E (\epsilon d_I + \beta_3 \gamma)^2, \\
 \tilde{\Theta}_3 = & (\epsilon d_I + \beta_3 \gamma) [(\beta_1 n \mu_1 \mu_2^2 d_2^2 d_V d_I d_E d_W + q \mu_1 \mu_2^2 d_1 d_2 d_I d_V^2 d_E + \lambda p q k \varphi d_V^2 d_I \mu_1 \mu_2) \\
 & - (\beta_1 n \lambda q \mu_1 \mu_2^2 d_2 d_V d_I d_E + \lambda d_V \mu_2 d_E (\epsilon d_I + \beta_3 \gamma) (\beta_1 n d_2 d_W \mu_2 \\
 & + \beta_2 (1-x) \varphi q d_V \eta R^*) + q \lambda \beta_1 n \mu_1 \mu_2^2 d_2 d_I d_E d_V)], \\
 \tilde{\Theta}_4 = & d_2 d_V d_E \mu_2 (\beta_1 n d_2 d_I \mu_1 \mu_2 + (d_2 \mu_2 + \beta_2 \varphi \eta R^*) (\epsilon d_I + \beta_3 \gamma)) (\mu_1 d_I (d_W + q) \\
 & + d_W (\epsilon d_I + \beta_3 \gamma)) - \lambda d_V \mu_2 (d_I \mu_1 (\beta_1 n d_I d_2 d_E \mu_1 \mu_2 q \\
 & + d_E (\epsilon d_I + \beta_3 \gamma) (\beta_1 n \mu_2 d_2 d_W + \beta_2 (1-x) \varphi q d_V \eta R^*)) \\
 & + d_E d_W (\epsilon d_I + \beta_3 \gamma) (\beta_1 n \mu_1 \mu_2 d_2 d_I + \beta_2 (1-x) \varphi q d_V \eta R^* (\epsilon d_I + \beta_3 \gamma))), \\
 \tilde{\Theta}_5 = & \mu_1 \mu_2 d_V d_I d_E d_W (\mu_1 \mu_2 d_1 d_2 d_V d_I - \lambda (\beta_1 n d_2 d_I \mu_1 \mu_2 \\
 & + \beta_2 (1-x) \varphi q d_V \eta R^* (\epsilon d_I + \beta_3 \gamma))). \tag{4.4}
 \end{aligned}$$

Using similar methods as in Sec. 3.1, we have the following result about the existence and stability of the disease-free periodic orbit and the endemic periodic orbit: Eq. (4.3) will have a unique positive root if either (i) $\tilde{\Theta}_i < 0$, for $i = 2, 3, 4, 5$ or (ii) $\tilde{\Theta}_2, \tilde{\Theta}_3, \tilde{\Theta}_4 > 0$ and $\tilde{\Theta}_5 < 0$.

- Remarks.** (1) Although \tilde{E} exists when $\tilde{R}_0 > 1$, it may or may not be stable, depending on parameters. If it is unstable, then we may have higher-order behavior, such as higher-order periodicity or chaos.
- (2) Note that, since \tilde{R}_0 is fluctuating due to the impulsive effect, we require $\tilde{R}_0 < 1$ to hold at all times for eradication to be guaranteed. Conversely, the theorem only guarantees existence of \tilde{E} and instability of \tilde{E}_0 when $\tilde{R}_0 > 1$ for all times. If \tilde{R}_0 fluctuates around 1, the results are indeterminate.

Now we have the following theorem which shows the dependence upon the strength and frequency of the vaccination.

Let us first define

$$R_1 = \frac{M}{\zeta_1}, \quad R_2 = \frac{M}{\zeta_2}, \quad \tau_1 = \frac{1}{g} \ln \left(1 + \frac{R^i}{M} \right) \quad \text{and} \quad \tau_2 = -\frac{1}{g} \ln \left(1 - \frac{R^i}{M} \right),$$

where $\zeta_1 = \frac{e^{-g\tau}}{1-e^{-g\tau}}$, $\zeta_2 = \frac{1}{1-e^{-g\tau}}$ and $M = \frac{\mu_1 \mu_2 d_2 (d_1 d_V - n \lambda \beta_1)}{\lambda \beta_2 (1-x) \gamma \varphi \eta d_V}$.

Theorem 4.1. *When $0 \leq R^i < R_2$ (so that $\tilde{R}_0 < 1$), \tilde{E}_0 is globally stable and \tilde{E}^* does not exist.*

Proof. From the relation (4.1), we have obtained $R^i \zeta_1 \leq R^* \leq R^i \zeta_2$. For a fixed dosing frequency, if $R^i < R_2$ (i.e., when the drug strength falls in the lower region

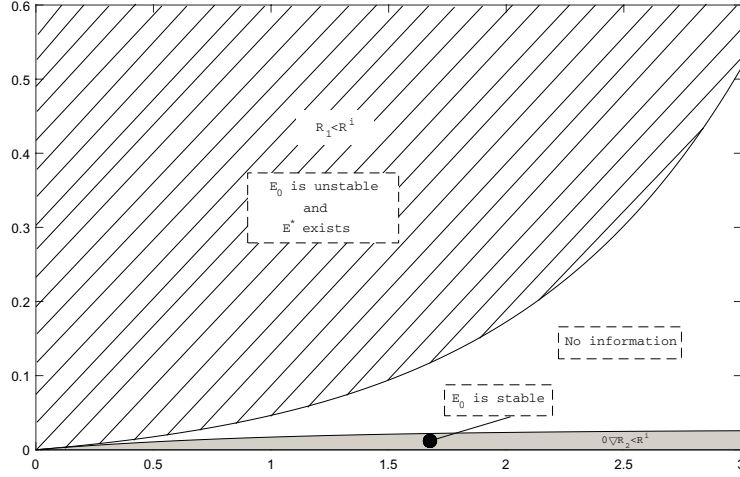


Fig. 3. Regions of stability. If R^i is sufficiently small and τ suitably large, then E_0 is guaranteed to be stable and E^* does not exist. If R^i is sufficiently large or τ is suitably small, then E_0 is guaranteed to be unstable and E^* exists. The exact threshold lies between the two regions.

of Fig. 3), then $R^i < \frac{M}{1-e^{-g\tau}} \Rightarrow M > R^i \zeta_2 > R^*$. Thus

$$\begin{aligned} \lambda\beta_2(1-x)\gamma\varphi\eta d_V R^* &< \mu_1\mu_2 d_2(d_1 d_V - n\lambda\beta_1), \\ &\Rightarrow \mu_1\mu_2 d_2 n\lambda\beta_1 + \lambda\beta_2(1-x)\gamma\varphi\eta d_V R^* < \mu_1\mu_2 d_2 d_1 d_V, \\ &\Rightarrow \tilde{R}_0 < 1. \end{aligned}$$

Now let $x_1 = (C_{D_4}^I, V, D_C^A)$ and note that $x_1 \geq 0$. One can easily verify that $\frac{dx_1}{dt} \leq (F - V)x_1$, where

$$F = \begin{pmatrix} 0 & \beta_1 C_{D_4}^0 & \beta_2(1-x)\eta C_{D_4}^0 R^* \\ n d_2 & 0 & 0 \\ \epsilon D_C^0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} d_2 & 0 & 0 \\ 0 & d_V & 0 \\ 0 & 0 & \mu_2 \end{pmatrix}.$$

We take $u = (C_{D_4}^0, \beta_1 C_{D_4}^0, \beta_2(1-x)\eta C_{D_4}^0 R^*) > 0$, and it then follows from the fact $\tilde{R}_0 = \rho(FV^{-1}) = \rho(V^{-1}F)$ that u is a left eigenvector associated with the eigenvalue \tilde{R}_0 of the matrix $V^{-1}F$; i.e., $uV^{-1}F = \tilde{R}_0 u$.

Let us consider a Lyapunov function

$$\mathcal{L} = uV^{-1}x_1.$$

Differentiating \mathcal{L} along the solution of (2.1), we have

$$\mathcal{L}' = uV^{-1}x_1' \leq uV^{-1}(F - V)x_1 = u(\tilde{R}_0 - 1)x_1.$$

Therefore, when $\tilde{R}_0 < 1$, $\mathcal{L}' < 0$ unless $x_1 = 0$, and the equality $\mathcal{L} = 0$ implies that $ux_1 = 0$. This leads to $C_{D_4}^I = V = D_C^A = 0$ by noting the positive components of u . Hence, when $\tilde{R}_0 < 1$, equations of (2.1) yield $C_{D_4}^I = D_C^A = V = W = E =$

$I = 0$ and $C_{D4}^I = C_{D4}^{I0}$, $D_C = D_C^0$. Therefore, the invariant set on which $\mathcal{L} = 0$ contains only one point, which is the DFE, and hence it is globally stable and \tilde{E}^* does not exist. \square

5. Numerical Simulations

To study the dynamical behavior of model (2.1), we perform numerical computations. The data used for the simulations are given in Table 1. Parameter n is composed of two factors: one is the probability that HIV virus is infectious; the other is the rate of production of virions per infected cell. Here, we choose $n = 0.1 \times 5400 = 540$,³² where 0.102 is the rate of infectious virus in total HIV virus offspring. The number of CD4⁺ T cells in the peripheral blood is approximately 460–1000/mm³, although it fluctuates both diurnally and with the total lymphocyte count.^{29,41} We assume there are, on average, 750/ml³ CD4⁺ T lymphocytes in a healthy individual; i.e., $C_{D4}(0) = 750$. On the other hand, the usual range for the CD4:CD8 ratio is between 0.9 and 1.9. This means that there are about 1–2 CD4 cells for every CD8 cell.⁴² So we choose $W(0) = 375$. Other initial conditions are: $C_{D4}^I(0) = 0$, $V(0) = 10$, $D_C(0) = 15$, $D_C^A(0) = 0$, $E(0) = 8.25$, $I(0) = 0.03$. The unit of each concentration is mm⁻³.

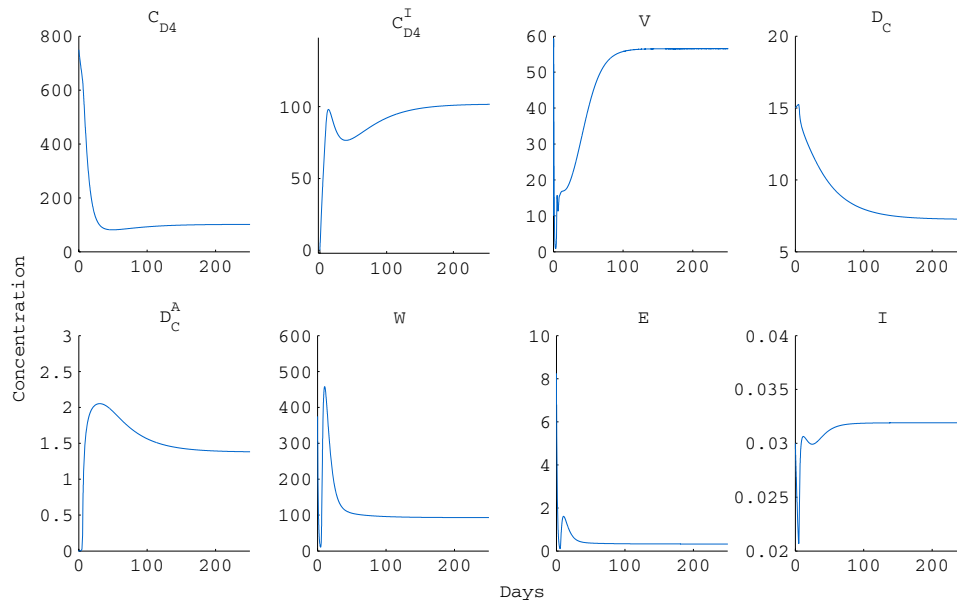


Fig. 4. Concentration changes with time in the absence of vaccination. Parameter values used were as in Table 1. Initial conditions were $C_{D4}(0) = 750$, $C_{D4}^I(0) = 0$, $V(0) = 10$, $D_C(0) = 15$, $W(0) = 375$, $D_C^A(0) = 0$, $E(0) = 8.25$ and $I(0) = 0.03$. With these parameters, we have $R_0 = 2.5528$, and hence the disease-free equilibrium is unstable and the endemic equilibrium stable.

Figure 4 shows how the concentration for each variable changes with time in the absence of vaccination. Under the parameters above, $R_0 = 2.5528 > 1$, which implies that the virus will persist.

First, we will illustrate the outcomes in the unstable and stable regions when the vaccination interval is fixed at $\tau = 2.5$. According to Theorem 4.1, we have two thresholds $R_1 = 0.39$ and $R_2 = 0.034$. Figure 5 illustrates the outcomes for $R^i = 0.4 > R_1 = 0.39$. In this case, the disease-free orbit is unstable and the endemic orbit is stable. Note that, due to high vaccination, the infected orbits (like C_{D4}^I and V) are significantly lower than those in Fig. 4, while the D_C^* orbit is a bit higher. On the other hand, the C_{D4} concentration is increased by a significant rate. Since the vaccination is oscillating, the state variables also oscillate.

We select $R^i = 0.03389 < R_2 = 0.034$ to check the changes in trajectories when safe vaccination is performed. For this fixed value, we find that the disease-free periodic orbit will be stable if $\tau > \tau_2 = 8.9$ days and unstable if $0 < \tau < \tau_1 = 0.69$ days (from Theorem 4.1). Therefore we perform our numerical simulations for three different cases under this fixed interval when (I) $0 < \tau < \tau_1$, (II) $\tau_1 < \tau < \tau_2$ and (III) $\tau > \tau_2$.

5.1. Case I: $0 < \tau < \tau_1$

In this case, vaccination is undertaken sufficiently often (twice a day), with $R^i = 0.03389$ and $\tau = 0.5 < \tau_1$. Figure 6 shows that all state variables oscillate. This

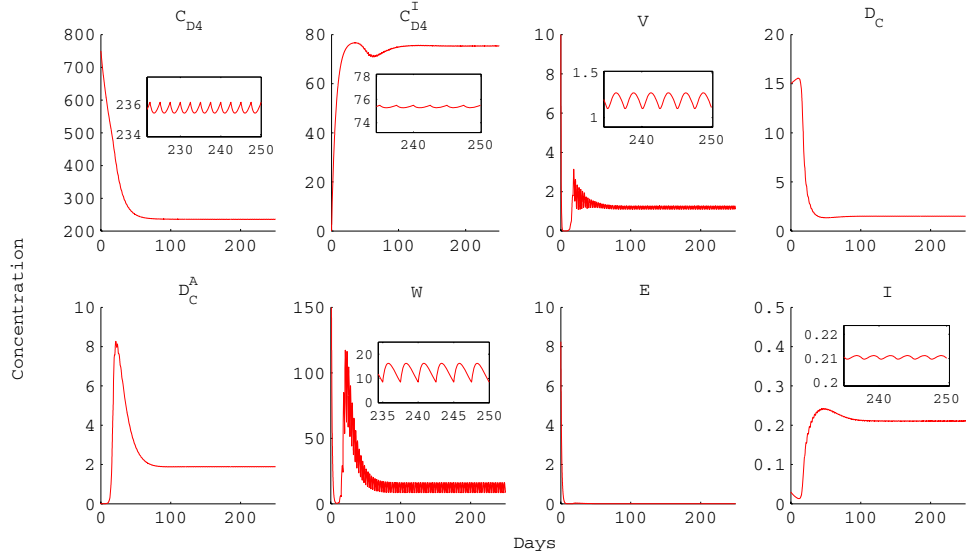


Fig. 5. Concentration changes with time under low vaccination, $R^i = 0.4 > R_1 = 0.39$. In this case, the disease-free orbit is unstable and the endemic orbit is stable. A significant increase in C_{D4} and decreases in C_{D4}^I and V can be noted compared to Fig. 4. Insets: Since the vaccination is oscillating, the state variables also oscillate.

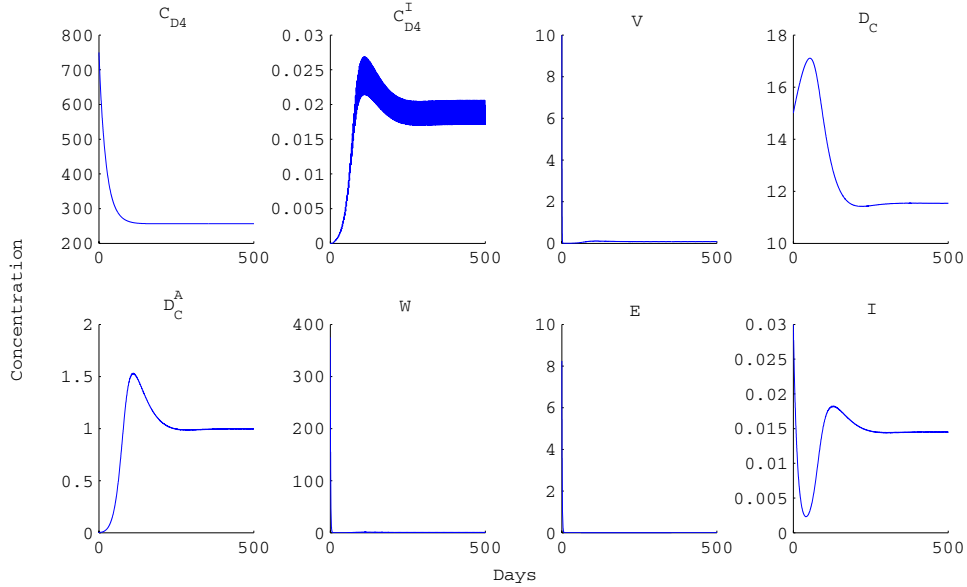


Fig. 6. In this case, vaccination is undertaken twice a day ($\tau = 0.5$). All state variables oscillate.

figure also indicates that, after approximately 20 days, the infected populations and virus population again start to increase; and the disease-free periodic orbit becomes unstable.

5.2. Case II: $\tau_1 < \tau < \tau_2$

Figure 7 shows the outcomes when τ is located between τ_1 and τ_2 . We choose $\tau = 2.75, 5.5$ and 7.75 days and $R^i = 0.03389$. In the first two cases (when $\tau = 2.75, 5.5$), the virus dominates, while the virus is controlled when τ is increased to 7.75 days. We can also see that the state variables are oscillating, since the vaccine oscillates, although the amplitude is decreasing as τ increases.

5.3. Case III: $\tau > \tau_2$

Figure 8 indicates that the disease-free orbit is stable and the endemic orbit does not exist. Here, $R^i = 0.03389$ and $\tau = 10 > \tau_2$, so the vaccine is taken for 10 days and stopped for 10 days. We also examined the changes when the vaccine is taken for 20 days and stopped for 20 days (Fig. 9). In this case, we find that disease control requires more time compared to the case when $\tau = 10$. Figure 9 shows the virus population (V) starting to increase and then decreasing to zero. Also, a change can be noted in the C_{D4} concentration between Figs. 8 and 9.

Finally, we explored the variation in some uncertain parameters by fixing the safe dosing concentration at $R^i = 0.03389$. Figure 10 gives the graph of \tilde{R}_0 as a

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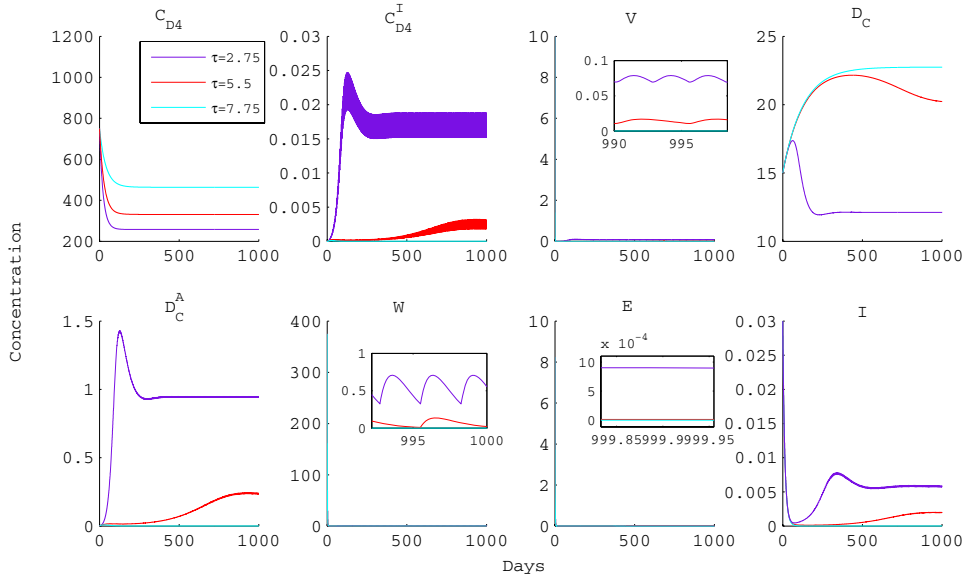


Fig. 7. In this case, outcomes show that concentration changes under moderate vaccination. All parameters used were the same as Fig. 6, except that the vaccination interval is $\tau = 2.75, 5.5$ and 7.75 , each satisfying $\tau_1 < \tau < \tau_2$.

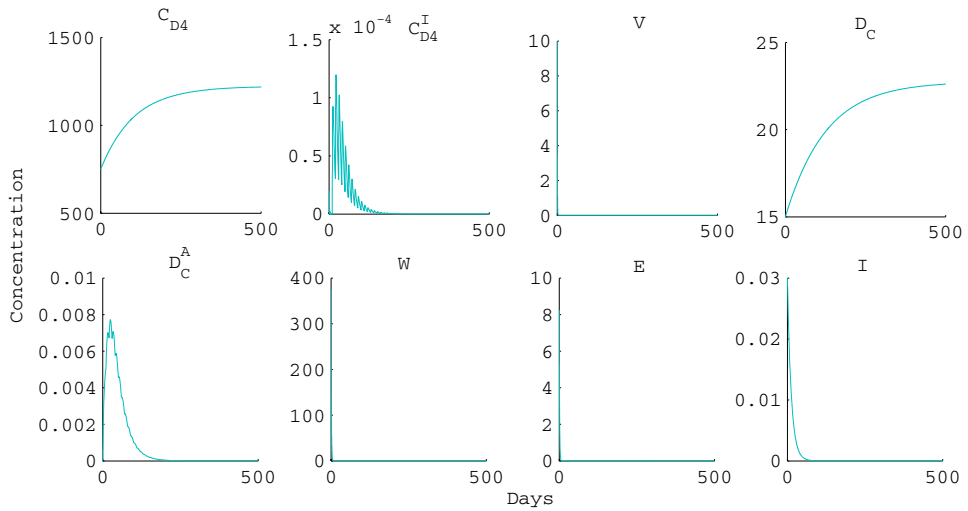


Fig. 8. Concentration changes with time under partial adherence. Here, vaccination is undertaken for intervals of 10 days and then vaccination is stopped for intervals of 10 days. All other parameters were the same as in Fig. 6.

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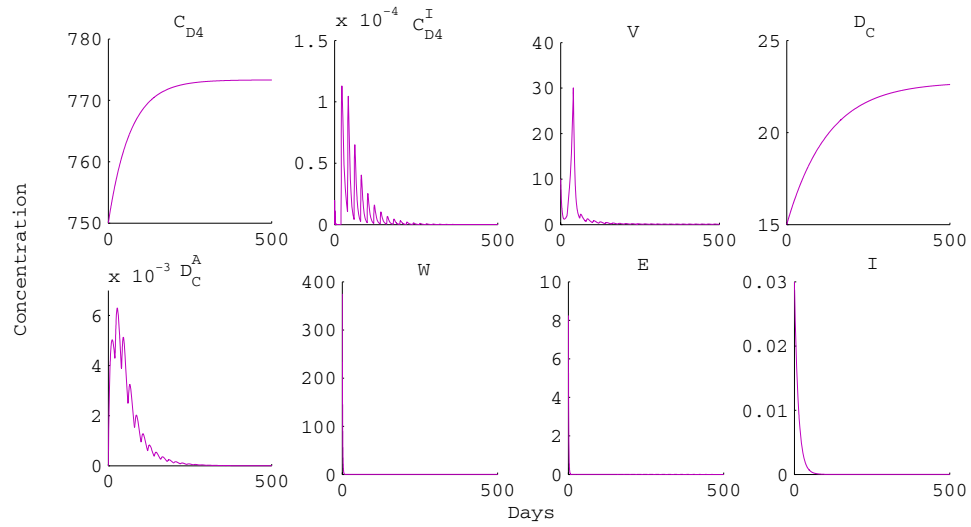


Fig. 9. Concentration changes with time under partial adherence. Here, vaccination is undertaken for intervals of 20 days and then vaccination is stopped for intervals of 20 days. All other parameters were the same as in Fig. 6.

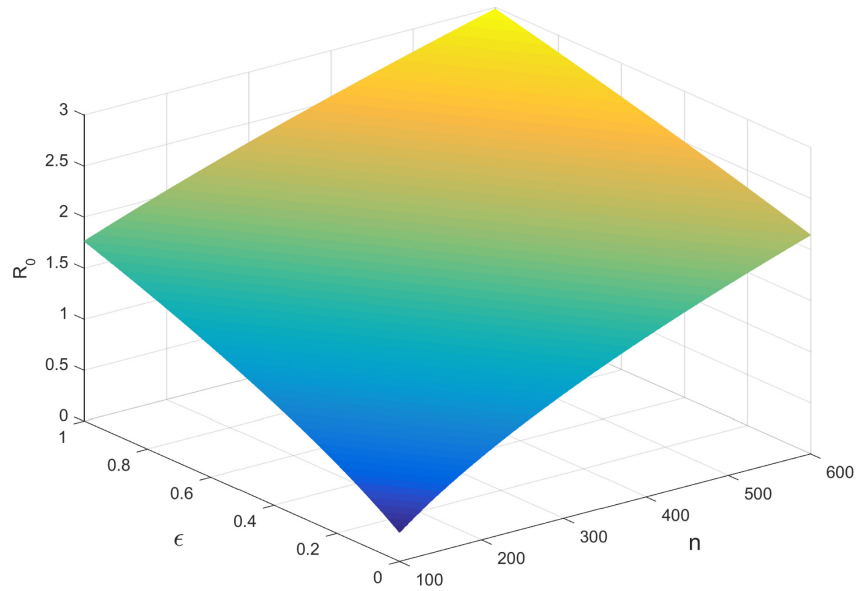


Fig. 10. The graph of \tilde{R}_0 as a function of n and ϵ .

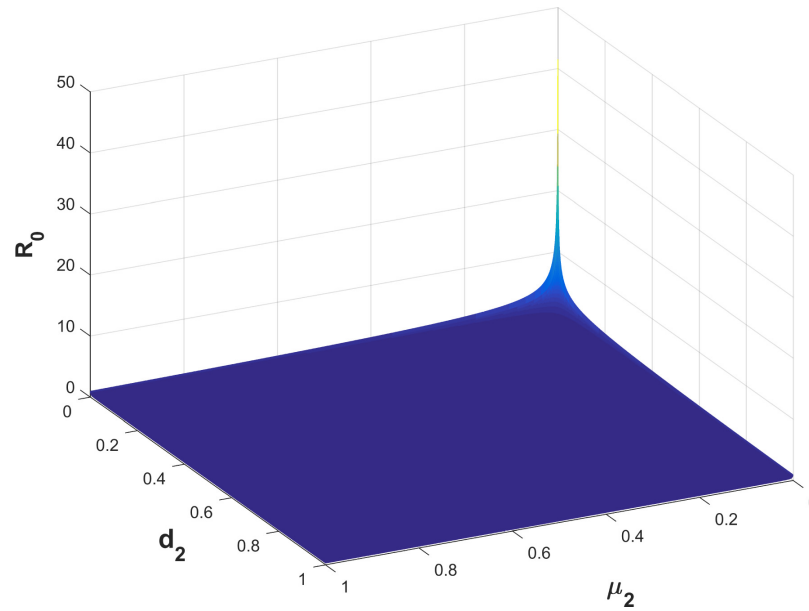


Fig. 11. The graph of \tilde{R}_0 as a function of d_2 and μ_2 .

function of n (the rate of production of virions per infected cell) and ϵ (transfer rate from D_C to D_C^*). These illustrate the change of the threshold parameter \tilde{R}_0 as n and ϵ vary. We also give the graph of \tilde{R}_0 as a function of d_2 and μ_2 (Fig. 11) and contours of parameters β_1 and d_V (Fig. 12). Clearly, if n and ϵ are small or d_2 and

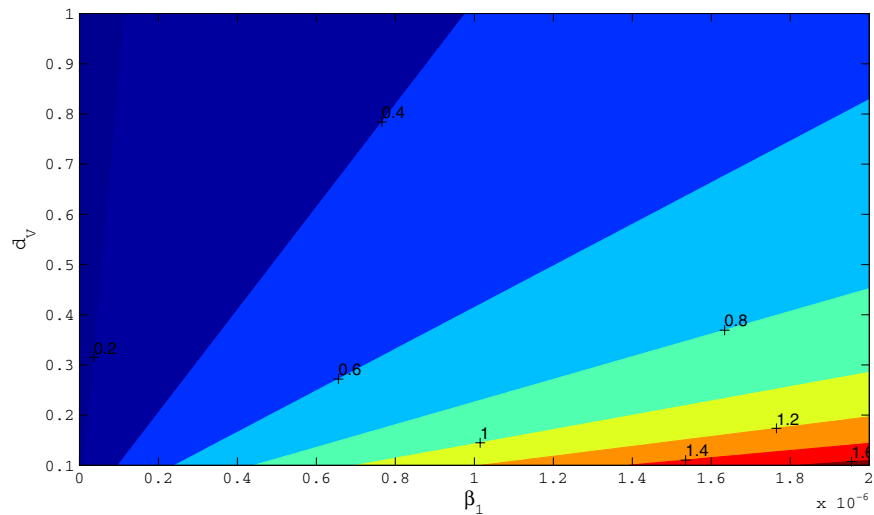


Fig. 12. Contour plots of \tilde{R}_0 as a function of β_1 and d_V .

μ_2 are large or β_1 is small and d_V is large, then \tilde{R}_0 can be less than 1. Conversely, if n and ϵ are both very large or if d_2 and μ_2 are both very small or if β_1 is large and d_V is small, then \tilde{R}_0 can blow up. For other values of the parameters, however, \tilde{R}_0 is relatively stable with respect to variations.

6. Discussion

We considered a mathematical model with moDC as a therapeutic vaccine against HIV/AIDS. We incorporated impulsive differential equations to model the dynamics of cell interaction and formulated a vaccination strategy, which plays an important role in clinical trials. In the absence of the vaccine, the disease-free equilibrium persists whenever R_0 lies below 1, but the system changes its stability whenever the value of R_0 exceeds unity. We found the threshold values, the relationship between vaccine strength and vaccination intervals for existence and stability of the disease-free and endemic equilibria when the therapeutic vaccine is taken. We have shown that a balance between cross and direct presentation is required for the successful establishment of CD8 memory in the model and hence prolonged viral control. From the model simulations, we found that, soon after the vaccine is administered, improved CD4⁺ T helper cell and CD8 memory cell levels can be achieved, as well as viral reduction.

There are several limitations of our modeling, which should be acknowledged. We assumed that the effect of the vaccine was instantaneous; in reality, there is a small delay as the vaccine reaches its time to peak. To avoid such problems or to improve the outcome of vaccination, treatment could be given earlier when the levels of CD4⁺ T helper cell impairment is still low. However, impulsive differential equations have been shown to be a reasonable approximation to the uptake of drug intake, provided the time between doses is not too small.³⁰ Alternatively, the frequency or strength of the vaccine may be increased; however, this may result in the overproduction of pro-inflammatory cytokine that could be detrimental to the patient. Furthermore, a viral rebound is likely to occur once the effect of the vaccine vanishes, which implies that the vaccination may have to be repeated for the rest of the patient's life. In designing a treatment schedule for repeated vaccination, one has to consider cost of the vaccination, the simplicity of the strategy to improve patient adherence to treatment and the maintenance of optimal CD8 memory cell levels to avoid overproduction of cytokines. This modeling study will assist in understanding the cell response to a therapeutic moDC vaccine, which will help in designing and assessing future studies.

Acknowledgments

The authors are grateful to Maia Martcheva and an anonymous reviewer, whose comments improved the paper. SS and PR are supported by the Department of

Science and Technology (INSPIRE Program), Government of India. RS? is supported by an NSERC Discovery Grant. For citation purposes, please note that the question mark in “Smith?” is part of his name.

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