Finite duration HIV treatment using mixed antiretroviral therapy and immunotherapy

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Abstract

Proposing a finite duration HIV treatment strategy is the main goal of the presented paper. Long term treatments cause many problems, such as drug resistance. Latently infected cells have an important role in HIV dynamics. The used HIV model not only consists of target cells and infected cells and viruses, but also includes latently infected cells. It is shown that the initial population of latently infected cells affects the final population of viruses. The dynamics of the model is examined by extracting equilibrium points and their stability. Two types of equilibrium points are derived, virus-free and viral equilibrium points. It is proved that the existence of a stable virus-free equilibrium point is essential for finite duration treatment. Also, the effect of immune system ability in HIV treatment is explored by considering the effect of changing the parameters of the system in its dynamics. It is shown that in some immune system abilities, HIV is cured without any external treatment. The number of equilibrium points of the system changes with changes in the immune system ability. Based on this fact, a novel mixed antiretroviral therapy and immunotherapy is presented. Antiretroviral therapy affects the states of the system, and immunotherapy affects the parameters of the system. The simulation results show the effectiveness of the novel presented treatment strategy.

Keywords:

HIV treatment, Antiretroviral therapy, Immunotherapy, Mathematical model, Bifurcation.
1. Introduction

As indicated by the Global Health Observatory data reported by the World Health Organization (WHO), about 0.9 million individuals have died of Acquired immune deficiency syndrome AIDS-related illnesses [1]. All-inclusive, 36.9 million individuals were living with it towards the end of 2017, that 69.93% were living in Africa, and about 9.52% in South-East Asia. Antiretroviral therapy (ART) coverages about 59% of people living with HIV. Antiretroviral therapy (ART) does not treat HIV. ART attempts to disturb the pathogenesis of the virus, which leads to the normal life of infected individuals. ART tries to keep the level of CD4+T cells count (> 200 Cells/mm) in the peripheral blood and reduce the amount of HIV load [2]. The highly active ART is the most predominant treatment methodology, which includes the utilization of multiple anti-HIV drugs to suspend the virus count of infected individuals to the desired level. This treatment methodology can maintain the CD4+T cell count at a passable level. Therefore, the infected person is recovered slowly [3]. CD4+ cells are The T helper cells (T-cells) that play an important task in the immune system. By releasing T cell cytokines, they help the activity of other immune cells. The CD4+ T-cells lifetime estimation in 1/d is 100 days[4, 5].

In recent years, a considerable number of studies have focused on providing mathematical models of HIV infection to develop a model-based control strategy for HIV treatment [2, 3, 6-13]. The mathematical model plays an important role in understanding the proliferation of HIV cells as well as designing a therapeutic plan to improve the individual. The HIV infection process has been modeled to demonstrate the interaction between HIV, AIDS pathogens, CD4+T cells and also antiviral drugs. Understanding this process plays an important role in creating mathematical models. Modeling also plays an important role in developing new ways to control the spread of HIV infection [3, 8, 10].

According to VISCONTI research, HIV-1 infection usually leads to AIDs by repeating stable viruses and losing the production of CD4+T cells [14]. Combined antiretroviral therapy (cART) reduces mortality and reduces the frequency of virus repression [14]. Nevertheless, infected cells cannot be eliminated. HIV
may conceal itself for years to come. With these interpretations, it is unclear how other patients will reach
the elite control area [15]. Some people can control HIV in the absence of treatment on their own. Elite
controllers (ECs) were first identified in 2005 [16]. These individuals naturally control HIV infection by
maintaining undetectable viral loads (<50 Copies per mL) [17, 18]. ECs have been focusing the study for
a long time, because understanding how to control the infection in these individuals may lead to progress
in the treatment and production of the vaccine [19]. Several important features about ECs have been
discovered. For example, ECs tend to maintain cytotoxic T lymphocytes (CTL) responsiveness
significantly more strongly than cytotoxic, But ECs make up only 1% of the HIV population patients
while post-treatment control (PTC) patients make up about 15% [15, 20]. The existence of a latent
reservoir is one of the major barriers to the eradication of HIV infection [21]. Latently infected cells are
not affected by ART and cannot be controlled [22], and then the infection is spreading rapidly [23, 24].

The non-linear optimal control is employed to determine the optimal methodology for administering anti-
viral drug therapies to HIV infection [25, 26]. A control system analysis on HIV infection dynamics is
investigated in [27], and to increase the immune response the intake of the drug is considered as an
impulsive control input. In [28], a four-state model has been used to express AIDS behavior, and an
optimal controller was designed to reduce the cost of chemotherapy to treat the disease. This method
minimizes systemic costs by maximizing T cells, and the described model is adapted from [29]. In [30], a
two states model was presented to show the effect of immunotherapy. This is to provide a better
pharmaceutical solution using optimal controls with two controllable inputs. In [31], a fuzzy
mathematical model of HIV dynamics was raised, in which a fuzzy optimal control problem by
minimizing both the viral load and drug costs simultaneously is studied. Although in the presence of
uncertainties the above-mentioned results may not produce desired results. Much research has been done
in recent years on the optimal control of the AIDS model. Including in [32], an optimal control problem
regarding the strategy of implementing public health education, along with its solution, is presented. In
solutions are presented using optimal control to combine the treatment of human immunodeficiency
virus and immunotherapy. The immune function has also been studied.

However, finite duration treatment is not considered in many studies. In a finite duration treatment, the
treatment schedule should be implemented in a finite time. In many cases, the treatment protocol should
be exerted for the whole life of the patient. For finite duration treatment, the dynamics of HIV should be
studied carefully. On the other hand, the mathematical models which describe these dynamics should be
comprehensive. In other words, the mathematical model should consider not only the infected cells and
viruses but also should consider latent cells and target cells. In this paper, a mathematical model that
considers all significant cells is regarded. Then, the dynamics of the model is carefully examined by
studying the equilibrium points and their stability and the effect of change in the parameters of the system
on the dynamics of the system. Based on this dynamics analysis a finite duration treatment is proposed.

The structure of the paper is as follows. In the next section, the mathematical HIV model is presented.
This model includes the latently infected cells. In section 3, the dynamics of the system is analyzed. The
equilibrium points of the system are derived. Then, the stability of these equilibrium points is examined
using the Lyapunov method. Changing the dynamics of the system due to changes in the parameters of
the system is also examined. Based on the dynamic analysis, the mixed treatment strategy is presented. It
is shown that just ART is not able to cure HIV in a finite duration.

2. Mathematical model of HIV:

In this study, according to the VISCONTI study [34], a mathematical model used to investigate 14
patients living with AIDS in the study was used, which includes a standard model of viral activity of HIV
infection and treatment [35, 36]. This model includes the dynamics of the hidden and dynamics of the
reservoir of effective CTL cells [37, 38]. The interaction among cells considered in this model is shown in
Fig. 1. Five types of states are considered, i.e. target cells (T), latently infected cells (L), productively
infected cells (I), effector cells (E) and viruses (V). Target cells (CD4+ T cells) may be infected by viruses. Some of them can be detected which are named as productively infected cells. Some infected cells are hidden for many years which are named as latently infected cells. Effector cells (Cytotoxic T cells) are the immune response to the presence of viruses.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{The interaction among target cells (T), latently infected cells (L), productively infected cells (I), effector cells (E) and viruses (V).}
\end{figure}

The target cells proliferate with the rate $\lambda$, and naturally die with the rate $d$. They also become infected due to interaction with viruses with the rate $\beta$. Productively infected cells (I) produce viruses at the rate $p$ and are died at the rate $\delta$, which is due to the effect of viral cytopathic. The viruses are cleared at the rate $c$. $\alpha_L$ is the fraction of newly productively infected cells that become latently infected. The latently infected cells are activated to become $I$ cells at the rate $a$ and die at the rate $d_L$. $\rho$ is the rate of proliferation of these cells. Based on [39] and [38], I cells are killed by effector cells at the rate $m$, which $m$ is the constant rate of CTL killing. The effector cells are excited to proliferate in the presence of
viruses \( (b_E \frac{I}{k_B + I}) \). An induce immune exhaustion exist [40] due to the high density of infected cells, which is an impairment of immunity \( (d_E \frac{I}{k_D + I}) \).

Based on the described interactions, the mathematical model of HIV is as follows [45]:

\[
\frac{dT}{dt} = \lambda - dT - \beta VT, \tag{1}
\]

\[
\frac{dL}{dt} = \alpha_L \beta VT + (\rho - a - d_L) L, \tag{2}
\]

\[
\frac{dI}{dt} = (1 - \alpha_L) \beta VT - \delta I + aL - mEI, \tag{3}
\]

\[
\frac{dV}{dt} = pI - cV, \tag{4}
\]

\[
\frac{dE}{dt} = \lambda_E + \left( b_E \frac{I}{K_B + I} - d_E \frac{I}{k_D + I} - \mu \right) E. \tag{5}
\]

The parameters of the system and their description are in Table 1. The parameters’ values are presented from different references. These values are based on clinical tests.

<table>
<thead>
<tr>
<th>parameter</th>
<th>Description</th>
<th>Value</th>
<th>Units</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \lambda )</td>
<td>production of Target cell</td>
<td>( 10^4 )</td>
<td>Cells/mL per day</td>
<td>[4]</td>
</tr>
<tr>
<td>( d )</td>
<td>Death rate of target cell</td>
<td>0.01</td>
<td>1 per day</td>
<td>[5]</td>
</tr>
<tr>
<td>( \beta )</td>
<td>Mass-action infectivity</td>
<td>1.5e-8</td>
<td>mL per day</td>
<td>[41]</td>
</tr>
<tr>
<td>( \delta )</td>
<td>Death rate of Infected cell</td>
<td>1</td>
<td>1 per day</td>
<td>[42]</td>
</tr>
<tr>
<td>( \rho )</td>
<td>Rate of viral production</td>
<td>2000</td>
<td>1 per day</td>
<td>[43]</td>
</tr>
<tr>
<td>( c )</td>
<td>Rate of viral clearance</td>
<td>23</td>
<td>1 per day</td>
<td>[44]</td>
</tr>
<tr>
<td>( \varepsilon )</td>
<td>Drug efficacy</td>
<td>0.9</td>
<td></td>
<td>[45]</td>
</tr>
<tr>
<td>( a )</td>
<td>Rate of latent activation</td>
<td>0.001</td>
<td>1 per day</td>
<td>[45]</td>
</tr>
<tr>
<td>( d_L )</td>
<td>Death rate of latently infected</td>
<td>0.004</td>
<td>1 per day</td>
<td>[46]</td>
</tr>
<tr>
<td>( \rho )</td>
<td>Proliferation rate of L</td>
<td>0.0045</td>
<td>1 per day</td>
<td>[47]</td>
</tr>
<tr>
<td>( \alpha_L )</td>
<td>Fraction of newly I cells that become L</td>
<td>( 10^6 )</td>
<td>---</td>
<td>[45]</td>
</tr>
<tr>
<td>Parameter</td>
<td>Description</td>
<td>Value</td>
<td>Units</td>
<td>Source</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------------------------</td>
<td>-------------</td>
<td>-----------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>$\lambda_E$</td>
<td>Production rate of E</td>
<td>1</td>
<td>Cell/mL per day</td>
<td>[45]</td>
</tr>
<tr>
<td>$b_E$</td>
<td>Proliferation co-efficient of E</td>
<td>1</td>
<td>1 per day</td>
<td>[48]</td>
</tr>
<tr>
<td>$d_E$</td>
<td>Saturation of immune impairment co-efficient</td>
<td>2</td>
<td>1 per day</td>
<td>[49]</td>
</tr>
<tr>
<td>$k_B$</td>
<td>Production Hill function scaling of E</td>
<td>0.1</td>
<td>Cells/mL</td>
<td>[38]</td>
</tr>
<tr>
<td>$k_D$</td>
<td>Saturation of immune impairment Hill function scaling</td>
<td>5</td>
<td>Cells/mL</td>
<td>[38]</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Loss rate of E</td>
<td>2</td>
<td>1 per day</td>
<td>[45]</td>
</tr>
<tr>
<td>$m$</td>
<td>Killing rate of E</td>
<td>0.42</td>
<td>mL /cells per day</td>
<td>[45]</td>
</tr>
<tr>
<td>$\mu_m$</td>
<td>Effectiveness of the immunotherapy drug</td>
<td>1</td>
<td>Estimated</td>
<td></td>
</tr>
<tr>
<td>$k_m$</td>
<td>Saturation limit of the killing rate of E</td>
<td>0.84</td>
<td>Estimated</td>
<td></td>
</tr>
</tbody>
</table>

The open-loop behavior of the system with the initial conditions $T = 10^6$, $V = 50$, $I = 0$, $L = 1$, $E = 0.5$ [45] is shown in Figure 2. As shown in this figure, the target cells and latently infected cells decrease monotonically. The rate of variations of latently infected cells is very slow. But, the effector cells and productively infected cells grow monotonically. The viruses decrease at first and then grow to a fixed value. After approximately 80 days, the viral cells count increase and is fixed at greater than 20.

Fig. 2. The open-loop behavior of the system with initial conditions target cells ($T$)=$10^6$, viruses ($V$)=50, productively
infected cells ($I$)=0, latently infected cells ($L$)=1, effector cells ($E$)=0.5. The system moves to a non-zero population of viruses.

The behavior of the system with different initial latently infected cells is shown in Fig. 3. In this case, $L=100$. The behavior of the system is oscillatory and finally settles to a fixed value. The population of viruses grows drastically at first and then settles to a fixed value, which is very higher than the previous case.

Although latently cells are declining in these cases, the amount of viral cells is about $10^5$ in Fig. 3, which makes treatment difficult.

![Graphs showing system behavior](image)

Fig. 3. The open-loop behavior of the system with initial conditions target cells ($T$)= $10^6$, viruses ($V$)=50, productively infected cells ($I$)=0, latently infected cells ($L$)=100, effector cells ($E$)=0.5. The system moves to a non-zero population of viruses oscillatory.

3. Analysis of the dynamics of the free system

3.1. Equilibrium points of the free system

Generally, two types of equilibrium points exist in the system. The zero population of viruses called virus-free equilibrium point, and the non-zero population of viruses called viral equilibrium points.
The equilibrium points of the system are derived by setting zero the right hand of the equations 1-5 simultaneously and solving them. The virus-free equilibrium point is obtained by setting $V^* = 0$. The virus-free equilibrium point is as follows:

$$E_{vr} = (T_1^*, V_1^*, L_1^*, I_1^*, E_1^*) = (10^6, 0, 0, 0, 0.5)$$

To obtain viral equilibrium points, all equations are derived versus virus population $V$.

By setting equation (1) to zero, the following equation is derived:

$$T = t_1 = \frac{\lambda}{d + \beta V}$$

By setting equation (4) to zero, the relationship between $V$ and $I$ can be obtained as follows:

$$I = \frac{c}{p} V$$

Considering equation (7) and setting equation (2) to zero, we have:

$$L = \frac{\alpha_i \beta \lambda V}{(d + \beta V)(\rho - a - d_e)}$$

By setting equation (5) to zero and using equation (8), the following equation is derived:

$$E = -\frac{\lambda e}{A}$$

where $A = b_E \left( \frac{c}{p} \right) - d_E \left( \frac{c}{p} \right) - \mu$.

At the end, by setting equation (3) to zero the following equation is obtained:
The intersections of the equations (7) and (11) are the viral equilibrium points of the system, which shows in Fig. 4 using the parameters presented in Table 1.

There are three viral equilibrium points using the parameters presented in Table 1.

\[
E_{1,v} = (T_{1v}^*, V_{1v}^*, L_{1v}^*, I_{1v}^*, E_{1v}^*) = (10^6, 21.9, 6.56 \times 10^{-4}, 0.252, 0.724)
\]

(12)

\[
E_{2,v} = (T_{2v}^*, V_{2v}^*, L_{2v}^*, I_{2v}^*, E_{2v}^*) = (10^6, 66.3, 0.002, 0.762, 0.724)
\]

(13)

\[
E_{3,v} = (T_{3v}^*, V_{3v}^*, L_{3v}^*, I_{3v}^*, E_{3v}^*) = (8.714 \times 10^5, 9.6 \times 10^4, 2.52, 1.104 \times 10^3, 0.334)
\]

(14)
3.2. Stability analysis

The indirect Lyapunov method is used to analyze the stability of the equilibrium points of the 5-DOF model. At first, the Jacobian matrix of the system is derived, and then the eigenvalues of each equilibrium point are calculated.

It is assumed that the Jacobian matrix of the system is $A_{ij}, i, j = 1 \text{to } 5$, such that:

\[
A_{11} = -d - \beta V
\]

\[
A_{44} = -\beta T
\]

\[
A_{21} = \alpha_t \beta V
\]

\[
A_{22} = \rho - a - d_L
\]

\[
A_{34} = \alpha_t \beta T
\]

\[
A_{31} = (1 - \alpha_L) \beta V
\]

\[
A_{32} = a
\]

\[
A_{33} = -(\delta + mE)
\]

\[
A_{34} = (1 - \alpha_L) \beta T
\]

\[
A_{35} = -mL
\]

\[
A_{43} = p
\]

\[
A_{44} = -c
\]

\[
A_{53} = b_k k_B E l (k_B + I)^2 - d_l k_D E l (k_D + I)^2
\]

\[
A_{55} = b_k l (k_B + I) - d_l I l (k_D + I) - \mu
\]

Other elements that are not mentioned are zero.

The eigenvalues for each equilibrium point are listed in Table 2.
Table 2. The eigenvalues of the obtained equilibrium points using the parameters presented in Table 1

<table>
<thead>
<tr>
<th></th>
<th>$\lambda_1$</th>
<th>$\lambda_2$</th>
<th>$\lambda_3$</th>
<th>$\lambda_4$</th>
<th>$\lambda_5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{V,F}$</td>
<td>-0.01</td>
<td>-2</td>
<td>24.3</td>
<td>0.0893</td>
<td>-5x10^{-4}</td>
</tr>
<tr>
<td>$E_{1,V}$</td>
<td>-24.3</td>
<td>-1.356</td>
<td>-0.01</td>
<td>-0.023</td>
<td>-5x10^{-4}</td>
</tr>
<tr>
<td>$E_{2,V}$</td>
<td>-24.3</td>
<td>-1.4</td>
<td>-0.01</td>
<td>0.026</td>
<td>-5x10^{-4}</td>
</tr>
<tr>
<td>$E_{3,V}$</td>
<td>-24.137</td>
<td>-0.007 + 0.04i</td>
<td>-0.007 - 0.04i</td>
<td>-2.99</td>
<td>-5x10^{-4}</td>
</tr>
</tbody>
</table>

3.3. Bifurcation analysis

By equating the two equations obtained for the target cells, (7) and (11), a single equation containing only the viruses population can be derived. The result of this equation can show the effect of each parameter on the virus behavior.

$$t_1 = t_2 \rightarrow \zeta_1 V^3 + \zeta_2 V^2 + \zeta_3 V + \zeta_4 = 0$$

(15)

Where,

$$\zeta_1 = \beta \left( \lambda_E m + (\mu + d_E - b_E) \delta \right) \left( \frac{c}{p} \right)^3$$

$$\zeta_2 = \left[ d \lambda_E m \frac{c}{p} - (\mu + d_E - b_E) \times \left( -d \delta \frac{c}{p} + \lambda (1 - \alpha_L) \beta + \frac{a \beta \alpha_L}{(\rho - a - dL)} \right) \right] \left( \frac{c}{p} \right)^2$$

+ $\left( (\mu (k_D + k_B) + k_B d_E - k_B b_E) \delta + (k_D + k_B) \lambda_E m \right) \beta \left( \frac{c}{p} \right)^2$

$$\zeta_3 = \left( (k_D + k_B) d \lambda_E m \frac{c}{p} - (\mu (k_D + k_B) + k_B d_E - k_B b_E) \left( -d \delta \frac{c}{p} + \lambda (1 - \alpha_L) \beta + \frac{a \beta \alpha_L}{(\rho - a - dL)} \right) \right) \left( \frac{c}{p} \right)$$

+ $\left( \mu k_D k_B \delta + k_D k_B \lambda_E m \right) \beta \frac{c}{p}$

$$\zeta_4 = \left( -k_D k_B d \lambda_E m + \mu k_B k_B \left( -d \delta \frac{c}{p} + \lambda (1 - \alpha_L) \beta + \frac{a \beta \alpha_L}{(\rho - a - dL)} \right) \right) \left( \frac{c}{p} \right)$$
The roots of the equation (15) show the population of the virus in the feasible viral equilibrium points.

The locus of the virus population by changing the parameter $m$ is shown in Fig 5. The parameter $m$ shows the effect of the immune system's ability to remove viruses. In some values of $m$, there are not any viral equilibrium points in the system. It means that the immune system has the required ability to remove viruses without any external treatment. By increasing $m$, which shows the ability of the immune system, the population of the viruses in the viral equilibrium points becomes smaller. Hence, reinforcing the immune system must be one of the treatment strategies to have finite duration treatment.

![Bifurcation diagram](image)

Fig. 5. Bifurcation diagram versus parameters $m$. In some values of the parameter $m$ there is not any viral equilibrium point. In other words, the immune system is capable of removing viruses in the absence of any treatment.

The bifurcation diagram with changes in the parameter $\lambda_E$ is shown in Fig. 6. Similar to the parameter $m$, in some values of $\lambda_E$ there is not any viral equilibrium points in the system. In other words, reinforcing the immune system causes to elimination of the viral equilibrium points from the dynamics of the system.
Fig. 6. Bifurcation diagram versus parameters $\lambda_E$. In some values of the parameter $\lambda_E$ there is not any viral equilibrium point. In other words, the immune system is capable of removing viruses in the absence of any treatment.

The effect of changes in the both parameters $m$ and $\lambda_E$ is shown in Fig. 7. The number of feasible viral equilibrium points in each region is different from other. In region “A” one viral equilibrium point exists in the system. In region “B” and “C” there are three and two viral equilibrium points in the system, respectively. In region “D” there is not any viral equilibrium points in the system. In other words, if the system is settled in this region, the immune system is capable of removing all viruses without any external treatment.
Fig. 7. There are four regions based on the number of feasible viral equilibrium points in the system with changes in the parameters $m$ and $\lambda_E$. In region “A” one viral equilibrium points exists in the system. There are two and three viral equilibrium points in the system in regions “C” and “B”, respectively. There is no viral equilibrium point in the system in region “D”.

Considering the effect of parameters $m$ and $\lambda_E$ on the number and amount of equilibrium points, we consider the uncertainties in the two parameters whose changes have the greatest impact on the behavior of the system. In this way, we consider constant behavior of parameter $\lambda_E$ and try to improve the model performance by considering variable parameter $m$.

4. HIV treatment strategy

The mathematical model of the system during the mixed antiretroviral therapy and immunotherapy is as follows.

\[
\frac{dT}{dt} = \dot{\lambda} - dT - (1 - \varepsilon) \beta VT, \quad (16)
\]

\[
\frac{dL}{dt} = \alpha_L (1 - \varepsilon) \beta VT + (\rho - a - d_L) L, \quad (17)
\]
\[
\frac{dI}{dt} = (1- \alpha_L)(1 - \varepsilon) \beta VT - \delta I + aL - mEI, 
\]
(18)
\[
\frac{dV}{dt} = pI - cV,
\]
(19)
\[
\frac{dE}{dt} = \lambda_E + \left[ b \frac{I}{K_n + I} - d_E \frac{I}{k_D + I} - \mu \right] E.
\]
(20)
\[
\frac{dm}{dt} = \mu_m v_m (t) \left( 1 - \frac{m}{k_m} \right)
\]
(21)

Where, \( \varepsilon \) shows the effectiveness of the antiretroviral drugs, such as RTI and PI. In the absence of the treatment \( \varepsilon = 0 \). Immunotherapy affects the parameters of the system \( (m) \), which is shown by \( v_m(t) \) [50, 51]. The rate of variation of these parameters is assumed to be proportional to the input \( v_m(t) \). The value of \( \mu_m \) depends on the dynamics of \( m \). These coefficients are saturated to the final limits \( k_m \) that is related to the biological limitations of body organs and the accumulation of external effects [52].

Immunotherapy modifies the dynamics of HIV. After immunotherapy, the system’s dynamics have been changed. Antiretroviral therapy affects the states of the system.

Suppose an input \( u(t) \) exerted to a system at a finite duration \( \Delta t = t_2 - t_1 \) in the following form:

\[
\begin{cases}
\dot{\zeta}(t) = f(\zeta(t), \theta) \\
\theta(t) = h(\zeta(t), u(t))
\end{cases} \quad t_1 < t < t_2
\]
(22)

Where \( \zeta \in \mathcal{R}^n \) is the state vector of the system, \( u(t) \in \mathcal{R}^m \) is the input vector exerted to the system in a finite-duration \( \Delta t = t_2 - t_1 \), and \( \theta \in \mathcal{R}^r \) is some parameters of the system affected by the input \( u(t) \). In this case, after the input cessation for \( t > t_2 \), the dynamics of the system is

\[
\dot{\zeta}(t) = f(\zeta(t), \theta') \neq f(\zeta(t), \theta),
\]
because:
\[ \theta' = \theta + \int_{\alpha}^{\beta} h(\zeta(t), u(t)) \, dt \]  

(23)

In other words, the dynamics of the free system before and after the exertion of the input are different. When the values of some parameters of the system varied, it causes changes in the dynamics of the system. Some inputs have permanent effects on the system. These effects may be on the parameters of the system by changing their values. These inputs may be exerted to the system in the integral form (Equation 23). Equation 23 is the integral form of the second part of the equation (22). If the integral of the function \( h(\zeta(t), u(t)) \) is nonzero, then the effect of the input is accumulated on the parameter \( \theta \).

In this paper, immunotherapy is used after antiretroviral therapy. In other words, when the populations of viruses are controlled by antiretroviral therapy, immunotherapy is imposed to modify the dynamics of the system. This modification is applied by changing the parameters of the system and reinforcing the immune system’s strength.

4.1. Finite duration antiretroviral therapy

The ART with \( \varepsilon = 0.3 \) every 80 days is imposed on the system up to 600 days [45]. The initial condition is \( T = 10^6, V = 50, I = 0, L = 1, E = 0.5 \). As shown in Fig. 8, after the termination of ART, the trajectory of the system comes back to its stable viral equilibrium point. In other words, due to the instability of the virus-free equilibrium point, alone ART is not able to cure HIV in a finite duration. In this case, the system comes back to \( E_{1,V} \).
The behavior of the system during finite duration ART with initial conditions target cells \(T = 10^6\), viruses \(V = 50\), productively infected cells \(I = 0\), latently infected cells \(L = 1\), effector cells \(E = 0.5\). Due to the instability of the virus-free equilibrium point, the system comes back to the stable viral equilibrium point \(E_{1,V}\).

The behavior of the system during finite duration ART with initial condition \(T = 10^6, V = 50, I = 0, L = 100, E = 0.5\) is shown in Fig. 9. The finite duration ART is unsuccessful due to the instability of the virus-free equilibrium point. In this case, the system comes back to \(E_{3,V}\).
Fig. 9. The behavior of the system during finite duration ART with initial conditions: target cells (T) = $10^6$, latently infected cells (L) = 100, productively infected cells (I) = 0, effector cells (E) = 0.5 and viruses (V) = 50. Due to the instability of the virus-free equilibrium point, the system comes back to the stable viral equilibrium point $E_{3,V}$.

4.2. Finite duration mixed treatment

Immunotherapy changes the parameter $m$. The strength of the CTL response, $m$, is a key parameter. In other words, it causes the immune system to be reinforced. The variation of the parameter $m$ during immunotherapy is shown in Fig. 10. During immunotherapy, the parameter $m$ is changed from 0.42 to 0.8. The choice of $m$ affects the predictions of the viral rebound time. It is expected that the distribution of the parameter $m$ should be continuous on [0, 1]. However, there is no information about the distribution of $m$. It should be noted that the values of $m$ parameter near 1, corresponding to EC, must be very rare [34].

When immunotherapy implemented, the immune system activated. Therefore, the strength of the immune system increased. In other words, the immune cells (CTL) can remove agents with more power. This power is reflected in the parameter $m$.

![Fig. 10. Changing the parameter $m$ using immunotherapy. Immunotherapy reinforces the immune system.](image)

As shown in Fig. 10, immunotherapy shifts the parameter $m$ from region A to region D, which there is no viral equilibrium point in the system, and the immune system is capable of removing viruses without
any external treatment. After immunotherapy, ART imposed. As shown in Figs. 11 and 12, after finite duration ART, the virus population converges to zero due to the stability of the virus-free equilibrium point.

Fig. 11. The behavior of the system during finite duration mixed treatment with initial condition target cells (T) = $10^6$, latently infected cells (L) = 1, productively infected cells (I) = 0, effector cells (E) = 0.5 and viruses (V) = 50. Due to the stability of the virus-free equilibrium point, the system goes to $E_{VF}$.

Fig. 12. The behavior of the system during finite duration mixed treatment with initial condition target cells (T) = $10^6$, latently infected cells (L) = 100, productively infected cells (I) = 0, effector cells (E) = 0.5 and viruses (V) = 50. Due to the stability of...
the virus-free equilibrium point the system goes to $E_{VF}$.

5. Conclusion

A novel finite duration treatment protocol is presented using mixed ART and immunotherapy. It is shown that just ART is not able to cure HIV in a finite duration. Hence, mixed ART-immunotherapy is proposed. The ART affects the states of the system and immunotherapy modifies the dynamics of the system. Immunotherapy reinforces the immune system. To find which parameter should be modified, the dynamics of the system is analyzed. To achieve finite duration treatment, the virus-free equilibrium point must be stable. The bifurcation analysis shows that the killing rate of effector cells has a significant role in modifying the dynamics of the system. So, immunotherapy modifies the killing rate of effector cells. The simulation results show that the proposed treatment strategy can cure HIV in a finite duration.
6. References:


