OPTIMAL INTERVENTION STRATEGIES OF A SI-HIV MODELS WITH DIFFERENTIAL INFECTIVITY AND TIME DELAYS

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ABSTRACT. HIV infection is divided into stages of infection which are determined by the CD4 cells count progression. Through each stage, the time delay for the progression is important because the duration of HIV infection varies according to the infectious. Retarded optimal control theory is applied to a system of delays ordinary differential equations modeling the evolution of HIV with differential infectivity. Seeking to reduce the population of the infective individuals with low CD4 cells, we use the ARV drug to control the fraction of infective individuals that is identified and will be put under treatment. We use optimal control theory to study our proposed system. Numerical simulations are provided to illustrate the effect of the Antiretroviral treatment (ART) taking into account the delays.

1. Introduction. The human immunodeficiency virus (HIV) is a lentivirus (a subgroup of retrovirus) that causes HIV infection and over time acquired immunodeficiency syndrome (AIDS) [26, 6]. HIV weakens your immune system by destroying cells that are essential for fighting diseases and infections. Without treatment, the immune system becomes too weak and the CD4 becomes lower and lower in the body. The use of drugs to suppress replication of the HIV has transformed the face of AIDS in the developed world [27]. Pronounced reductions in illness and death have been achieved and health care utilization has diminished [27]. Many models have been done for the spread of HIV [2, 12, 18, 21]. HIV models with control or delays have been proposed [23, 9, 14, 25, 19, 20, 5] but few deal with control of delayed staged progression models as in the context of this work. In this paper we divided the HIV infection in fives stages, as in [8]. The first stage is the Primary infection, the second is the infected people with $CD4 > 350$ cells/µL, the third, fourth and fifth stages are respectively, the infectives individuals with, $200 \leq CD4 \leq 350$ cells/µL, $100 \leq CD4 \leq 200$ cells/µL, and $CD4 \leq 100$ cells/µL [8]. Moreover, to be

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more realistic we take into account the time that infected people $I_j$ take to become $I_{j+1}$. Typically $I_1$ take 2.9 months to progress in $I_2$, and $I_2, I_3, I_4$ take 4.56 years, 4.60 years, 4.17 years, 1.03 year to HIV death, to progress in $I_5, I_4, I_5$ respectively [8]. The complexity of HIV infection is linked to many elements that particularly involve the specific mechanism of infection [13]. Host factors such as age, HLA and CYP polymorphisms and psychosocial factors remain important, though often unalterable, predictors of disease progression. Although gender and mode of transmission have a lesser role in disease progression, they may impact other markers such as viral load [15]. So we assume that the infective $I_j$ progress to $I_{j+1}$ with a delay $\tau_j$. In the first part of this article, we do the presentation of the delayed model and study the well posedness. Also, we compute the basic reproduction number $R_0$ and study the sensitivity analysis to determine how $R_0$ varies due to the uncertainty in the estimation of parameter values used in the model. In the second part optimal control is used to limit the amount of drug usage with maximum benefit from it. This approach makes the benefit from the treatment is maximum at a certain stage of medication, not because of taking it in high amount. The optimal control is characterized by using retarded optimal control derived by Tchinda et al. [17]. Then utilizing the representation of the optimal control, we solve numerically the optimality system, which is defined as the original state system coupled with the adjoint system. We conclude by discussing the results of the numerical simulations.

2. Presentation of the model. In this paper, we introduce four time delays in an HIV model. The first delay is as mentioned above the delay that takes the infective individual of class $I_1$ to becomes infective of class $I_2$. This delay is defined by $\tau_1$. So, to become infective of class $I_2$ at time $t$, an infective individual of class $I_1$ needs to be in the class $I_1$ at time $t - \tau_1$. With the same idea, the second, third and fourth delays are the time delay to an infective individual $I_j$ take to become infective in the class $I_{j+1}, j = 2, 3, 4$, these delays are denoted by $\tau_j, j = 2, 3, 4$. However, for the model to be biologically reasonable, it may be more realistic to assume that not all those infected $I_j$ will survive after $\tau_j$ time units, and this claim support the introduction of the survival term $e^{-\mu \tau_j}, j = 1, 2, 3, 4$. So, the model in this paper is given by:

$$
\begin{align*}
\dot{S}(t) &= \Lambda - \mu S(t) - \sum_{m=1}^{r} c_{\beta m} \frac{I_m(t)}{N(t)} S(t); \\
\dot{I}_1(t) &= \sum_{m=1}^{r} c_{\beta m} \frac{I_m(t)}{N(t)} S(t) - (k_1 + \mu) I_1; \\
\dot{I}_2(t) &= k_1 e^{-\mu \tau_1} I_1(t - \tau_1) - (k_2 + \mu) I_2(t); \\
&\vdots \\
\dot{I}_{m-1}(t) &= k_{m-1} e^{-\mu \tau_{m-1}} I_{m-1}(t - \tau_{m-1}) - (k_m + \mu) I_m(t); \\
&\vdots \\
\dot{I}_r(t) &= k_{r-1} e^{-\mu \tau_{r-1}} I_{r-1}(t - \tau_{r-1}) - (\mu + d_r) I_r(t).
\end{align*}
$$

We consider that the total population is divided into $(r+1)$ subclasses: one class of susceptibles $(S)$ and $r$ classes of the infective $(I_r), r = 1, \ldots, 5$. The number of total population is denoted by $N(t)$, at time $t$. We assume that the susceptibles become HIV infected via sexual contacts with infective. The transition rate, from
the class $I_m$ to $I_{m+1}$ is as in [16] $k_m I_m$. All recruitment in the population is in the susceptible class, at the rate $bN = \Lambda$. $\mu$ is the natural death rate, the over-mortality due to the infection after sequential progression through these five stages is $d_r$ at $I_r$. The force of infection associated to the model is given by $\lambda = c \beta_m \frac{I_m(t)}{N(t)}$ where $\beta_m$ is the probability that a contact between an infected of the class $I_m$ and a susceptible results in infection and $c$ is the number of contacts for a susceptible per unit time.

3. Main results.

3.1. Well posedness of the model and basic reproduction number. As system (1) is a system of delay differential equations with fixed delays $\tau_i, i = 1, ..., 4$, let $\tau = \max\{\tau_i, i = 1, ..., 4\}$. The initial conditions for the system are defined on the interval $[-\tau, 0]$. Let $C = C([-\tau, 0], \mathbb{R}^6)$ be the Banach space of continuous function from $[-\tau, 0]$ to $\mathbb{R}^6$ equipped with the sup-norm. It is biologically reasonable to consider the following initial conditions for the system (1):

$$
\begin{cases}
S(\theta), I_1(\theta), I_2(\theta), I_3(\theta), I_4(\theta), I_5(\theta) \in C, \forall \theta \in [-\tau, 0] \\
S(\theta) \geq 0, I_1(\theta) \geq 0, I_2(\theta) \geq 0, I_3(\theta) \geq 0, I_4(\theta) \geq 0 \text{ and } I_5(\theta) \geq 0
\end{cases}
$$ (2)

In many cases, these will be assumed to be constant and equal to the value of the state variables at $t = 0$.

Using the result obtained by Hale and Verduyn [11], there is a unique solution $(S(t), I_1(t), I_2(t), ..., I_r(t))$ of the model system (1) with initial conditions (2). It is clear that the solution $(S(t), I_1(t), ..., I_r(t))$ of the model (1) remains positive for all time $t > 0$. Let show that solutions are bounded. It is easy to find that $S(t)$ is bounded. In fact, $\dot{S}(t) \leq \Lambda - \mu S(t)$. Therefore, $\limsup_{t \to +\infty} S(t) \leq \frac{\Lambda}{\mu}$.

Now, let $H(t) = e^{-\mu t} S(t - \tau_1) + e^{-\mu \tau_1} I_1(t - \tau_1) + I_2(t) + e^{\mu \tau_1} I_3(t) + e^{\mu \tau_2 + \mu \tau_3} I_4(t) + ... + e^{\mu \tau_2 + \mu \tau_3 + ... + \mu \tau_{r-1}} I_r(t)$. We obtain

$$
\dot{H}(t) \leq e^{-\mu \tau_1} \Lambda - \mu H(t) \Rightarrow \limsup_{t \to +\infty} H(t) \leq \frac{\Lambda e^{-\mu \tau_1}}{\mu}.
$$

So $H(t)$ is bounded; this implies that trajectories are bounded. One of the most important thresholds while studying infectious disease models is the basic reproduction number $[7]$. The basic reproduction number, denoted $R_0$, is the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual. Many epidemiological models have a disease free equilibrium (DFE) at which the population remains in the absence of disease. A more general basic reproduction number can be defined as the number of new infections produced by a typical infective individual in a population at a the DFE. For model (1), DFE is obtained when $\dot{S} = 0$, $\dot{I}_m = 0$ and $I_m = 0, m = 1, 2, ..., r$. So, the DFE is $(S_0, 0, 0, 0, 0, 0)$ where $S_0 = \frac{\Lambda}{\mu}$. For compute the basic reproduction number $R_0$, we can rewrite our system as follows:

$$
\begin{align*}
\dot{S} &= \mu (S_0 - S) - \frac{S}{N} < B/I > \\
\dot{I} &= \frac{S}{N} < B/I > e_1 + AI
\end{align*}
$$
where \( I = (I_1, I_2, I_3, I_4, I_5)^T, B = (c\beta_1, c\beta_2, c\beta_3, c\beta_4, c\beta_5)^T, e_1 = (1, 0, 0, 0, 0)^T \) and
\[
A = \begin{pmatrix}
-E_1 & 0 & 0 & 0 & 0 \\
 k_1e^{-\mu \tau_1} & -E_2 & 0 & 0 & 0 \\
 0 & k_2e^{-\mu \tau_2} & -E_3 & 0 & 0 \\
 0 & 0 & k_3e^{-\mu \tau_3} & -E_4 & 0 \\
 0 & 0 & 0 & k_4e^{-\mu \tau_4} & -(\mu + d_5)
\end{pmatrix}
\]
with \( E_m = k_m + \mu, m = 1, \ldots, 5 \). Using the method of Van Den Driessche and James Watmough we have \( R_0 = \rho \left( \frac{S}{N}B^T e_1(-A)^{-1} \right) \). So
\[
R_0 = B^T(-A)^{-1}e_1.
\]
Therefore,
\[
R_0 = \frac{R_0^{num}}{(k_1 + \mu)(k_2 + \mu)(k_3 + \mu)(k_4 + \mu)(d_5 + \mu)}
\]
(3)
where
\[
R_0^{num} = c\beta_1(k_2 + \mu)(k_3 + \mu)(k_4 + \mu)(d_5 + \mu) + c\beta_2k_1e^{-\mu \tau_1}(k_3 + \mu)(k_4 + \mu)(d_5 + \mu) + c\beta_3k_1k_2e^{-\mu(\tau_1 + \tau_2)}(k_4 + \mu)(d_5 + \mu) + c\beta_4k_1k_2k_3e^{-\mu(\tau_1 + \tau_2 + \tau_3)}(d_5 + \mu) + c\beta_5k_1k_2k_3k_4e^{-\mu(\tau_1 + \tau_2 + \tau_3 + \tau_4)}
\]
The following result holds.

**Theorem 3.1.** If \( R_0 \leq 1 \), the DFE \( p_0 = \left( \frac{\lambda}{\mu}, 0, 0, 0, 0 \right) \) is the unique equilibrium and is globally asymptotically stable. If \( R_0 > 1 \), \( p_0 \) is instable and the endemic equilibrium exist and is globally asymptotically stable and so the disease is uniformly persistent.

3.2. **Sensitivity analysis.** In what follows, we do a sensitivity analysis for the basic reproduction number (3). Such analysis tells us how important each parameter is to disease transmission. This information is crucial not only for experimental design, but also to data assimilation and reduction of complex nonlinear models [22]. Sensitivity analysis is commonly used to determine the robustness of model predictions to parameter values, since there are usually errors in data collection and presumed parameter values. It is used to discover parameters that have a high impact on \( R_0 \) and should be targeted by intervention strategies. More precisely, sensitivity indices allows to measure the relative change in a variable when parameter changes. For that we use the normalized forward sensitivity index of a variable, with respect to a given parameter, which is defined as the ratio of the relative change in the variable to the relative change in the parameter. If such variable is differentiable with respect to the parameter, then the sensitivity index is defined using partial derivatives, as follows (see [4, 24]). The sensitivity index of \( R_0 \) with respect to a parameter \( \beta_x \) is defined by
\[
\Upsilon_{R_0}^{\beta_x} = \frac{\partial R_0}{\partial \beta_x} \times \frac{\beta_x}{R_0}.
\]
By calculating, we have the following result about sensitivity of $R_0$ with respect to parameters (see Table 2). A larger absolute value of sensitivity indices suggests a stronger correlation and the positive sign of sensitivity indices suggests positive correlation.

| Parameter | Sensitivity index | Value     |
|-----------|-------------------|-----------|
| $\Lambda$ | 0                 | 10^4      |
| $c$       | 1                 | +0.3      |
| $\beta_1$ | +0.7557           | 0.03      |
| $\beta_2$ | +0.2033           | 0.0384    |
| $\beta_3$ | +0.0388           | 0.03      |
| $\beta_4$ | +0.0021           | 0.02      |
| $\beta_5$ | +3.095 x 10^{-8}  | 0.01      |
| $k_1$     | +0.033            | 3 x 10^{-5} |
| $k_2$     | -0.010            | 4 x 10^{-5} |
| $k_3$     | -0.0012           | 10^{-5}   |
| $k_4$     | -1.7060 x 10^{-4} | 10^{-5}   |
| $d_5$     | -2.99 x 10^{-5}   | 3.3 x 10^{-3} |

Note that the sensitivity index may depend on several parameters of the system, but also can be constant, independent of any parameter. For example, according to Table 2, $Y_{R_0} = +1$, meaning that increasing (decreasing) $c$ by a given percentage increases (decreases) always $R_0$ by that same percentage. Furthermore, the most influential parameters in this case are $\beta_1$ and $\beta_2$. That is, decreasing the contact rates $\beta_1$ and $\beta_2$ is more effective in reducing $R_0$. 

![Graphs showing susceptible, infective, and immune individuals over time with and without delay.](image-url)
3.3. Numerical comparison of the system 1 with delay and without delay.

4. Optimal control. Antiretroviral therapy (ART) is the use of HIV medicines to treat HIV infection. So, we include an ART treatment in the model. Our control represents the fraction of infective individuals that is identified and will be put under treatment to help all infective of class $I_s$, $s \geq 3$ to have an undetectable viral load, increase the CD4 cells [3] and so come back to $I_2$. This control is represented in the model by $u(t)$. $a_i$ is the treatment rate of infective individuals $I_i$, $i = 1, ..., r$. We choose as our control class, measurable functions defined on $[t_0, t_f]$, with the restriction $a \leq u(t) \leq b$. A finite interval of treatment is necessary since we assume HIV has the ability to mutate at such a fast pace that it is able to build up resistance to the chemotherapy treatment after a finite time. The treatment period is finite in any treatment scenario. Also, the treatment has potentially harmful side effects [1]. Therefore, our control strategy is applied during the period $[t_0; t_f]$ where $t_f - t_0 \leq 2$ years. With this in mind, the state system would be:

$$
\begin{align*}
\dot{S}(t) &= \Lambda - \mu S(t) - \sum_{m=1}^{r} c\beta_m \frac{I_m(t)}{N(t)} S(t); \\
\dot{I}_1(t) &= \sum_{m=1}^{r} c\beta_m \frac{I_m(t)}{N(t)} S(t) - (k_1 + \mu) I_1(t) \\
\dot{I}_2(t) &= k_1 e^{-\mu \tau_1} I_1(t - \tau_1) - (k_2 + \mu) I_2(t) + u(t) \sum_{s=3}^{5} a_s I_s(t); \\
\dot{I}_3(t) &= k_2 e^{-\mu \tau_2} I_2(t - \tau_2) - (k_3 + \mu) I_3(t) - a_3 u(t) I_3(t); \\
\dot{I}_4(t) &= k_3 e^{-\mu \tau_3} I_3(t - \tau_3) - (k_4 + \mu) I_4(t) - a_4 u(t) I_4(t); \\
\dot{I}_5(t) &= k_4 e^{-\mu \tau_4} I_4(t - \tau_4) - (\mu + d_5) I_5(t) - a_5 u(t) I_5(t).
\end{align*}
$$

Our objective functional to be minimized is

$$
J(u) = \int_{t_0}^{t_f} \left( \sum_{m=3}^{5} A_m I_m(t) - A_2 I_2(t) + Bu^2(t) \right) dt
$$

where we want to minimize population of infective groups $I_s$, $s = 3, 4, 5$ and maximize the infective group $I_2$ while also keeping the cost of the treatments low. We assume that the costs of the treatments are nonlinear and take quadratic form here.
This is based on the fact that there is not a linear relationship between the effects of treatment and infective populations. The coefficient $B$ is a balancing cost factor due to size and importance of parts of the objective functional. We seek to find an optimal control $u^*$, such that

$$J(u^*) = \min_{u \in \Omega} J(u)$$

where $\Omega = \left\{ u \in L^1(t_0, t_f) \mid a \leq u \leq b \right\}$.

Now we state the results on the existence of the optimal control for system (5). According to the transformation technique given by Tchinda et al. [17], the ratios of delays are rational numbers. Let us consider the following assumption

**Assumption 4.1.** Assume that $\tau_1, \tau_2, \tau_3,$ and $\tau_4$ are positive and $\frac{\tau_k}{\tau_s} \in \mathbb{Q}$ where $k \neq s, \tau_s > 0$ and $s, k \in \{1; 2; 3; 4\}$.

**Theorem 4.2.** Consider the control problem with system equations (5). There exists $u^* \in \Omega$ such that

$$\min_{u \in \Omega} J(u) = J(u^*).$$

**Proof.** According to notation of theorem 7 of [17], we can rewrite the system (5) as $X(t) = f(X(t), X(t - \tau_1), ..., X(t - \tau_4), u(t))$ where $X = (S, I_1, ..., I_3)^T$. We make the following transformations to convert the retarded problem into a non delayed problem.

We introduce a state variable $\Sigma = (\xi_0, ..., \xi_{N-1}) \in \mathbb{R}^{(6)N}$ and a control variable $\Phi = (\theta_0, ..., \theta_{N-1}) \in \mathbb{R}^N$ where $\xi_i(t) = (S_i(t), I_1^i(t), I_2^i(t), ..., I_6^i(t))^T \in \mathbb{R}^6$ and $\theta_i(t) = u^i(t) \in \mathbb{R}$ with $S_i(t) = S(t + ih), I_1^i(t) = I_1(t + ih), I_2^i(t) = I_2(t + ih), ..., I_6^i(t) = I_6(t + ih), u^i(t) = u(t + ih), i = 0, ..., N - 1$ and $t \in [0, h]$. Since $S(t), I_1(t), I_2(t), ..., I_6(t)$ are continuous on $[0, t_f]$, we have $\xi_i(t) = \xi_i(0), i = 0, ..., N - 1$. We use these new state variables and control variables to transform the retarded optimal control problem into an equivalent nondelayed optimal control problem on the time interval $[0, h]$. Hence (5)–(7) is equivalent to the following problem:

$$\min J(\Phi) = \int_0^h \sum_{i=0}^{N-1} \left[ \sum_{s=3}^{1} A_i I_s^i(t) - A_2 I_2^i(t) + B(u^i)^2(t) \right] dt$$

subject to

$$\dot{\xi}_i(t) = f(\xi_i(t), \xi_{i-1}(t), ..., \xi_{i-k}(t), \theta_i(t)), t \in [0, h], \quad i = 0, ..., N - 1,$$  

where $\theta_i \in \Omega, \quad i = 0, ..., N - 1$. We define the variables $\xi_{-k}, ..., \xi_{-1}$ as follow:

$$\begin{align*}
\xi_j(t) &= \theta_1(t + jh), & j = -k, ..., -1, & t \in [0, h], \\
\xi_x(t) &= \theta_2(t + xh), & x = -m, ..., -k - 1, & t \in [0, h], \\
\xi_y(t) &= \theta_3(t + yh), & y = -n, ..., -m - 1, & t \in [0, h] \\
\xi_v(t) &= \theta_4(t + vh), & v = -l, ..., -n - 1, & t \in [0, h]
\end{align*}$$

where $k, m, n, l$ are such that $\frac{\tau_1}{l} = \frac{\tau_2}{n} = \frac{\tau_3}{m} = \frac{\tau_4}{k}$ and $h = \frac{\tau_1}{l}$, i.e. $\tau_1 = lh, \tau_2 = nh, \tau_3 = mh, \tau_4 = kh$. The functions $\theta_1(t), \theta_2(t), ..., \theta_{r-1}(t)$ are defined by:
the augmented Hamiltonian for the control problem is given by

\[ \vartheta_1(t) = (S_{11}(t), I_{11}(t), ..., I_{51}(t))^T \quad \text{for} \quad t \in [-\tau_4, 0] \]

\[ \vartheta_2(t) = (S_{22}(t), I_{12}(t), ..., I_{52}(t))^T \quad \text{for} \quad t \in [-\tau_4, -\tau_3] \]

\[ \vartheta_3(t) = (S_{33}(t), I_{13}(t), ..., I_{53}(t))^T \quad \text{for} \quad t \in [-\tau_3, -\tau_2] \]

\[ \vartheta_4(t) = (S_{44}(t), I_{14}(t), ..., I_{54}(t))^T \quad \text{for} \quad t \in [-\tau_2, -\tau_1]. \]

It is easy to verify that the control set \( \Omega \) is closed and convex. The integrand of the objective function defined by (6) is convex on the control set. The model (5) is linear in the control variables and is bounded by a linear system in the state variables. So the conditions for the existence of optimal control are satisfied (see Fleming et al. [10]).

Since there exists an optimal control for minimizing the functional equation (6) subject to system (5), we derive necessary conditions of the optimal control. We use the theorem 7 of [17] that relates to the characterization of the optimal control. To this end, we define a Lagrangian (which is the Hamiltonian augmented with penalty terms for the control constraints). Let \( I_{jj}(t) = I_j(t - \tau_j), \quad j = 1, 2, \ldots, m, \ldots, r - 1 \), the augmented Hamiltonian for the control problem is given by

\[
H(S(t), I_1(t), ..., I_r(t), N(t), u(t)) = \sum_{m=3}^{5} A_m I_m(t) - A_2 I_2(t) + B u^2(t) + \\
\lambda_1(t) \left[ \Lambda - \mu S(t) - \sum_{m=1}^{5} c_{\beta m} \frac{I_m(t)}{N(t)} S(t) \right] + \lambda_2(t) \left[ \sum_{m=1}^{5} c_{\beta m} \frac{I_m(t)}{N(t)} S(t) - (k_1 + \mu) I_1(t) \right] \\
+ \lambda_3(t) \left[ k_1 e^{-\mu \tau_2} I_{11}(t) - (k_2 + \mu) I_2(t) + u(t) \sum_{s=3}^{5} a_s I_s(t) ; \right] \\
+ \lambda_4(t) \left[ k_2 e^{-\mu \tau_2} I_{22}(t) - (k_3 + \mu) I_3(t) - a_3 u(t) I_3(t) \right] \\
+ \lambda_5(t) \left[ k_3 e^{-\mu \tau_3} I_{33}(t) - (\mu + k_4 - a_4 u(t)) I_4(t) \right] \\
+ \lambda_6(t) \left[ k_4 e^{-\mu \tau_4} I_{44}(t) - (\mu + d_5 - a_5) I_5(t) \right] + w_{11}(b - u(t)) + w_{12}(u(t) - a) \]

where \( w_{11} \) and \( w_{12} \) are non-negative and satisfying \( w_{11}(b - u^*(t)) = w_{12}(u^*(t) - a) = 0 \) that there is not a linear relationship

**Theorem 4.3.** There exist optimal control \( u^* \) and solutions \( S^*, I_1^*, ..., I_r^* \) to the corresponding state system (5), there exists adjoint functions \( \lambda_1(t), \lambda_2(t), ..., \lambda_{r+1}(t) \) such that

\[
\dot{\lambda}_1(t) = \lambda_1(t) \left( \mu + \sum_{m=1}^{r} c_{\beta m} \frac{I_m^*(t) (I_1^*(t) + I_2^*(t) + ... + I_r^*(t))}{N^{*2}(t)} \right) \\
- \lambda_2(t) \sum_{m=1}^{r} c_{\beta m} \frac{I_m^*(t) (I_1^*(t) + I_2^*(t) + ... + I_r^*(t))}{N^{*2}(t)},
\]
\[
\dot{\lambda}_2(t) = \lambda_1(t) \sum_{m=1}^{5} \frac{cS^*(t)(\beta_1 S^* + (\beta_1 - \beta_m) I^*_m(t))}{N^{*2}(t)} - \lambda_2(t) \sum_{m=1}^{5} \frac{cS^*(t)(\beta_1 S^* + (\beta_1 - \beta_m) I^*_m(t))}{N^{*2}(t)} - k_1 - \mu
\]
\[
\dot{\lambda}_3(t) = A_2 + \lambda_1(t) \sum_{m=1}^{5} \frac{cS^*(t)(\beta_2 S^* + (\beta_2 - \beta_m) I^*_m(t))}{N^{*2}(t)} - \lambda_2(t) \sum_{m=1}^{5} \frac{cS^*(t)(\beta_2 S^* + (\beta_2 - \beta_m) I^*_m(t))}{N^{*2}(t)} + \lambda_3(t)(k_2 + \mu) - \chi_{[t_0, t_f - \tau_3]}(t_1)k_3 e^{-\mu \tau_3} \lambda_5(t + \tau_3),
\]
\[
\dot{\lambda}_4(t) = -A_3 + \lambda_1(t) \sum_{m=1}^{5} \frac{cS^*(t)(\beta_3 S^* + (\beta_3 - \beta_m) I^*_m(t))}{N^{*2}(t)} - \lambda_2(t) \sum_{m=1}^{5} \frac{cS^*(t)(\beta_3 S^* + (\beta_3 - \beta_m) I^*_m(t))}{N^{*2}(t)} - \lambda_3(t)a_3 u(t) + \lambda_4(k_3 + \mu + a_3 u^*(t)) - \chi_{[t_0, t_f - \tau_3]}(t_1)k_3 e^{-\mu \tau_3} \lambda_5(t + \tau_3),
\]
\[
\dot{\lambda}_5(t) = -A_4 + \lambda_1(t) \sum_{m=1}^{5} \frac{cS^*(t)(\beta_4 S^* + (\beta_4 - \beta_m) I^*_m(t))}{N^{*2}(t)} - \lambda_2(t) \sum_{m=1}^{5} \frac{cS^*(t)(\beta_4 S^* + (\beta_4 - \beta_m) I^*_m(t))}{N^{*2}(t)} - \lambda_3(a_4 u(t)) + \lambda_5(k_4 + a_4 u^*(t)) - \chi_{[t_0, t_f - \tau_4]}(t_1)k_4 e^{-\mu \tau_4} \lambda_6(t + \tau_4),
\]
\[
\dot{\lambda}_6(t) = -A_5 + \lambda_1(t) \sum_{m=1}^{5} \frac{cS^*(t)(\beta_5 S^* + (\beta_5 - \beta_m) I^*_m(t))}{N^{*2}(t)} - \lambda_2(t) \sum_{m=1}^{5} \frac{cS^*(t)(\beta_5 S^* + (\beta_5 - \beta_m) I^*_m(t))}{N^{*2}(t)} - \lambda_3 a_5 u(t) + \lambda_6(\mu + d_5 + a_5 u^*(t))
\]

with transversality conditions

\[
\lambda_i(t_f) = 0, \quad i = 1, ..., 6
\]

and \( N^* = S^* + I_1^* + ... + I_6^* \). The optimal control is given by

\[
\begin{align*}
\mathbf{u}^* &= \min \left\{ \max \left\{ a, \frac{1}{2B} \sum_{s=3}^{5} (\lambda_{s+1} - \lambda_3)a_s I_s \right\}, b \right\}.
\end{align*}
\]

Proof. The existence of the optimal control is given by Theorem 4.2. Then by using Pontryagin’s Maximum Principle for retarded optimal control problem (see [17]), the adjoint system can be written as:

\[
\begin{align*}
\dot{\lambda}_1(t) &= -\frac{\partial \mathcal{H}(t)}{\partial S} \\
\dot{\lambda}_2(t) &= -\frac{\partial \mathcal{H}(t)}{\partial I_1} - \chi_{[t_0, t_f - \tau_1]}(t) \frac{\partial \mathcal{H}(t + \tau_1)}{\partial I_{11}}
\end{align*}
\]
\[
\begin{align*}
\lambda_3(t) &= -\frac{\partial H(t)}{\partial I_2} - \chi_{[t_0, t_f - \tau_2]}(t) \frac{\partial H(t + \tau_2)}{\partial I_2} \\
\lambda_4(t) &= -\frac{\partial H(t)}{\partial I_3} - \chi_{[t_0, t_f - \tau_3]}(t) \frac{\partial H(t + \tau_3)}{\partial I_3} \\
\lambda_5(t) &= -\frac{\partial H(t)}{\partial I_4} - \chi_{[t_0, t_f - \tau_4]}(t) \frac{\partial H(t + \tau_4)}{\partial I_4} \\
\lambda_6(t) &= -\frac{\partial H(t)}{\partial I_5}
\end{align*}
\]

The optimality equation is
\[
\frac{\partial H}{\partial u} = 2Bu^* + \sum_{s=3}^5 (\lambda_s - \lambda_{s+1})a_s I_s - w_{11} + w_{12} = 0 \text{ at } u^*.
\]

According to standard control arguments involving the bounds on the control, we obtain the characterization of \(u^*\).

5. Numerical illustration. In this section, we investigate numerically the optimal solution to the model (5) by using numerical method described in Tchinda et al [17]. For this consideration, we have \(\tau_1 \in [14 \text{days} - 30 \text{days}]\) and \(\tau_2, \tau_3, \tau_4 \in [5 \text{months}; 1 \text{year}]\). The following parameters and initial values are used for numerical simulations: \(\Lambda = 10^5, \mu = 0.000112, \beta_1 = 0.03, \beta_2 = 0.0384, \beta_3 = 0.03, \beta_4 = 0.02, \beta_5 = 0.01, c = 0.3, k_1 = 0.00003, k_2 = 0.00004, k_3 = 0.00001, k_4 = 0.00001, d_5 = 0.0033\). For the figures presented here, we assume that the weight factor values are \(A_1 = 0.1, A_2 = 0.4, A_3 = 0.2, A_4 = 0.2, A_5 = 0.5, a_1 = 0.1, a_2 = 0.2\). Initial conditions are \(S(0) = 5000, I_1(s) = 1000, I_2(s) = 1000, I_3(s) = 1000, I_4(s) = 2000\) and \(I_5(s) = 1000\), where \(s \in [-\tau_2, 0]\). We suppose that \(0.2 \leq u(t) \leq 0.8\). With this values we obtain \(R_0 = 83, 5\).

Figure 2 shows the optimal treatment strategy. The control \(u\) is plotted as a function of time (see Fig.2 (g1)). We observe from these figures (see Fig.2 (a1) – (b1)) that the control has no effect on susceptible individuals and infective individuals of stage 1. This is due to the fact that the treatment of HIV cannot clear the virus in the body. So an infective individual after treatment cannot become susceptible (see Fig.2 (a1)). Moreover, we observe that the number of infective individuals of stage 2 increases (see Fig.2 (c1)). This means that the treatment can increases the number of CD4 cells and help infective individuals of stage 3, stage 4 and stage 5 to become infective of stage 2 (see Fig.2 (d1) – (f1)). Note that to obtain this result, we must increase the rate of treatment with an oscillatory manner from day 60 until the end of treatment strategy.
In Figure 3, we compare the optimal control of system (5) for $\tau_i = 0$, $i = 1, \ldots, 4$ (no delay) and in presence of time delays. When there is no delay, population of infective individual at stage 1 increase with the optimal control strategy. This can be explained by the fact that there is not time delay and the transfers of infective individuals of stages 2, 3, 4 and 5 are instantaneously (see Fig. 3 (b)). We can also observe that time delay increase reduction of infective individuals of stages 3, 4 and 5 (see Fig. 3 (d), (e), (f)), and rise of infective individuals of stages 2. So, our aim is achieved by the optimal strategy with time delay (see Fig. 3 (c)).
6. Conclusion. In this paper, we have used an optimal control theory to reduce the population of infective individuals with low CD4 cells and to increase the population of infective individuals with a high CD4 cells. Our approach uses an existing compartmental HIV model with r-stage of infections. We use result of retarded optimal control studied by Tchinda et al. [17] to determine the optimal dynamic control analytically, then use numerical methods to simulate different outcomes. Numerical results suggest that it is possible to reduce the population with low CD4 cells and to obtain a population with high CD4 cells.
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