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STABILITY AND OPTIMAL CONTROL OF A DELAYED HIV/AIDS-PREP MODEL

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Abstract. In this paper, we propose a time-delayed HIV/AIDS-PrEP model which takes into account the delay on pre-exposure prophylaxis (PrEP) distribution and adherence by uninfected persons that are in high risk of HIV infection, and analyze the impact of this delay on the number of individuals with HIV infection. We prove the existence and stability of two equilibrium points, for any positive time delay. After, an optimal control problem with state and control delays is proposed and analyzed, where the aim is to find the optimal strategy for PrEP implementation that minimizes the number of individuals with HIV infection, with minimal costs. Different scenarios are studied, for which the solutions derived from the Minimum Principle for Multiple Delayed Optimal Control Problems change depending on the values of the time delays and the weights constants associated with the number of HIV infected individuals and PrEP. We observe that changes on the weights constants can lead to a passage from *bang-singular-bang* to *bang-bang* extremal controls.

1. **Introduction.** Pre-exposure prophylaxis (PrEP) is the use of an antiretroviral medication (tenofovir and emtricitabine) to prevent the acquisition of Human immunodeficiency virus (HIV) infection by uninfected persons. PrEP has shown considerable impact in reducing new HIV infections when provided as an additional HIV prevention choice to gay men and other men who have sex with men, transgender people and sex workers [32]. Since 2015, the World Health Organization has recommended PrEP for people at substantial HIV risk. Although most experience of PrEP implementation has been in high-income countries, PrEP services are now being developed for low and middle-income countries. To date, more than 60 countries globally have national PrEP polices, including 20 in Africa [30, 31].

In this work, we generalize the HIV/AIDS-PrEP model, proposed in [24], to a system of delayed differential equations. The HIV/AIDS-PrEP model subdivides the human population into five mutually-exclusive compartments: susceptible individuals (S); HIV-infected individuals with no clinical symptoms of AIDS (the virus is living or developing in the individuals but without producing symptoms or only mild ones) but able to transmit HIV to other individuals (I); HIV-infected individuals under ART treatment (chronic stage) with a viral load remaining low (C); HIV-infected individuals with AIDS clinical symptoms (A); and individuals

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that take PrEP (E). The total population at time t, denoted by $N(t)$, is given by $N(t) = S(t) + I(t) + C(t) + A(t) + E(t)$.

The rate of infection of susceptible individuals, λ, is given by

$$\lambda = \frac{\beta}{N} \left(I + \eta_C \, C + \eta_A A \right), \tag{1}$$

where β is the transmission coefficient for HIV transmission. The modification parameters $\eta_A \geq 1$ and $\eta_C \leq 1$ accounts for the relative infectiousness of individuals with AIDS symptoms and under HIV treatment, in comparison to those infected with HIV with no AIDS symptoms, respectively [23, 24]. It is assumed that only individuals with AIDS symptoms, A, are subject to AIDS-induced mortality, at a rate d. All individuals suffer from natural death, at rate μ, and the population is increased by newborns and immigration, represented by the recruitment rate Λ. The proportion of susceptible individuals that takes PrEP is denoted by ψ, with $0 < \psi \leq 1$. And is assumed that PrEP is effective so that all susceptible individuals under PrEP treatment are transferred to class E. The efficacy of PrEP has been medically tested, see e.g. [1, 10].

The SICAE model, proposed in [24], is given by the following system of five ordinary differential equations,

$$\begin{cases} \dot{S}(t) = \Lambda - \frac{\beta}{N(t)} \left(I(t) + \eta_C \, C(t) + \eta_A A(t) \right) S(t) - (\mu + \psi) S(t) + \theta E(t), \\ \dot{I}(t) = \frac{\beta}{N(t)} \left(I(t) + \eta_C \, C(t) + \eta_A A(t) \right) S(t) - \xi_3 I(t) + \alpha A(t) + \omega C(t), \\ \dot{C}(t) = \phi I(t) - \xi_2 C(t), \\ \dot{A}(t) = \rho \, I(t) - \xi_1 A(t), \\ \dot{E}(t) = \psi S(t) - (\mu + \theta) E(t), \end{cases} \tag{2}$$

where $\xi_1 = \alpha + \mu + d$, $\xi_2 = \omega + \mu$ and $\xi_3 = \rho + \phi + \mu$, and the description of all parameters of the model is given in Table 1.

TABLE 1. Description of the parameters of the HIV/AIDS-PrEP model (2).

Symbol	Description
Λ	Recruitment rate
μ	Natural death rate
λ	Infection rate for S individuals
β	Transmission coefficient for HIV transmission
η_C	Modification parameter
η_A	Modification parameter
ϕ	HIV treatment rate for I individuals
ρ	Default treatment rate for I individuals
α	AIDS treatment rate
ω	Default treatment rate for C individuals
d	AIDS induced death rate
ψ	Proportion of susceptible individuals that takes PrEP
θ	Proportion of susceptible individuals who default PrEP

In this paper, we generalize the model (2) to a system of delayed differential equations, by the introduction of a discrete time delay which represents a delayed implementation of PrEP. We analyze the stability of the equilibrium points of the delayed model, for any positive time delay. Time delayed differential models have been extensively investigated in biomedicine and epidemiology, see e.g. [5, 11, 18], and in many other fields see e.g. [3, 17]. However, not so many papers study delayed differential compartmental models in the framework of optimal control theory, see e.g. [8, 15, 19, 21, 22]. Here, we introduce a control function in the delayed differential model and propose an optimal control problem with state and control delays. In order to derive the extremals for the delayed optimal control problem we apply a necessary optimality condition given by the Minimum Principle for Multiple Delayed Optimal Control Problems of [7] and compute the respective numerical solutions.

The paper is organized as follows. In Section 2, a new delayed HIV/AIDS-PrEP model is proposed considering a biologically feasible region. The existence of two equilibrium points and their stability are proved, for any positive time delay. A control function is introduced in the delayed model, in Section 3, which represents the proportion of susceptible individuals that is taking PrEP. The effect of a delayed PrEP implementation is reinforced by the introduction of a time delay in the control function. Considering a control system with delays in the state and control variables, an optimal control problem is formulated where the goal is to find the optimal strategy for PrEP implementation that minimizes the number of individuals with HIV infection, I, with minimal cost. In Section 4, the optimal control problem is solved numerically and the extremal solutions are analyzed from an epidemiological point of view. We end the paper with Section 5 where the impact of the delay on PrEP distribution and adherence is analyzed. Some future work directions will be pointed.

2. **Delayed HIV/AIDS-PrEP model.**

PrEP implementation may suffer time delays that are associated with barriers that block an effective implementation of PrEP, such as, stigma, cost and adherence. Moreover, the access and delivery of PrEP to population in high risk faces serious limitations, and many times the population that should benefit from PrEP are those who have more difficulties to come routinely to a health service [2]. Adherence problems and high costs of the medicines may also be responsible for a delayed implementation of PrEP at the target population. In this work, we generalize the HIV/AIDS-PrEP model, from [24], and consider the case where the implementation of PrEP suffers a discrete time-delay, represented by τ, with $\tau \geq 0$. The delayed model is given by the following system of delayed differential equations:

$$\begin{cases} \dot{S}(t) = \Lambda - \frac{\beta}{N(t)} \left(I(t) + \eta_C\, C(t) + \eta_A A(t)\right) S(t) - \mu S(t) - \psi\, S(t) + \theta E(t), \\ \dot{I}(t) = \frac{\beta}{N(t)} \left(I(t) + \eta_C\, C(t) + \eta_A A(t)\right) S(t) - \xi_3 I(t) + \alpha A(t) + \omega C(t), \\ \dot{C}(t) = \phi I(t) - \xi_2 C(t), \\ \dot{A}(t) = \rho\, I(t) - \xi_1 A(t), \\ \dot{E}(t) = \psi\, \mathrm{e}^{-\mu\tau} S(t-\tau) - (\mu + \theta) E(t)\,, \end{cases} \tag{3}$$

where the term $\mathrm{e}^{-\mu\tau}$ allows for the extinction of PrEP before it comes effectively implemented.

Let Ω be the biologically feasible region of model (3)

$$\Omega = \left\{ (S,I,C,A,E) \in \mathbb{R}^5_{+0} \,:\, S \leq \frac{(\theta+\mu)\,\Lambda}{\mu\,(\theta+\psi+\mu)}, E \leq \frac{\psi\,\Lambda}{\mu\,(\theta+\psi+\mu)}, N \leq \frac{\Lambda}{\mu} \right\}.$$

and the initial conditions given by

$$S(\theta) = \varphi_1(\theta), \quad I(\theta) = \varphi_2(\theta), \quad C(\theta) = \varphi_3(\theta), \quad A(\theta) = \varphi_4(\theta), \quad E(\theta) = \varphi_5(\theta),$$

with $\varphi_i(\theta) \geq 0$ and $\theta \in [-\tau, 0]$, for $i = 1, \ldots, 5$, and where $\varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5)^T \in \mathbf{C}$ with $\mathbf{C}$ the Banach space $\mathbf{C}\left([-\tau, 0], \mathbb{R}^5\right)$ of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^5$. The usual local existence, uniqueness and continuation results apply [9, 12]. Moreover, from biological meaning, we further assume that the initial functions are nonnegative:

$$\varphi_i(\theta)\,, \quad \text{for } \theta \in [-\tau, 0]\,, \quad i = 1, \ldots, 5\,.$$

Lemma 2.1. *The solutions $(S(t), I(t), C(t), A(t), E(t))$ of system (3) with initial conditions (2) remain non-negative, for all $t \geq -\tau$.*

Proof. From system (3) we have that, when $S(t) = 0$ and $(S(t), I(t), C(t), A(t), E(t)) \in \mathbf{C}\left([-\tau, 0], \mathbb{R}^+_0\right)$, for all $t \in [-\tau, +\infty]$, there holds $\dot{S}(t) = \Lambda + \theta E(t) > 0$. Analogously, if $I(t) = 0$, then $\dot{I}(t) = \beta\left(\eta_C C(t) + \eta_A A(t)\right) S(t) + \alpha A(t) + \omega C(t) \geq 0$; if $C(t) = 0$ then $\dot{C}(t) = \phi I(t) \geq 0$; if $A(t) = 0$ then $\dot{A}(t) = \rho\, I(t) \geq 0$; and if $E(t) = 0$ then $\dot{E}(t) = \psi\, \mathrm{e}^{-\mu\tau} S(t-\tau) \geq 0$. By Lemma 2 of [29], any solution of system (3) remains non-negative, for all $t \geq -\tau$. □

2.1. **Equilibrium points and basic reproduction number.** The model (3) has a disease free equilibrium, Σ_0, given by

$$\begin{aligned} \Sigma_0 &= (S_0, I_0, C_0, A_0, E_0) \\ &= \left(\frac{(\theta+\mu)\,\Lambda}{\theta\,\psi(1-\mathrm{e}^{-\tau\,\mu}) + \mu(\mu+\psi+\theta)}, 0, 0, 0, \frac{\psi\,\mathrm{e}^{-\tau\,\mu}\Lambda}{\theta\,\psi(1-\mathrm{e}^{-\tau\,\mu}) + \mu(\mu+\psi+\theta)} \right). \end{aligned} \tag{4}$$

Let $\xi_4 = \theta + \mu$. For any time delay $\tau \geq 0$, the point (4) is the only biologically meaningful equilibrium whenever the basic reproduction number, denoted by $R_0(\tau)$, is such that, $R_0(\tau) < 1$, where $R_0(\tau)$ is given by

$$R_0(\tau) = \frac{\beta\,\xi_4 \mathcal{N}_0}{(\psi \mathrm{e}^{-\tau\,\mu} + \mu + \theta)\,\mathcal{D}_0} = \frac{\mathcal{N}}{\mathcal{D}}\,, \tag{5}$$

with $\mathcal{N}_0 = (\xi_2(\eta_A\rho + \xi_1) + \eta_C\phi\,\xi_1)$ and $\mathcal{D}_0 = \xi_1\xi_2\xi_3 - \xi_1\omega\phi - \xi_2\alpha\rho$.

Proposition 1. *Let $\tau \geq 0$. The basic reproduction number $R_0(\tau)$ increases with τ.*

Proof. A direct calculation from (5) shows that

$$\frac{\partial R_0}{\partial \tau}(\tau) = \frac{\beta\,\xi_4\,\mathcal{N}_0\,\psi\mu\,\mathrm{e}^{-\tau\,\mu}}{(\psi \mathrm{e}^{-\tau\,\mu} + \mu + \theta)^2 \mathcal{D}_0} > 0\,.$$

Note that the term $\mathcal{D}_0$ can be written in by the sum $\mathcal{D}_0 = \mu\,(\xi_2(\rho + \xi_1) + \phi\xi_1 + \rho d) + \rho\omega d > 0$, since all parameters take positive values. When τ goes to infinity the basic reproduction number tends to the fixed value $\frac{\beta\,\xi_4\,\mathcal{N}_0}{(\mu+\theta)\mathcal{D}_0}$. □

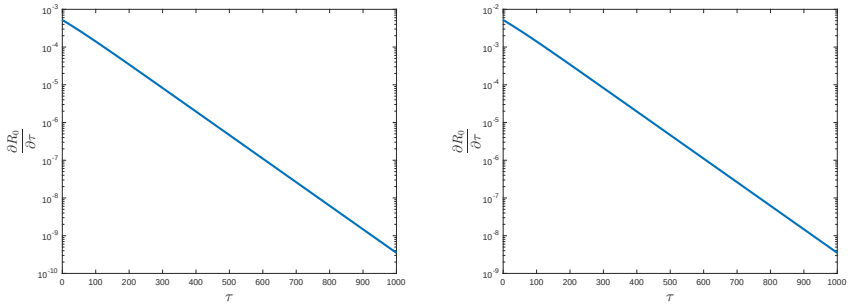
Example 2.2. Take the following initial conditions from [24]

$$\begin{aligned} &S_0 = S(0) = 323911\,, \quad I_0 = I(0) = 61\,, \quad C_0 = C(0) = 0\,, \\ &A_0 = A(0) = 0\,, \quad E_0 = E(0) = 0\,, \end{aligned} \tag{6}$$

then $N(0) = 323972$. Assume that $\Lambda = 2.2\mu N(0)$, $d = 1$ and take the other parameter values from the Table 2 (see Section 4).

For $\beta = 0.0752$, Figure 1 (a) represents the partial derivative $\frac{\partial R_0}{\partial \tau}(\tau)$ that is always positive, for $\tau \in [0, 1000]$. For these parameter values, we have $R_0(0) = 0.4508 < 1$ and $R_0(1000) = 0.4902 < 1$.

When $\beta = 0.752$ and $\tau \in [0, 1000]$, Figure 1 (b) represents the partial derivative $\frac{\partial R_0}{\partial \tau}(\tau)$ that is remains positive. For these parameter values, we have $R_0(0) = 4.5078 > 1$ and $R_0(1000) = 4.9020 > 1$.



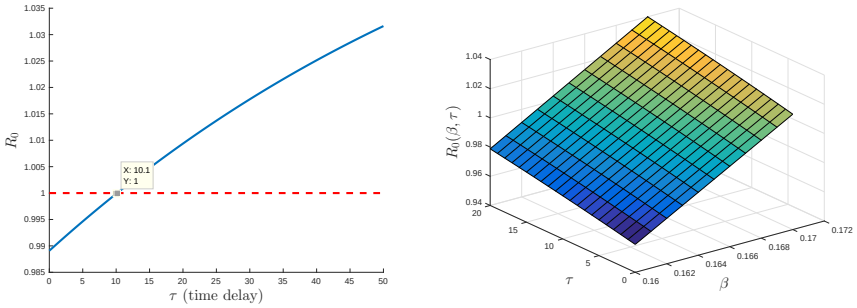
(A) $\beta = 0.0752$ (B) $\beta = 0.752$

FIGURE 1. Partial derivative of $R_0(\tau)$ with respect to τ (with logarithmic scale in the Y axis): (a) $\beta = 0.0752$ corresponding to $R_0(\tau) < 1$; (b) $\beta = 0.752$ corresponding to $R_0(\tau) > 1$.

Example 2.3. Taking the same initial conditions from Example 2.2 and $\beta = 0.165$, corresponding to a basic reproduction number close to 1 for $\tau = 0$, precisely, $R_0(\tau) = 0.9891 < 1$ we observe that an increase of the time delay τ leads to a basic reproduction number greater than 1. For example, for $\tau = 50$ there holds $R_0(50) = 1.0316 > 1$, see Figure 2.

When $R_0(\tau) > 1$, for any time delay $\tau \geq 0$, the system (3) has a unique endemic equilibrium $\Sigma_+ = (S_+, I_+, C_+, A_+, E_+)$ given by

$$\begin{aligned} S_+ &= \frac{\Lambda\xi_4 k}{-\psi \mathrm{e}^{-\mu\tau}(k\theta + \mathcal{D}_0) + l}, \\ I_+ &= \frac{\Lambda\xi_1\xi_2(\mathcal{N} - \mathcal{D})}{[\mathcal{N} - \mathcal{D} + k(\psi\theta(1 - \mathrm{e}^{-\tau\mu}) + \mu\xi_5)]\mathcal{D}_0}, \\ C_+ &= \frac{\Lambda\phi\xi_1(\mathcal{N} - \mathcal{D})}{[\mathcal{N} - \mathcal{D} + k(\psi\theta(1 - \mathrm{e}^{-\tau\mu}) + \mu\xi_5)]\mathcal{D}_0}, \\ A_+ &= \frac{\Lambda\xi_2\rho(\mathcal{N} - \mathcal{D})}{[\mathcal{N} - \mathcal{D} + k(\psi\theta(1 - \mathrm{e}^{-\tau\mu}) + \mu\xi_5)]\mathcal{D}_0}, \\ E_+ &= \frac{\Lambda k\psi \mathrm{e}^{-\mu\tau}}{-\psi \mathrm{e}^{-\mu\tau}(k\theta + \mathcal{D}_0) + l} \end{aligned} \tag{7}$$



(A) $R_0(\tau)$, $\tau \in [0, 50]$

(B) $R_0(\tau, \beta)$, $\tau \in [0, 20]$, $\beta \in [0.16, 1.72]$

FIGURE 2. Influence of the time delay on $R_0(\tau)$, for $\tau \in [0, 50]$ and $\beta \in [0.16, 1.72]$.

with $k = (\xi_2 + \phi)\xi_1 + \rho\xi_2$ and $l = (\theta + \mu)((\xi_2(\eta_A\rho + \xi_1) + \eta_C\phi\xi_1)\beta + \psi k - d\rho\xi_2)$

Remark 1. For $\tau = 0$, the expression of the equilibrium points Σ_0, Σ_+ and basic reproduction number $R_0(0)$ coincides with the one from [24, 25].

The stability of the equilibrium points Σ_0 and Σ_+, for any time delay $\tau \geq 0$, will be analyzed in the next section.

2.2. **Stability of the equilibrium points.** The transcendental characteristic equation of the linearized system associated to system (3), at the disease free equilibrium Σ_0, is given by

$$\Delta(\lambda, \tau) = p_1(\lambda, \tau)p_2(\lambda, \tau) = 0\,, \tag{8}$$

where

$$p_1(\lambda, \tau) = -\frac{1}{\psi e^{-\mu\tau} + \mu + \theta}\left(e^{-\lambda\tau}e^{-\mu\tau}\psi\theta - (\lambda + \xi_4)(\lambda + \mu + \psi)\right)$$

and

$$p_2(\lambda, \tau) = p_3(\lambda)e^{-\mu\tau} + p_4(\lambda)$$

with

$$p_3(\lambda) = a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 \quad \text{and} \quad p_4(\lambda) = b_3\lambda^3 + b_2\lambda^2 + b_1\lambda + b_0\,,$$

where

$$a_3 = \psi,\ a_2 = \psi(\xi_1 + \xi_2 + \xi_3),\ a_1 = \psi(k + \mu(\xi_1 + \xi_3 + \omega) + d\rho),\ a_0 = \psi\,\mathcal{D}_0,$$
$$b_3 = -\xi_4,\ b_2 = -\beta\xi_4 + \xi_4(\xi_1 + \xi_2 + \xi_3,\ b_0 = -\xi_4(\mathcal{N}_0\beta - \mathcal{D}_0),$$
$$b_1 = -\xi_4\left[\beta(\eta_A\rho + \eta_C\phi + \xi_1 + \xi_2) - \mu(\xi_1 + \xi_2 + \rho + \phi) - d\rho - k\right].$$

Let $\xi_5 = \psi + \mu + \theta$. For $\tau = 0$, we have

$$\Delta(\lambda, 0) = p_1(\lambda, 0)\, p_2(\lambda, 0) = 0\,, \tag{9}$$

with

$$p_1(\lambda, 0) = \frac{1}{\xi_5}(\lambda + \mu)(\lambda + \xi_5)$$

and

$$p_2(\lambda, 0) = (a_3 + b_3)\lambda^3 + (a_2 + b_2)\lambda^2 + (a_1 + b_1)\lambda + a_0 + b_0\,.$$

The roots $-\mu$ and $-\xi_5$ of $\Delta(\lambda,0)$ have negative real parts. Therefore, we must focus on the roots of $p_2(\lambda,0)$ that are the same as the one of the equation

$$p_5(\lambda)=\lambda^3+\frac{a_2+b_2}{a_3+b_3}\lambda^2+\frac{a_1+b_1}{a_3+b_3}\lambda+\frac{a_0+b_0}{a_3+b_3}\,.$$

From the Routh-Hurwitz criterion for third order polynomials, $p_5(\lambda)$ has all roots in the open left half plane if and only if $\frac{a_2+b_2}{a_3+b_3}>0$, $\frac{a_0+b_0}{a_3+b_3}>0$ and $(a_2+b_2)(a_1+b_1)>(a_0+b_0)(a_3+b_3)$.

As

$$a_2+b_2=\xi_5(\xi_1+\xi_2+\xi_3)-\beta\xi_4 \quad \text{and} \quad a_3+b_3=\xi_5\,,$$

then

$$\frac{a_2+b_2}{a_3+b_3}=\xi_1+\xi_2+\xi_3-\frac{\beta\xi_4}{\xi_5}\,.$$

Moreover,

$$\frac{a_0+b_0}{a_3+b_3}=\frac{\mathcal{D}_{\tau=0}-\mathcal{N}_{\tau=0}}{\xi_5}\,,$$

where

$$R_{0,\tau=0}=\frac{\beta\,\xi_4\mathcal{N}_0}{\xi_5\mathcal{D}_0}=\frac{\mathcal{N}_{\tau=0}}{\mathcal{D}_{\tau=0}}\,,$$

is the basic reproduction number of undelayed model corresponding to system (3) with $\tau=0$.

Therefore, $\frac{a_2+b_2}{a_3+b_3}>0$ and $\frac{a_0+b_0}{a_3+b_3}>0$ hold whenever $R_{0,\tau=0}<1$.

The last inequality $(a_2+b_2)(a_1+b_1)>(a_0+b_0)(a_3+b_3)$ is equivalent to

$$\frac{(a_2+b_2)(a_1+b_1)}{\xi_5(\mathcal{D}_{\tau=0}-\mathcal{N}_{\tau=0})}>0$$

which holds for $R_{0,\tau=0}<1$.

For $\tau>0$, we can prove the global asymptotic stability of the disease free equilibrium (4), Σ_0, when $R_0<1$, by constructing appropriate Lyapunov functionals.

Theorem 2.4. *The disease free equilibrium (4), Σ_0, is globally asymptotically stable, whenever $R_0<1$, for any positive time delay $\tau>0$.*

Proof. Consider the following Lyapunov function:

$$\begin{aligned}V=&\left(\xi_1\xi_2+\xi_1\phi\eta_C+\xi_2\rho\eta_A\right)I+\left(\xi_1\omega+\xi_1\xi_3\eta_C+\rho\eta_A\omega-\eta_C\rho\alpha\right)C\\&+\left(\alpha\xi_2+\xi_2\xi_3\eta_A+\phi\eta_C\alpha-\phi\eta_A\omega\right)A.\end{aligned}$$

The time derivative of V computed along the solutions of (2) is given by

$$\begin{aligned}\dot V=&\left(\xi_1\xi_2+\xi_1\phi\eta_C+\xi_2\rho\eta_A\right)\dot I+\left(\xi_1\omega+\xi_1\xi_3\eta_C+\rho\eta_A\omega-\eta_C\rho\alpha\right)\dot C\\&+\left(\alpha\xi_2+\xi_2\xi_3\eta_A+\phi\eta_C\alpha-\phi\eta_A\omega\right)\dot A\\=&\left(\xi_1\xi_2+\xi_1\phi\eta_C+\xi_2\rho\eta_A\right)\left(\frac{\beta}{N}\left(I+\eta_C\,C+\eta_A A\right)S-\xi_3 I+\alpha A+\omega C\right)\\&+\left(\xi_1\omega+\xi_1\xi_3\eta_C+\rho\eta_A\omega-\eta_C\rho\alpha\right)\left(\phi I-\xi_2 C\right)\\&+\left(\alpha\xi_2+\xi_2\xi_3\eta_A+\phi\eta_C\alpha-\phi\eta_A\omega\right)\left(\rho\,I-\xi_1 A\right).\end{aligned}$$

After some simplifications, we have

$$\begin{aligned}
\dot{V} &= (\xi_1\xi_2+\xi_1\phi\eta_C+\xi_2\rho\eta_A)\frac{\beta IS}{N}+(-\xi_1\xi_2\xi_3+\xi_1\omega\phi+\alpha\xi_2\rho)I\\
&\quad+\eta_C(\xi_1\xi_2+\xi_1\phi\eta_C+\xi_2\rho\eta_A)\frac{\beta CS}{N}+\eta_C(-\xi_1\xi_3\xi_2+\xi_1\phi\omega+\rho\alpha\xi_2)C\\
&\quad+\eta_A(\xi_1\xi_2+\xi_1\phi\eta_C+\xi_2\rho\eta_A)\frac{\beta AS}{N}+\eta_A(-\xi_2\xi_3\xi_1+\phi\omega\xi_1+\xi_2\rho\alpha)A\\
&=\mathcal{D}_0\left(\frac{\beta\mathcal{N}_0}{\mathcal{D}_0}\frac{S}{N}-1\right)I+\eta_C\mathcal{D}_0\left(\frac{\beta\mathcal{N}_0}{\mathcal{D}_0}\frac{S}{N}-1\right)C+\eta_A\mathcal{D}\left(\frac{\beta\mathcal{N}_0}{\mathcal{D}_0}\frac{S}{N}-1\right)A\\
&\leq\mathcal{D}_0\left(\frac{\beta\mathcal{N}_0}{\mathcal{D}_0}-1\right)I+\eta_C\mathcal{D}_0\left(\frac{\beta\mathcal{N}_0}{\mathcal{D}_0}-1\right)C+\eta_A\mathcal{D}\left(\frac{\beta\mathcal{N}_0}{\mathcal{D}_0}-1\right)A\\
&\quad(\text{since } S\leq N \text{ in } \Omega)\\
&\leq\mathcal{D}(R_0-1)I+\eta_C\mathcal{D}(R_0-1)C+\eta_A\mathcal{D}(R_0-1)A\\
&\leq 0\quad\text{for } R_0<1,
\end{aligned}$$

since, for any $\tau>0$, we have

$$0<\xi_4<\psi e^{-\tau\mu}+\mu+\theta\quad\text{and}\quad 0<\mathcal{N}_0<\mathcal{D}_0\,,$$

thus

$$\xi_4\mathcal{N}_0<\left(\psi e^{-\tau\mu}+\mu+\theta\right)\mathcal{D}_0\,.$$

Because all model parameters are nonnegative, if follows that $\dot{V}\leq 0$ for $R_0<1$ with $\dot{V}=0$ if, and only if, $I=C=A=0$. Substituting $(I_0,C_0,A_0)=(0,0,0)$ into the equations for S and E in system (2) shows, respectively, that $S\to S^0$ and $E\to E^0$ as $t\to\infty$. Thus, it follows from LaSalle's Invariance Principle [13] that every solution of system (2) with initial conditions in Ω approaches the disease free equilibrium Σ_0 as $t\to\infty$ whenever $R_0<1$, for any positive time delay τ. □

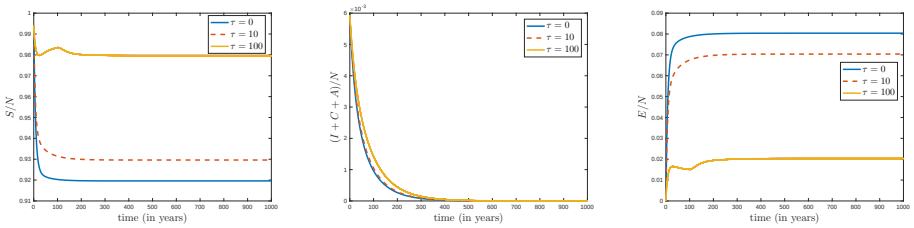
Example 2.5. Consider the following initial conditions

$$\begin{aligned}
&S_0=S(0)=336974\,,\quad I_0=I(0)=100\,,\quad C_0=C(0)=1900\,,\\
&A_0=A(0)=10\,,\quad E_0=E(0)=0\,,
\end{aligned}\tag{10}$$

and the parameter values from Table 2 with the exception of the parameters $d=1$, $\Lambda=10724$ and $\beta=0.0752$. Taking $\tau\in\{0,10,100\}$, there holds $R_0(0)=0.4508$, $R_0(100)=0.4802$. In Figure 3, we observe the stability of disease free equilibrium point for $\tau\in\{0,10,100\}$.

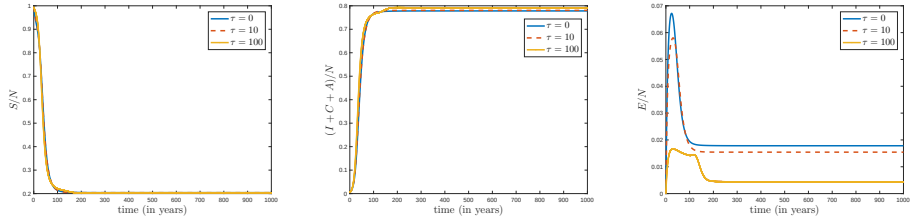
Deriving the expression of the transcendental characteristic equation of the linearized system associated to system (3), at the endemic equilibrium Σ_+, is hard and cumbersome. However, numerically we can observe that the endemic equilibrium Σ_+, given by (7), is stable for positive values of the time delay τ. Consider the parameter values taken in the Example 2.5 and $\beta=0.752$. For these parameter values the basic reproduction number takes the values $R_0(0)=4.5078$, $R_0(10)=4.5569$ and $R_0(100)=4.8023$.

In Figure 4, we observe the stability of the endemic equilibrium Σ_+ for $\tau=10$ and $\tau=100$, for the time interval $[0,t_f]=[0,1000]$. We remark the effect of the time delay τ on the fraction of individuals under PrEP, at each instant of time t, given by $E(t)/N(t)$, see Figure 4 (c), that increases with τ, and this increase is also observable in the fraction of individuals with HIV infection, $(I(t)+C(t)+A(t))/N(t)$, see Figure 4 (b).



(A) S/N (B) $(I+C+A)/N$ (C) E/N

FIGURE 3. Stability of the disease free equilibrium Σ_0 for $d = 1$, $\Lambda = 10724$, $\beta = 0.0752$ and the other parameter values from Table 2, with $t \in [0, 1000]$ and $\tau \in \{0, 10, 100\}$.



(A) S/N (B) $(I+C+A)/N$ (C) E/N

FIGURE 4. Stability of the endemic equilibrium Σ_+ for $d = 1$, $\Lambda = 10724$, $\beta = 0.752$ and the other parameter values from Table 2, with $t \in [0, 1000]$ and $\tau \in \{0, 10, 100\}$.

In the next section, we introduce a control function $u(\cdot)$, that represents the effort on PrEP implementation and introduce a time delay on the control function with the aim of strengthening of effect of the delay on the implementation of PrEP. An optimal control problem with state and control delays is going to be proposed and solved.

3. **Time-delayed HIV/AIDS-PrEP model with one control representing PrEP implementation strategy.** In this section, we consider the delayed model (3) and introduce a control function $u(\cdot)$ that represents the proportion of susceptible individuals that takes PrEP, at each instant of time, that is, the parameter ψ is replaced by the control function $u(\cdot)$, i.e. $\psi \equiv u(t)$, $t \in [0, t_f]$. The control function must take values between 0 and 1, where the case $u(t) = 0$, represents that no susceptible individual takes PrEP at time t; and the case $u(t) = 1$, stands for the case where all susceptible individuals are taking PrEP at time t.

Moreover, we assume that the total population N is constant, with a recruitment rate proportional to the natural death rate, $\Lambda = \mu N$, and a negligible AIDS-induced mortality $d = 0$, considering a final time $t_f = 25$ years, which represents a time interval where HIV infection can be considered as a chronic disease, see e.g. [16, 28] for studies on a *functional cure* for AIDS. We remark that the assumption of considering a constant total population N is done for simplification purposes, namely in Section 4 of numerical simulations.

We propose an optimal control problem that consists to find the optimal strategy for PrEP implementation $\tilde{u}(\cdot)$, subject to time delays in the state variable $S(\cdot)$ and the control function $u(\cdot)$, where the goal is to minimize the number of individuals infected with HIV, I, as well as the cost associated with PrEP distribution.

3.1. **Optimal control problem with delays in state and control variables.** In order to analyze the impact of a delayed implementation of PrEP on the number of individuals with HIV infection I, we consider the delayed model (3) and associate a constant time delay $\tau_u \geq 0$ to the control function $u(t-\tau_u)$, with $u(t) \equiv 0$ for $-\tau_u \leq t < 0$. Therefore, the delayed control system is given by the following system of delayed differential equation, with delays in state and control variables:

$$\begin{cases} \dot{S}(t) = \mu N - \frac{\beta}{N}\left(I(t) + \eta_C\, C(t) + \eta_A A(t)\right) S(t) - \mu S(t) - u(t-\tau_u)\, S(t) + \theta E(t), \\ \dot{I}(t) = \frac{\beta}{N}\left(I(t) + \eta_C\, C(t) + \eta_A A(t)\right) S(t) - \xi_3 I(t) + \alpha A(t) + \omega C(t), \\ \dot{C}(t) = \phi I(t) - \xi_2 C(t), \\ \dot{A}(t) = \rho\, I(t) - \xi_1 A(t), \\ \dot{E}(t) = u(t-\tau_u)\, \mathrm{e}^{-\mu\tau} S(t-\tau) - (\mu+\theta) E(t)\,. \end{cases} \tag{11}$$

The initial conditions for the state variables I, C, A, E and, due to the delays, initial functions for the state variables S and control u, are given by

$$\begin{aligned} &S(t) \equiv S_0\,, \quad -\tau \leq t < 0\,, \\ &I(0) = I_0\,, \quad C(0) = C_0\,, \quad A(0) = A_0\,, \quad E(0) = E_0\,, \\ &u(t) \equiv 0\,, \quad -\tau_u \leq t < 0\,. \end{aligned} \tag{12}$$

We consider the following set of admissible control functions:

$$\Omega = \left\{ u(\cdot) \in L^1\left([0,t_f],\mathbb{R}\right) \,|\, 0 \leq u(t) \leq 1\,,\, \forall\, t \in [0,t_f] \right\}, \tag{13}$$

and the L^1 objective functional

$$J(u(\cdot)) = \int_0^{t_f} \left[w_1 I(t) + w_2 u(t)\right] dt, \tag{14}$$

which measures the number of individuals with HIV infection I and the costs associated with the implementation of PrEP, where w_1 and w_2 are constants weights, representing the cost associated to each individual in the class I and to the effort on distribution and adherence of PrEP, respectively.

Let

$$x(t) = (x_1(t), \ldots, x_5(t)) = (S(t), I(t), C(t), A(t), E(t)) \in R^5.$$

We propose the optimal control problem that consists to find the optimal strategy for PrEP implementation $\tilde{u}(\cdot) \in L^1\left([0,t_f],\mathbb{R}\right)$ and the associated optimal state trajectories $\tilde{x}(\cdot)$, satisfying the delayed control system (11), the initial conditions (12) and where the control $\tilde{u} \in \Omega$ minimizes the objective functional (14).

We will now apply a necessary optimality condition given by the Minimum Principle for Multiple Delayed Optimal Control Problems of [7, Theorem 3.1], and introduce the delayed state variable $\mathbf{S}(t)$ and the control variable $\mathbf{u}(t)$, defined by

$$\mathbf{S}(t) = S(t-\tau) \qquad \text{and} \qquad \mathbf{u}(t) = u(t-\tau_u)\,.$$

Using the adjoint variable $\lambda = (\lambda_{x_1}, \ldots, \lambda_{x_5}) \in \mathbb{R}^5$, the Hamiltonian for the cost functional (14) and the control system (11) is given by

$$\begin{aligned} H(x,\mathbf{S},\lambda,u,\mathbf{u}) &= w_1 x_2 + w_2 u + \lambda_{x_1} \left(\mu N - \frac{\beta}{N} \left(x_2 + \eta_C\, x_3 + \eta_A x_4 \right) x_1 \right. \\ &\quad \left. -\mu x_1 - \mathbf{u}\, x_1 + \theta x_5 \right) \\ &\quad + \lambda_{x_2} \left(\frac{\beta}{N} \left(x_2 + \eta_C x_3 + \eta_A x_4 \right) x_1 - \xi_3 x_2 + \alpha x_4 + \omega x_3 \right) + \lambda_{x_3} \left(\phi x_2 - \xi_2 x_3 \right) \\ &\quad + \lambda_{x_4} \left(\rho x_2 - \xi_1 x_4 \right) + \lambda_{x_5} \left(\mathbf{u}\, \mathrm{e}^{-\mu\tau}\, \mathbf{S} - (\mu + \theta) x_5 \right). \end{aligned} \tag{15}$$

The adjoint system is

$$\begin{aligned} \dot{\lambda}_{x_1}(t) &= -H_{x_1}[t] - \chi_{[0,t_f-\tau]}(t)\, H_{\mathcal{S}}[t+\tau], \\ \dot{\lambda}_{x_2}(t) &= -H_{x_2}[t], \qquad \dot{\lambda}_{x_3}(t) = -H_{x_3}[t], \\ \dot{\lambda}_{x_4}(t) &= -H_{x_4}[t], \qquad \dot{\lambda}_{x_5}(t) = -H_{x_5}[t], \end{aligned} \tag{16}$$

where the subscripts denote partial derivatives and $\chi_{[0,t_f-\tau]}$ is the characteristic function on the interval $[0, t_f - \tau]$ (see [7]).

Since the terminal state $(x_1(t_f), x_2(t_f), x_3(t_f), x_4(t_f), x_5(t_f))$ is free, the transversality condition

$$\lambda(t_f) = (0,0,0,0,0)$$

holds.

The minimizing control $\tilde{u}$ is determined by the *switching function*

$$\begin{aligned} \phi(t) &= H_u[t] + \chi_{[0,t_f-\tau_u]}(t)\, H_{\mathbf{u}}[t+\tau_u] \\ &= w_2 + \chi_{[0,t_f-\tau_u]}(t) \left(-\lambda_{x_1}(t+\tau_u) x_1(t-\tau+\tau_u) \right. \\ &\quad \left. +\lambda_{x_5}(t+\tau_u) \mathrm{e}^{-\mu\tau} x_1(t-\tau+\tau_u) \right), \end{aligned} \tag{17}$$

according to the *control law*

$$\tilde{u}(t) = \begin{cases} 0 & \text{if} \quad \phi(t) > 0, \\ 1 & \text{if} \quad \phi(t) < 0, \\ \text{singular} & \text{if} \quad \phi(t) = 0 \ \text{ on } I_s \subset [0, t_f]. \end{cases} \tag{18}$$

In Section 4, we observe the existence of singular arcs and the change from *bang-singular-bang* to *bang-bang* extremal controls, depending on the weight constants w_i, $i = 1, 2$.

4. **Numerical simulations.**

Consider the initial conditions

$$\begin{aligned} &S(0) = S_0 = 10000\,, \quad I(0) = I_0 = 200\,, \quad C(0) = C_0 = 0\,, \\ &A(0) = A_0 = 0\,, \quad E(0) = E_0 = 0\,, \end{aligned} \tag{19}$$

with $N = S_0 + I_0 + C_0 + A_0 + E_0 = 10200$.

For the delayed case consider the initial functions

$$S(t) \equiv S_0 \quad \text{for} \quad -\tau \le t < 0\,, \qquad \text{and} \qquad u(t) \equiv 0 \quad \text{for} \quad -\tau_u \le t < 0\,. \tag{20}$$

Assume the fixed final time $t_f = 25$ years. And the parameter values given in Table 2 and described in Table 1.

TABLE 2. Parameters values of models (3) and (11), taken from [24].

Symbol	Value	Symbol	Value
μ	1/69.54	ρ	0.1
Λ	10724	α	0.33
β	0.582	ω	0.09
η_C	0.04	d	0
η_A	1.35	ψ	0.1
ϕ	1	θ	0.01

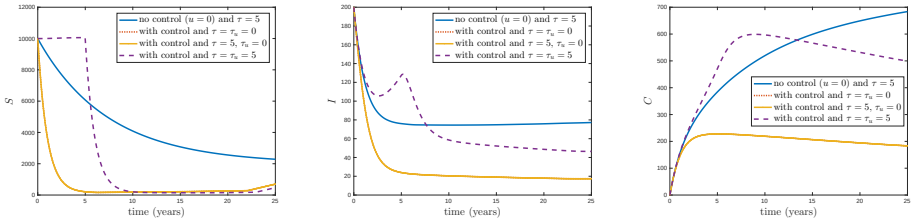
4.1. **Comparison between undelayed, state-delayed and state-control delayed optimal control problems.** In this section, we present the numerical solutions of the delayed optimal control problem (11)-(14) in the time interval $[0, 25]$ (years) and consider three cases:

- **case 1:** $\tau = \tau_u = 0$ **(no delays);**
- **case 2:** $\tau = 5$**,** $\tau_u = 0$ **(state delay only);**
- **case 3:** $\tau = \tau_u = 5$ **(state and control delays).**

In the three cases, we assume that $w_1 = w_2 = 1$ (see Subsection 4.2 for the analysis with different values of the weight constants).

Analogously to the approach used in [20, 21] we use the discretization method developed in [7], discretizing the optimal control problem on a sufficiently fine grid. In these section, we use $n = 1000$ grid nodes and the *Euler's method* as integration method, and write the resulting large-scale nonlinear programming problem using the Applied Modeling Programming Language AMPL [6] which is then linked to the optimization solver Interior-Point IPOPT [26], setting the error tolerance to $tol = 10^{-10}$.

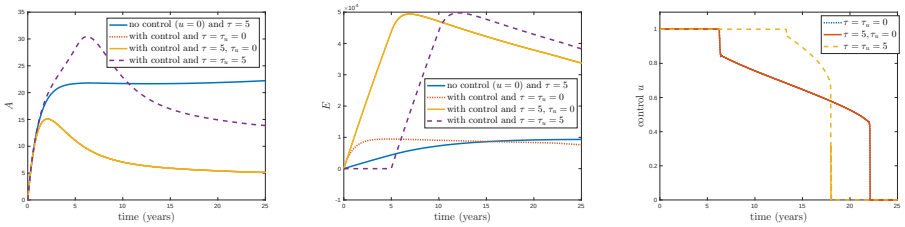
The extremal solutions $\tilde{S}$, $\tilde{I}$, $\tilde{C}$, $\tilde{A}$ and $\tilde{E}$ associated to the extremal control $\tilde{u}$, given by (18), are depicted in Figures 5-6. We observe that uncontrolled solution



(A) $\tilde{S}$ (B) $\tilde{I}$ (C) $\tilde{C}$

FIGURE 5. Extremal solutions $\tilde{S}$, $\tilde{I}$ and $\tilde{C}$ associated to the extremal control $\tilde{u}$, given by (18).

($u = 0$) where the control function is replaced by the fixed parameter $\psi = 0.1$, meaning that 10% of the susceptible sub-population is under PrEP, is associated with a bigger number individuals with HIV infection I, C and A at the last period of 10 years. In Figure 6 (B) we observe that the delayed solution $\tilde{E}$ with control (for state delay only or state and control delays) is associated with a significant number of individuals under PrEP. The extremal control $\tilde{u}$ in both cases 2 and 3, is of type



(A) $\tilde{A}$ (B) $\tilde{E}$ (C) $\tilde{u}$

FIGURE 6. Extremal solutions $\tilde{A}$, $\tilde{E}$ and extremal control $\tilde{u}$.

bang-singular-bang, see Figure 6 (C). The delay in the control is associated with a bigger interval of time where the extremal control $\tilde{u}$ takes the maximum value 1.

Case 1 and case 2 differ only on the number of individuals under PrEP $\tilde{E}$. Therefore, in what follows we will compare case 1 and case 2 together with case 3.

In Figure 5 (B) and (C), we observe that the curve of HIV infection individuals $\tilde{I}$ is a decreasing function in all interval of time $[0, 25]$, in cases 1 and 2, but in case 3 the number of individuals in the class I increases in the period of time $[2.6, 5.2]$, approximately. It is evident the increase on the number of individuals in the chronic stage C when both state and control delays are considered. The negative impact of the delays in state and control variables is bigger in the class of individuals with AIDS symptoms, that increases for the first 6.3 years, approximately, and presents bigger values in all interval of time when compared with the cases 1 and 2, see Figure 6 (A).

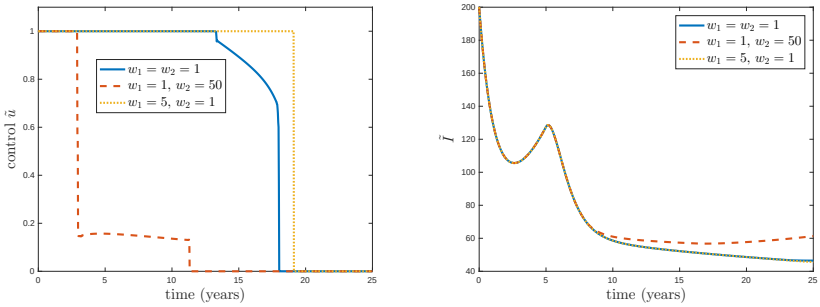
The extremal control $\tilde{u}$ in case 3, takes the maximum value for $t \in [0, 13.3]$, which is associated with an increase of the number of individuals under PrEP, see Figures 6 (B) and (C). However, the singular arc has a shorter length in case 3 and PrEP can stop being implemented first in case 3 than in case 2.

4.2. **Analysis of the change of the weights w_i, $i = 1, 2$, and the existence of singular controls.** The costs associated to the number of individuals with HIV infection I and with the effective distribution of PrEP can assume different values, depending on the region under consideration. In this Subsection, we assume different values for the weight constants w_i, $i = 1, 2$, considered in the cost functional (14). We consider three cases:

- $w_1 = w_2 = 1$ (subsection 4.1);
- $w_1 = 1$, $w_2 = 50$;
- $w_1 = 5$, $w_2 = 1$.

In the three cases, both state and control delays are considered, that is, $\tau = \tau_u = 5$.

The change on the weight constants w_i, $i = 1, 2$, influences the behavior of the extremal control $\tilde{u}$, whereas the number of individuals in the class I is approximately the same for the first 8.38 years. After this period of time, the number of infected individuals I increases from 46 to 61, where the bigger number of cases occurs for $w_1 = 1$ and $w_2 = 50$. When the cost associated to PrEP implementation increases ($w_2 = 50$), the extremal control takes the maximum values only for $t_1 = 2.93$ years, approximately, that is, 10.37 years less than in the case 1 of equal weights constants (see Figure 7 and Table 3). In the cases $w_1 = w_2 = 1$ and $w_1 = 1$, $w_2 = 50$, the extremal control has singular arcs, being of the type *bang-singular-bang*. Whereas,



(A) Control $\tilde{u}$. (B) $\tilde{I}$

FIGURE 7. Extremal control $\tilde{u}$ and associated state trajectory $\tilde{I}$, for different weight constants: $w_1 = w_2 = 1$; $w_1 = 1$, $w_2 = 50$; $w_1 = 5$, $w_2 = 1$.

in the case $w_1 = 5$, $w_2 = 1$ the extremal control does not have singular arcs, being of the *bang-bang* type (see Figure 7).

TABLE 3. Cost functional and switching times for different weight constant values.

Weight constant values	Cost functional $J(\tilde{u})$	Switching time t_1	Switching time t_2
$w_1 = w_2 = 1$	$J(\tilde{u}) \simeq 1818.64$	$t_1 \simeq 13.30$	$t_2 \simeq 18.02$
$w_1 = 1$, $w_2 = 50$	$J(\tilde{u}) \simeq 2125.28$	$t_1 \simeq 2.93$	$t_2 \simeq 11.28$
$w_1 = 5$, $w_2 = 1$	$J(\tilde{u}) \simeq 9020.09$	$t_1 \simeq 19.10$	

5. **Conclusion and discussion.** In this work we proposed a generalization of the HIV/AIDS-PrEP model, from [24], by introducing a time delay that represents the delay on PrEP distribution and adherence from uninfected susceptible individuals. We proved existence conditions for the two equilibrium points of the delayed model and their stability, for any positive time delay. The fixed value of the proportion of individuals that takes PrEP, ψ, was after replaced by a control function $u(\cdot)$, that is bounded between 0 and 1. Moreover, a time delay was also introduced in the control function, reinforcing the mathematical modeling of the delay on PrEP implementation. An optimal control problem with delays in state and control variables was formulated and a necessary optimality condition was applied to derive the extremal control and associated state trajectories. Although, recently sufficient optimality conditions for non-linear optimal control problems with state and control delays have been proved, see e.g. [14], these conditions are difficult to apply in the proposed problem.

From the numerical solutions, we observed that the extremal control $\tilde{u}$ for the minimization of the number of individuals with HIV infection I leads to a substantial increase of the number of individuals under PrEP, which is in agreement with the World Health Organization recommendations [30, 31]. We concluded that a delay on the implementation of PrEP can be responsible for a bigger effort on the PrEP distribution that must take the maximum value (100%) for bigger intervals of time,

implying high social and economical costs. Therefore, delays on PrEP distribution should be avoided and efforts must done in order to implement this strategy in an effective way. On the other hand, the delays in state and control variables, imply an increase of the number of HIV infected individuals I and with AIDS symptoms A, increasing the probability of new HIV infections, since the individuals in these two classes are highly infectious. We observed an evident increase of the number of individuals in the chronic stage C when both state and control delays are considered, which also has big economical and social effects. Variations on the weight constant values, w_i, $i = 1, 2$, were considered and we observed that the increase of PrEP implementation costs leads to a bigger number of individuals in the class I, whereas the opposite happens if the weight constant associated with the number in the class I is smaller than PrEP costs. The value of cost functional increases more significantly when the cost associated with the number of individuals in the class I is bigger than PrEP implementation costs. From the social and public health point of view, this conclusion goes in the direction of the importance of the reduction of HIV infectious individuals in order to stop the spread of the infection and the number of new cases. Until there is no cure, HIV can only the eliminated worldwide if we stop the transmission with zero new infectious.

From the optimal control point of view, it was interesting to observe that the change of the weights constants can be used to show that extremal controls can have singular arcs or be of only bang-bang type. As future work, we would like to generalize the delayed optimal control problem considering pure-state and mixed state-control constraints, representing the several limitations that are still related to PrEP implementation. Moreover, considering the general case of a non constant population in the optimal control problem is a future challenge, since many countries using a PrEP policy have a population that is clearly increasing.

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