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OPTIMAL CONTROL OF CARDIOVASCULAR DISEASES AMONG HIV INFECTED

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Abstract. In this article, we formulated a new model of cardiovascular diseases as a complication of HIV infection and its HAART treatment with optimal control strategies. The stability of the equilibrium point for the model without control is established via the Routh Hurwitz criterion. In addition, our model is linked to three control measures, including the organization of programs to prevent HIV infection, awareness of the infected about the impact of HIV and HAART, and regular diagnosis and monitoring of risk factors of cardiovascular diseases in HIV-positive people. The objective function of optimal control problem aims to minimize the number of complications and associated costs. Then, we characterized the optimal controls by applying Pontryagin's Maximum Principle after having proven its existence. We used Gauss Siedel's iterative approaches to solve the resulting system. We used HIV data from Burundi to estimate fixed and adjusted parameters, to be able to provide numerical simulations to illustrate our theoretical results. Ultimately, the controls reduce the risk of cardiovascular diseases and improve public health.

Keywords: optimal control; mathematical modeling; HIV; cardiovascular diseases; stability.

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1. INTRODUCTION

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels [1] which we mention: Coronary heart disease, Cerebrovascular disease, Peripheral arterial disease, Rheumatic heart disease, Congenital heart disease, deep vein thrombosis and pulmonary embolism. CVDs can be caused by a combination of socio-economic, metabolic, behavioral, and environmental risk factors, these include unhealty diet, tobacco use, harmful use of alcohol, physical inactivity, stress, obesity and others; we call them traditional risk factors. CVDs are the leading cause of death globally, representing one-third of all global deaths; over three-quarters of CVD deaths take place in low- and middle-income countries, people living in these contries often do not benefit from a preventive and early detection or treatment program, especially for people who represent risk factors for CVDs. An estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths, 85% of which were due to heart attack and stroke; which are usually acute events and are mainly caused by a blockage that prevents blood from flowing to the heart or brain [1]. The estimated number of deaths due to CVDs increased from around 12.1 million in 1990 to 20.5 million in 2021 [2].

Human immunodeficiency virus (HIV) is a virus that attacks the body's immune system, particularly the $CD4^+$ cells that initiate the immune system's response; this means that the infection is permanent; HIV infection goes through three phases: the primary infection phase, which lasts a few weeks, the symptoms of which are manifested by a feverish state; the asymptomatic phase which is recognized by the permanent activation of adaptive immunity, of which the human body is put in defense against the virus which unfortunately escapes any immune response thanks to its capacity to produce other mutant viruses, the specificity of this last phase is that the infected person cannot, one way or another, realize their infection, because in most cases, and if there are symptoms, they are very similar to other infections; unless he is screened; The acquired immunodeficiency syndrome (AIDS) is the most advanced form of the disease, this last phase is recognized by the appearance of opportunistic diseases. HIV can be transmitted through the exchange of a variety of body liquids from contaminated individuals, through sexual intercourse, unsafe injection, blood transfusion, tissue transplantation, from mother to child during pregnancy or childbirth. In 2022, an estimated 39 million people globally were

living with HIV and 1.3 million people became newly infected with HIV[3]. there is currently no effective cure, but with the advent of effective antiretroviral therapy, specially Highly Active Antiretroviral Therapy (HAART), HIV has become a chronically controllable disease.

People living with HIV are twice as likely to develop cardiovascular disease [4]; HIV has an important role on the increment of CVDs at an early age and even for those HIV infected without a prior history of CVDs [5]. The onset of CVDs in HIV-infected people is linked with subsequent immunosuppression [6], immune activation and chronic inflammation[7], these last two are important responses used to control HIV infection; higher levels of inflammatory and immune activation markers, such as interleukin-6, C-reactive protein, tumor necrosis factor and $CD16^{+}$ have been found in HIV-infected compared to noninfected people; and have been associated with the occurrence of Stroke, Atherosclerosis and Myocardial infarction[8]. HIV can indirectly damage the cardiac structure.

HAART is a combination of at least two major HIV drug classes [9]; Protease inhibitors, which inhibit the viral protease enzymes such as Idinavir; Nucleoside Reverse Transcriptase inhibitors such as Zidovudine, which block the viral RNA to DNA transcription, and Non-Nucleoside Reverse Transcriptase inhibitors such as Nevirapine, which inhibit the reverse transcriptase enzyme. HAART has significantly improved the survival of patients with HIV and has increased the life expectancy of HIV-infected; mortality and morbidity have decreased dramatically among HIV infected patients. In 2022, a wide of 630000 people died from AIDS-related illnesses compared to 2.0 million in 2004 and 1.3 million in 2010. 86% of all people living with HIV knew their HIV status; among them, 89% were assessing treatment; among these, 93% were virally suppressed [3]. HAART is qualified effective because it can reduce the virus level in the blood, which is commonly called undetectable level; however, even under treatment, the virus continues to infect immune cells in the lymph nodes and in the lymphatic tissues; therefore, the immune activation and permanent inflammation [10] persist, even at low level and in the long term could gradually weaken the immune system and cause CVDs; on the other hand, HAART has side effects detrimental to cardiovascular health, such as impaired glucose and lipid metabolism, mitochondrial toxicity and subsequent, widespread cardiomyopathy. HAART can directly damage the cardiac structure.

Optimal control has generalized the classical calculus of variations by extending to problems that involve constraints in ordinary differential equations(ODEs) form. Pontryagin and his co-workers developed the Maximum Principle, which was the key to responding to these extending problems. Optimal control theory has been successfully applied to several epidemiological models, therefore it has provided several results favoring decision-making in the form of an effective strategy or effective combined strategies to reduce an endemic state, minimizing the costs of such intervention to reduce expenses, and maximizing profits.

We cite, among the published works evoking optimal control for HIV: C. J. Silva[11] has controlled his system by Pre-exposure prophylaxis to prevent acquisition of HIV. O. M. Ogunlaran [12] which considers, in turn, two controls representing the effectiveness of drug treatment in blocking the infection of new cells and inhibiting the production of viruses. Marsudi et al[13] controlled their system through education on condoms, and both antiretroviral therapies for pre-AIDS and full-blown AIDS. However, we claim that our work is the first to apply optimal control to an HIV/AIDS model with CVDS. Specifically, we consider the HIV/AIDS model with HAART treatment and formulate an optimal control problem with the aim of determining strategies that minimize the number of HIV-infected individuals, the number of HIV/AIDS individuals having develop cardiovascular complications, as well as the costs associated with these strategies.

2. Model Formulation

Propelled by the malignant functioning of this terrible virus; which is truly a human catastrophe, by the compartimental mathematical modelling which have played a significant part in progressing our understanding of epidemics and their mecanisms, and by the optimal control which offers optimal ways to control dynamics of a system envolving over time; we establish this work in order to model and control the situation of cardiovascular complications associated with both HIV and its treatment; for this, we formulated a new compartimental mathematical model using a linear ordinary differential equations.

The total population is divided into five subgroups, namely, H represents the number of HIV-infected patients in primo-infection and in second phase of infection; A represents AIDS subgroup; T_H represents infected people who are receiving HAART treatment; T_A represents

infected people who are developping AIDS and who are both under HAART treatment and opportunistic diseases treatment. C subgroup represents infected people who are developing CVDs. An individual in H compartment may progress to the AIDS subgroup with rate σ or may develop cardiovascular diseases with rate ξ or may be treated if he know his HIV status with rate γ_H; an individual in compartment A may develop cardiovascular diseases with rate α or may be treated for both HIV infection and opportunistic diseases with rate γ_A, or may die due to the opportunistic diseases with rate δ_A. An element of the T_H subgroup can develop an opportunistic disease even under HAART treatment and joins T_A subgroup with rate ϕ or can join C compartment if he develop both HIV and HAART-associated CVDs with rate ε or can develop another complication with rate δ_{OC}. Each individual in compartment C may die due to the complication with δ_C. All individuals in each compartment have a natural mortality rate δ_N and a mortality rate δ_H due to HIV infection, and we simply note $\delta = \delta_N + \delta_H$.

An individual in the AIDS phase can develop the complication more quickly than an infected person in the first and second phases if we compare their immune state, so we assume that $\xi < \alpha$. An individual in T_A subgroup can develop the complication more quickly than another one in T_H subgroup if we take into consideration the cumbersome treatment of opportunistic infection, so we assume that $\varepsilon < \beta$.

Assuming that the population is homogeneous in each subgroup, that the overall human population is variable, and all parameters are positive. The above description is appears in the following diagram:

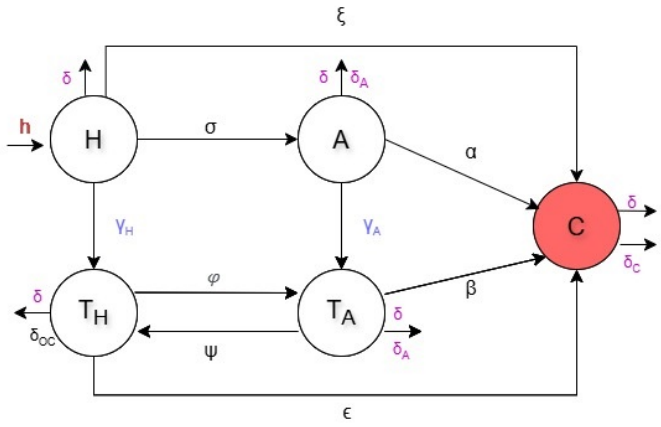

FIGURE 1. Flow diagram of the model

Using the flow diagram 1, the system of differential equations modeling the cardiovascular complication is given as follows:

$$(1)\qquad \begin{cases} \dfrac{dH}{dt} = h-(\delta+\sigma+\xi+\gamma_H)H \\ \dfrac{dA}{dt} = \sigma H-(\delta+\delta_A+\alpha+\gamma_A)A \\ \dfrac{dT_H}{dt} = \gamma_H H+\psi T_A-(\delta+\delta_{OC}+\varphi+\varepsilon)T_H \\ \dfrac{dT_A}{dt} = \varphi T_H+\gamma_A A-(\delta+\delta_A+\psi+\beta)T_A, \\ \dfrac{dC}{dt} = \xi H+\alpha A+\varepsilon T_H+\beta T_A-(\delta+\delta_C)C \end{cases}$$

3. Model Analysis

This section explores the existence and stability of the equilibrium point of the system (1).

3.1. Positivity and boundedness of the system solution.

On the one hand, the right hand side function of system (1) is continuous and satisfy the Lipschitz condition [14], that is to say that the system (1) has a unique solution $(H(t),A(t),T_H(t),T_A(t),C(t))$ with positive initial conditions. On the other hand, it is required to prove that all the state variables $H(t),A(t),T_H(t),T_A(t)$ and $C(t)$ are positive for all $t \geq 0$ since the model describes the human population.

Theorem 3.1. *Taking account the initial conditions* $(H(0),A(0),T_H(0),T_A(0),C(0)) \in \mathbb{R}^5_+$*, the state variables* $H(t),A(t),T_H(t),T_A(t)$ *and* $C(t)$ *are all positive and eventually bounded.*

Proof. Let us define: $t^* = \sup\{t \geq 0; H(t)>0, A(t)>0, T_H(t)>0, T_A(t)>0, C(t)>0\}$, the positivity of the initial conditions and the continuity of the state variables guarantee that $t^* > 0$; if $t^* = +\infty$ then the positivity holds; but if $0 < t^* < +\infty$, then $H(t^*) = 0$ or $A(t^*) = 0$ or $T_H(t^*) = 0$ or $T_A(t^*) = 0$ or $C(t^*) = 0$. In this case, from the first equation of (1), we have got:

$$\frac{dH}{dt}+(\delta+\sigma+\xi+\gamma_H)H = h;$$

To solve it, we use the Method of Integrating Factors. Multiplying the precedent equation by the integrating factor $IF = e^{(\delta+\sigma+\xi+\gamma_H)t}$ and integrating both sides from 0 to t^* will give us:

$$H(t^*)e^{(\delta+\sigma+\xi+\gamma_H)t^*} - H(0) = \frac{h}{x_1}\left(e^{(\delta+\sigma+\xi+\gamma_H)t^*}-1\right),$$

Hence,

$$H(t^*) = \left(H(0) + \frac{h}{x_1} \left(e^{(\delta+\sigma+\xi+\gamma_H)t^*} - 1 \right) \right) e^{-(\delta+\sigma+\xi+\gamma_H)t^*}.$$

Since $H(0) > 0$, $e^{(\delta+\sigma+\xi+\gamma_H)t^*} - 1 > 0$, we get that $H(t^*) > 0$, it yields $H(t^*) \neq 0$. We proceed in the same way, we obtain that all state variables are non-zero at t^*, which means that t^* is not finite; therefore, all solutions of the system (1) are positive.

Now, let us consider the biologically feasible region:

$$\Gamma = \left\{ (H(t), A(t), T_H(t), T_A(t), C(t)) \in \mathbb{R}_5^+; N(t) \leq \frac{h}{\delta} \right\},$$

with $N(t) = H(t) + A(t) + T_H(t) + T_A(t) + C(t)$.

The positive invariance of Γ (i.e., all solutions in Γ remain in Γ for all time) is established via steps listed below.

The rate of change of the total population obtained by adding the equations of the system (1) is:

$$\frac{dN}{dt} = h - \delta N - \delta_A A - \delta_{OC} T_H - \delta_A T_A - \delta_C C.$$

It follows that for all $t \geq 0$,

$$\frac{dN}{dt} \leq h - \delta N;$$

After some operations, we can show that:

$$N(t) \leq N(0) e^{-\delta t} + \frac{h}{\delta} \left(1 - e^{-\delta t} \right),$$

where $N(0)$ represents the initial values of the total population.

Thus,

$$\lim_{t \to +\infty} N(t) \leq \frac{h}{\delta},$$

which implies that $N(t)$ is bounded and all the solutions starting with initial conditions in Γ remains in Γ for all $t \geq 0$. As a result, the region Γ is positively invariant, and the model is well posed mathematically and epidemiologically in that region.

□

3.2. Equilibrium point.

In order to obtain the equilibrium points of the system (1), we proceed to solve the following set of equations:

$$\begin{cases} h - x_1 H = 0 \\ \sigma H - x_2 A = 0 \\ \gamma_H H + \psi T_A - x_3 T_H = 0 \\ \gamma_A A + \varphi T_H - x_4 T_A = 0 \\ \xi H + \alpha A + \varepsilon T_H + \beta T_A - x_5 C = 0, \end{cases} \tag{2}$$

with:

$$\begin{cases} x_1 = \delta + \sigma + \xi + \gamma_H \\ x_2 = \delta + \delta_A + \alpha + \gamma_A \\ x_3 = \delta + \delta_{OC} + \varphi + \varepsilon \\ x_4 = \delta + \delta_A + \psi + \beta \\ x_5 = \delta + \delta_C. \end{cases}$$

The first equation of the system (2) yields:

$$H^* = \frac{h}{x_1}, \tag{3}$$

and the second equation gives:

$$A^* = \frac{\sigma H^*}{x_2}, \tag{4}$$

so,

$$A^* = \frac{\sigma h}{x_2 x_2}. \tag{5}$$

Similarly, we can obtain from the third equation the following:

$$T_H^* = \frac{\gamma_H H + \psi T_A}{x_3}, \tag{6}$$

by substituting (6) in the fourth equation of the system (2), we have the expression of T_A^* as follows:

$$T_A^* = \frac{-h(\varphi\gamma_H x_2 + \sigma\gamma_A x_3)}{x_1 x_2 y}, \tag{7}$$

where: $y = \varphi\psi - x_3 x_4$.

The substitution of H^* and T_A^* in the equation (6) gives:

$$T_H^* = \frac{-h(\gamma_H x_2 x_4 + \psi\sigma\gamma_A)}{x_1 x_2 y}. \tag{8}$$

Finally, using (3), (5),(7) and (8), we obtain the expression of C^* as follows:

$$C^* = \frac{hy(\alpha\sigma + \xi x_2) - h(\beta(\varphi\gamma_H x_2 + \sigma\gamma_A x_3) + \varepsilon(\gamma_H x_2 x_4 + \psi\sigma\gamma_A))}{x_1 x_2 x_5 y} \tag{9}$$

Consequently, the system (1) has a unique equilibrium point $\vec{\mathscr{P}}^* = (H^*, A^*, T_H^*, T_A^*, C^*)$, where:

$$\begin{cases} H^* & = \frac{h}{x_1} \\ A^* & = \frac{\sigma h}{x_2 x_2} \\ T_H^* & = \frac{-h(\gamma_H x_2 x_4 + \psi\sigma\gamma_A)}{x_1 x_2 y} \\ T_A^* & = \frac{-h(\varphi\gamma_H x_2 + \sigma\gamma_A x_3)}{x_1 x_2 y} \\ C^* & = \frac{hy(\alpha\sigma + \xi x_2) - h(\beta(\varphi\gamma_H x_2 + \sigma\gamma_A x_3) + \varepsilon(\gamma_H x_2 x_4 + \psi\sigma\gamma_A))}{x_1 x_2 x_5 y}. \end{cases}$$

3.3. Stability of the equilibrium point.

Theorem 3.2. *The endemic equilibrium point $\vec{\mathscr{P}}^*$ is asymptotically stabe.*

We write the system (1) in matrix form to make the analysis of its stability simpler to perform. Then, we have:

$$\dot{\vec{X}} = A\vec{X} + \vec{B},$$

where:

$$\dot{\vec{X}} = \begin{pmatrix} \dot{H} \\ \dot{A} \\ \dot{T}_H \\ \dot{T}_A \\ \dot{C} \end{pmatrix} \qquad \vec{X} = \begin{pmatrix} H \\ A \\ T_H \\ T_A \\ C \end{pmatrix}$$

$$A = \begin{pmatrix} -x_1 & 0 & 0 & 0 & 0 \\ \sigma & -x_2 & 0 & 0 & 0 \\ \gamma_H & 0 & -x_3 & \psi & 0 \\ 0 & \gamma_A & \varphi & -x_4 & 0 \\ \xi & \alpha & \varepsilon & \beta & -x_5 \end{pmatrix} \qquad \vec{B} = \begin{pmatrix} h \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

The characteristic polynomial of the system (1) is identified by computing the determinant of the matrix $A - xI$ with the eigenvalue x as follows:

$$P(x) = \begin{vmatrix} -x_1 - x & 0 & 0 & 0 & 0 \\ \sigma & -x_2 - x & 0 & 0 & 0 \\ \gamma_H & 0 & -x_3 - x & \psi & 0 \\ 0 & \gamma_A & \varphi & -x_4 - x & 0 \\ \xi & \alpha & \varepsilon & \beta & -x_5 - x \end{vmatrix}.$$

It yields that:

$$P(x) = (-x_1 - x)(-x_2 - x)(-x_5 - x)\left(x^2 + a_1 x + a_0\right),$$

where:

$$\begin{cases} a_1 = x_3 + x_4 \\ a_0 = x_3 x_4 - \varphi\psi \end{cases}.$$

Clearly, the polynomial $P(x)$ admits tree eigenvalues $-x_1$, $-x_2$ and $-x_5$ which are strictly negatives, since all the parameters of the system are strictly positives. The other eigenvalues of $P(x)$ are the roots of the equation above:

$$x^2 + a_1 x + a_0 = 0. \tag{10}$$

To determine the sign of its roots, we thought utilizing the Routh hurwitz criterion[15]. Applying the Routh test, the equation (10) will have roots with negative real parts if and only if $a_1 > 0$ and $a_0 > 0$.

It's obvious that a_1 is strictly positive. Moreover, we show that $a_0 > 0$ as follows:

$$a_0 = x_3x_4 - \varphi\psi$$
$$= (\delta+\delta_{OC}+\varepsilon)(\delta+\delta_A+\beta)+\psi(\delta+\delta_{OC}+\varepsilon)+\varphi(\delta+\delta_A+\beta).$$

Given that all the parametres of the model are strictly positive, it becomes that:

$$a_0 > 0.$$

As a result, the equilibrium point $\vec{\mathscr{P}}^*$ is asymptotically stable.

4. Optimal Control of Cardiovascular Complications

4.1. Optimal Control Problem.

In this section, we incorporate optimal control strategies that will be useful in reducing cardiovascular complications in HIV subjects. Our optimal control model will be an extension of the model (1); for this, we introduce three controls described as follows:

u_1: a prevention effort, that protect susceptible from contacting HIV infection.

u_2: a sensibilisation effort among infected people about cardiovascular complications due to the virus.

u_3: control focuses on the diagnosis and monitoring traditional risk factors for cardiovascular diseases throughout antiretroviral treatment with and without opportunistic diseases, and on promoting treatment compliance.

A controlled system is given by:

$$\begin{cases} \dfrac{dH}{dt} = (1-u_1)h-(\delta+\xi+\gamma_H+\sigma)H = f_1 \\ \dfrac{dA}{dt} = \sigma H-(\delta_A+\delta+\gamma_A)A-(1-u_2)\alpha A = f_2 \\ \dfrac{dT_H}{dt} = \gamma_H H+\psi T_A-(\delta+\delta_{OC}+\varphi)T_H-(1-u_3)\varepsilon T_H = f_3 \\ \dfrac{dT_A}{dt} = \varphi T_H+\gamma_A A-(\delta+\delta_A+\psi)T_A-(1-u_3)\beta T_A = f_4 \\ \dfrac{dC}{dt} = \xi H+(1-u_2)\alpha A+(1-u_3)\left[\beta T_A+\varepsilon T_H\right]-(\delta+\delta_C)C = f_5 \end{cases} \tag{11}$$

Our objectif is to minimize the functional:

$$\mathscr{J}(\vec{u}) = \int_0^T H(t)+C(t)+(B_1u_1^2+B_2u_2^2+B_3u_3^2)dt,$$

whose the integrand function is $f(t) = H(t) + C(t) + (B_1u_1^2 + B_2u_2^2 + B_3u_3^2)$, contains the terms $H(t)$ and $C(t)$ which represent the number of HIV infections and the number of people who have developed cardiovascular complications, that we seek to minimize; contains also the form $\sum_1^3 B_i u_i^2$ with positive coefficients B_i, $i = 1..3$ which represent the constant weight associated with relative costs of implementing the respective control strategies on a finite time horizon $[0,T]$, where the finite time is $T = 10$ in years. The form $\sum_1^3 B_i u_i^2$ is quadratic because we assume that costs are nonlinear in its nature. We seek to find the vector optimal controls $\vec{u}^* = (u_1^*, u_2^*, u_3^*)$ that satisfy :

$$\mathscr{J}(\vec{u}^*) = \min_{\vec{u}\in\mathbf{U}} \mathscr{J}(\vec{u}),$$

where $\mathbf{U} = \{\vec{u} = (u_1,u_2,u_3)/u_i$ is lebesgue measurable$, 0 \leqslant u_i(t) \leqslant 1, i = 1..3, \forall t \in [0,T]\}$

4.2. Optimal control Analysis.

4.2.1. *Existence of optimal control.*

Theorem 4.1. *There is an optimal control $\vec{u}^*$ to problem* $\min \mathscr{J}(\vec{u})$ *subject to system (11), where $\vec{u}^* \in \mathbf{U}$.*

Proof. To prove the existence, we should verify the conditions cited in both theorem 4.1 and corollar 4.1 by Feming and Rishel[16].

Firstly, let pose: $l(t,\vec{x},\vec{u}) = (f_1,f_2,f_3,f_4,f_5)$. By construction, the function l is of class C^1, we mentionned that parameters are bounded, what gives existence of some $M > 0$ such that $|l_{\vec{x}}| \leq M(1+|\vec{u}|)$, $|l_{\vec{u}}| \leq M(1+|\vec{x}|)$ and $|l(t,0,0)| \leq M$; the variables are also bounded in the region Ω and with constant controls, then the set of admissible solutions to system (11) with controls is not empty, see Lukes[17] (th 9.2.1 page 182).

Secondly, It is shown that the application l is linear with respect to u, we can verify that $l(t,\vec{x},\vec{u}) = a_1(t,\vec{x}) + a_2(t,\vec{x})\vec{u}$; where

$$a_1(t,\vec{x}) = \begin{pmatrix} h-(\delta+\xi+\gamma_H+\sigma)H \\ \sigma H-(\delta_A+\delta+\gamma_A+\alpha)A \\ \gamma_H H+\psi T_A-(\delta+\delta_{OC}+\varphi+\varepsilon)T_H \\ \varphi T_H+\gamma_A A-(\delta+\delta_A+\psi+\beta)T_A \\ \xi H-(\delta+\delta_C)C+\beta T_A+\varepsilon T_H \end{pmatrix},$$

and

$$a_2(t,\vec{x}) = l_{\vec{u}} = \begin{pmatrix} -h & 0 & 0 \\ 0 & \alpha A & 0 \\ 0 & 0 & \varepsilon T_H \\ 0 & 0 & \beta T_A \\ 0 & -\alpha A & -(\beta T_A + \varepsilon T_H) \end{pmatrix}.$$

Thirdly, the set of controls $\mathbf{U}$ is convex and closed by definition.

Fourthly, the integrand f is convex with respect to the control $\vec{u}$; to verify this, we have to show that:

$$(1-q)f(t,\vec{x},\vec{u}) + qf(t,\vec{x},\vec{v}) \geq f(t,\vec{x},(1-q)\vec{u}+q\vec{v}) \quad \forall(\vec{u},\vec{v}) \in \mathbf{U}^2 \quad \forall q \in [0,1].$$

We have,

$$\begin{aligned} (12)\quad & (1-q)f(t,\vec{x},\vec{u}) + qf(t,\vec{x},\vec{v}) \\ & = H(t) + C(t) + B_1\left[(1-q)u_1^2 + qv_1^2\right] + B_2\left[(1-q)u_2^2 + qv_2^2\right] + B_3\left[(1-q)u_3^2 + qv_3^2\right], \end{aligned}$$

and

$$\begin{aligned} (13)\quad & f(t,\vec{x},(1-q)\vec{u}+q\vec{v}) \\ & = H(t) + C(t) + B_1\left[(1-q)u_1 + qv_1\right]^2 + B_2\left[(1-q)u_2 + qv_2\right]^2 + B_3\left[(1-q)u_3 + qv_3\right]^2 \end{aligned}$$

then we have,

$$\begin{aligned} & (12) - (13) \\ & = B_1\left[(1-q)u_1^2 + qv^2 - \left[(1-q)u_1 + qv_1\right]^2\right] + B_2\left[(1-q)u_2^2 + qv_2^2 - \left[(1-q)u_2 + qv_2\right]^2\right] \\ & + B_3\left[(1-q)u_3^2 + qv_3^2 - \left[(1-q)u_3 + qv_3\right]^2\right] \\ & = B_1\left[\sqrt{q(1-q)}u_1 + \sqrt{q(1-q)}v_1\right]^2 + B_2\left[\sqrt{q(1-q)}u_2 + \sqrt{q(1-q)}v_2\right]^2 \\ & + B_3\left[\sqrt{q(1-q)}u_3 + \sqrt{q(1-q)}v_3\right]^2 \end{aligned}$$

We conclude that the integrand function is convex in $\mathbf{U}$.

Finaly, $\exists \alpha_1 > 0, \quad \alpha_2 > 0$ and $\alpha > 0$ such that $f(t,\vec{x},\vec{u}) \geq \alpha_1 + \alpha_2|\vec{u}|^\alpha$; we can choose $\alpha_1 = \frac{1}{2}\inf(H(t)+C(t)), \quad \alpha_2 = \min(B_1,B_2,B_3)$ and $\alpha = 2$.

□

4.2.2. *Characterization of Optimal Control.*

The necessary conditions of optimal control come from Pontryagin's Maximum Principle[18]; which makes it possible to characterize the optimal control in the event of existence; by this principle, we define the Hamiltonian as follows:

$$\begin{aligned}\mathscr{H} &= f(t,\vec{x},\vec{u}) + \lambda^{\top} l(t,\vec{x},\vec{u}) \\ &= H + C + B_1u_1^2 + B_2u_2^2 + B_3u_3^2 + \lambda_1\frac{dH}{dt} + \lambda_2\frac{dA}{dt} + \lambda_3\frac{dT_H}{dt} + \lambda_4\frac{dT_A}{dt} + \lambda_5\frac{dC}{dt} \\ &= H + C + B_1u_1^2 + B_2u_2^2 + B_3u_3^2 + \lambda_1((1-u_1)h - (\delta+\xi+\gamma_H+\sigma)H) \\ &+ \lambda_2(\sigma H - (\delta_A+\delta+\gamma_A)A - (1-u_2)\alpha A) + \lambda_3(\gamma_H H + \psi T_A - (\delta+\delta_{OC}+\varphi)T_H \\ &- (1-u_3)\varepsilon T_H) + \lambda_4(\varphi T_H + \gamma_A A - (\delta+\delta_A+\psi)T_A - (1-u_3)\beta T_A) \\ &+ \lambda_5(\xi H + (1-u_2)\alpha A + (1-u_3)[\beta T_A + \varepsilon T_H] - (\delta+\delta_C)C)\end{aligned}$$

Theorem 4.2. *For an optimal control* $\vec{u^*} = (u_1^*, u_2^*, u_3^*)$ *that minimizes* $\mathscr{J}(\vec{u})$ *over* **U**, *there is an adjoint vector* $\lambda(t) = (\lambda_1,\lambda_2,\lambda_3,\lambda_4,\lambda_5)$ *that satisfy:*

$$\frac{d\lambda_i}{dt} = -\frac{\partial\mathscr{H}}{\partial x_i}, \quad i = 1..5,$$

where $\vec{x} = (x_1,x_2,x_3,x_4,x_5) = (H,A,T_H,T_A,C)$*; with the transversality conditions* $\lambda_i(T) = 0$ *for* $i = 1..5$. *Morever, we obtain the follow characterization of optimal control:*

$$\begin{aligned} u_1^* &= min\left(max\left(\frac{\lambda_1 h}{2B_1},0\right),1\right), \\ u_2^* &= min\left(max\left(\frac{\alpha A^*(\lambda_5-\lambda_2)}{2B_2},0\right),1\right), \\ u_3^* &= min\left(max\left(\frac{\varepsilon T_H^*(\lambda_5-\lambda_3)+\beta T_A^*(\lambda_5-\lambda_4)}{2B_3},0\right),1\right). \end{aligned} \tag{14}$$

Proof. Applying Pontryagin's Maximum Principle, and having proven in the previous part the existence of an optimal control and an associated solution of the system (11) , there exists an adjoint vector $\lambda = (\lambda_1,\lambda_2,\lambda_3,\lambda_4,\lambda_5)$ such that λ_i is absolutely continuous over $[0,T]$ and verify:

$$
(15)\qquad \begin{cases} \dfrac{d\lambda_1}{dt} = -\dfrac{\partial \mathscr{H}}{\partial H} = -1 + (\delta + \xi + \gamma_H + \sigma)\lambda_1 - \sigma\lambda_2 - \gamma_H\lambda_3 - \xi\lambda_5 \\ \dfrac{d\lambda_2}{dt} = -\dfrac{\partial \mathscr{H}}{\partial A} = [(\delta_A + \delta + \gamma_A) - (1-u_2)\alpha)]\,\lambda_2 - \psi\lambda_3 - \gamma_A\lambda_4 - (1-u_2)\alpha\lambda_5 \\ \dfrac{d\lambda_3}{dt} = -\dfrac{\partial \mathscr{H}}{\partial T_H} = [(\delta + \delta_{OC} + \varphi) + (1-u_3)\varepsilon]\,\lambda_3 \\ \dfrac{d\lambda_4}{dt} = -\dfrac{\partial \mathscr{H}}{\partial T_A} = -\psi\lambda_3 + [(\delta + \delta_A + \psi) + (1-u_3)\beta]\,\lambda_4 - (1-u_3)\beta\lambda_5 \\ \dfrac{d\lambda_5}{dt} = -\dfrac{\partial \mathscr{H}}{\partial C} = -1 + (\delta + \delta_C)\lambda_5 \\ \lambda_i(T) = 0 \quad \forall i = 1..5 \end{cases}
$$

The optimal control $\vec{u}^*$ is obtained from the following optimal necessary conditions $\frac{d\mathscr{H}}{du_i} = 0$; that's to say:

$$
\left(\frac{\partial \mathscr{H}}{\partial u_1}\right)_* = 2B_1u_1^* - h\lambda_1 = 0 \Longrightarrow u_1^* = \frac{h\lambda_1}{2B_1},
$$

$$
\left(\frac{\partial \mathscr{H}}{\partial u_2}\right)_* = 2B_2u_2^* + \alpha A^*(\lambda_2 - \lambda_5) = 0 \Longrightarrow u_2^* = \frac{\alpha A^*(\lambda_5 - \lambda_2)}{2B_2},
$$

$$
\left(\frac{\partial \mathscr{H}}{\partial u_3}\right)_* = 2B_3u_3^* + \varepsilon T_H^*(\lambda_3 - \lambda_5) + \beta T_A^*(\lambda_4 - \lambda_5) = 0 \Longrightarrow u_3^* = \frac{\varepsilon T_H^*(\lambda_5 - \lambda_3) + \beta T_A^*(\lambda_5 - \lambda_4)}{2B_3}.
$$

Let us respect the bounds of controls in $\mathbf{U}$, we arrive at the formulas (14). □

5. Numerical Simulations

5.1. Data and Parameters Estimation.

A study [19, 20] conducted on a large HIV-infected population in Burundi reported a high prevalence of hypertension among HIV-infected patients; which is considered key towards cardiovascular diseases. The results revealed that long duration of HIV infection and long duration of HAART as well as other behavioral factors were consistently associated with hypertension. To give a mathematical illustration, we collected data of HIV cases and deaths in Burundi from WHO to generate the recruitment rate h and the HIV mortality rate δ_H from 2013 to 2022; the recruitement rate is the mean of all new cases from this period; we will consider that the mortality rate is constant, therefore the value that will take is the average of the rates during this period. The natural mortality rate δ_N during the same period is generated from Macrotrends [21]. According to WHO, the mean duration for progression from stage I-II to stage III-IV of

HIV infection is 5 years to 20 years, so the progression rate σ will check a value in the interval $[\frac{1}{20}; \frac{1}{5}]$. Mortality rates from cardiovascular diseases and AIDS-related causes are generated from iAHO data bank. The above data and results are tabulated in table (1).

TABLE 1. Data to generate fixed Parameters

Year	Number of new infected cases	Number of people dying from HIV-related causes	Number of deaths attributed to cardiovascular	Life expectancy	Population
2013	1700	4500	9051	58.92	10,149,577
2014	1500	4200	9048	59.34	10,494,913
2015	1400	3700	9158	59.76	10,727,148
2016	1100	2900	9408	60.18	10,903,327
2017	1200	2400	9655	60.6	11,155,593
2018	1100	2000	9920	61.02	11,493,472
2019	1100	1800	10159	61.36	11,874,838
2020	1300	1500	-	61.7	12,220,227
2021	1200	1300	-	62.03	12,551,213
2022	1300	1300	-	62.37	12,889,576
The average from 2013 to 2022	$h \simeq 1290$	$\delta_H \simeq 0.0004$	$\delta_C \simeq 0.0008$	$\delta_N = \frac{1}{\text{life expectancy}} \simeq 0.016$	

5.2. Fitting Model to Data.

We used data on HIV cases in Burundi from WHO over the period 2013-2022 to be able to provide a good estimate of the other parameters of the model; while optimizing, more precisely, minimizing the mean square error between the observed and predicted data from the model: $\sum_{2013}^{2022}(yH(i) - H_i)^2$, which will be considered as the objective function of our optimization problem; where H_i are data values; $yH(i)$ are the same time points corresponding to predicted values from the model.

The data set[22] used for calibration model to data is listed in table (2).

TABLE 2. Data to generate fitted Parameters

Year	New infected cases	AIDS- cases	HIV cases under treatment	AIDS cases under treatment
2013	58041	2030	32755	64
2014	52204	2000	36728	68
2015	43000	2007	41899	94
2016	30400	3124	51385	91
2017	24300	3020	55583	97
2018	20800	2153	59948	99
2019	16613	2000	64288	99
2020	13500	2523	65877	100
2021	12700	2154	67446	10
2022	10150	1473	68279	100

Using a Matlab program, we called the fminsearsh function to be able to minimize the error, we arrive at a good calibration of the model, the results are illustrated by the two curves on Figure 2, which represent a curve of new infections before and after adjustment to the data.

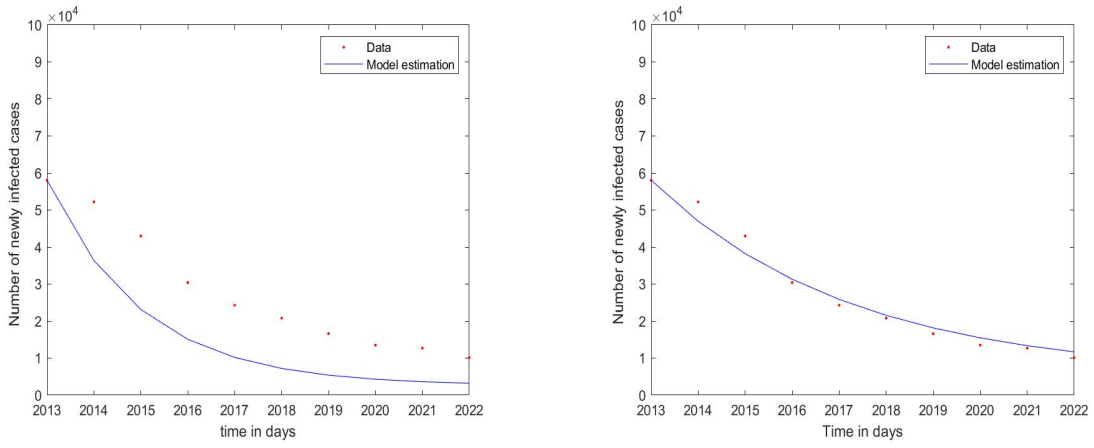

FIGURE 2. Model estimation before and after fitting parameters

We use an implicit Gauss-Seidel method; we simultaneously use progressive finite differences for approximation of the derivatives of state variables and regressive finite differences for adjoint variables. Numerical simulations are performed with Matlab to describe the behavior of the system solutions over time for the model defined by the system (11). The simulation parameters are listed in Table (3):

TABLE 3. The model parameters

Parameter	Value	Source
h	1290	Genereted from WHO
$\delta = \delta_N + \delta_H$	0.016+0.004	Generated from [21]
δ_C	0.0008	Generated from[23]
σ	0.0551	Fitted
ξ	0.0207	Fitted
α	0.0450	Fitted
ε	0.046	Fitted
β	0.076	Fitted
φ	0.029	Fitted
ψ	0.3157	Fitted
γ_H	0.1444	Fitted
γ_A	0.3805	Fitted
δ_A	0.0005	Fitted
δ_{OC}	0.0109	Fitted
B_1	0.0003	estimated
B_2	0.002	estimated
B_3	0.0005	estimated

Using the numerical simulations, Figure (3) illustrates the impact of optimal controls at each infected class of model.

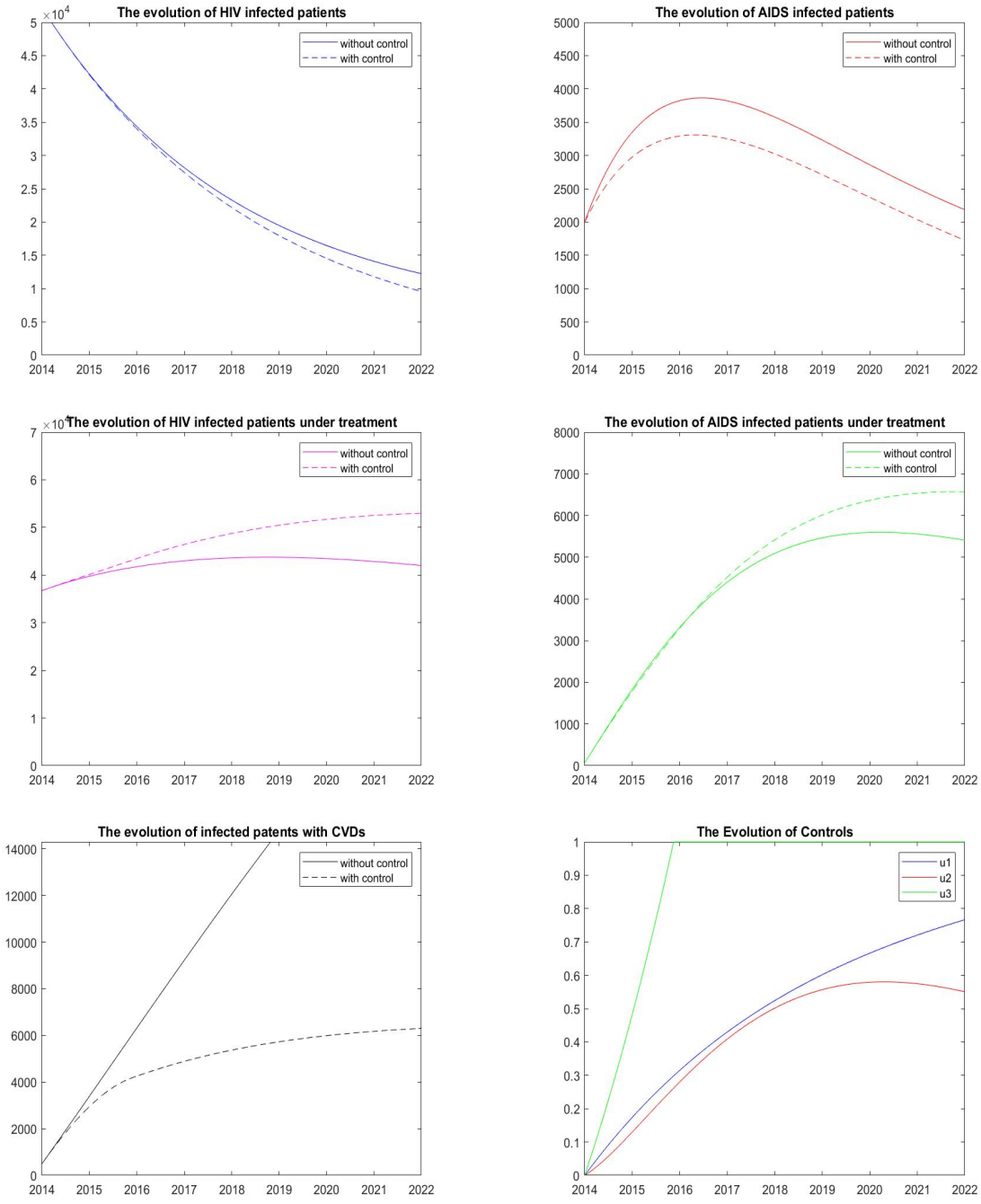

FIGURE 3. Evolution of HIV (a) and AIDS (b) infected with and without controls. Evolution of HIV (c) and AIDS (d) infected under treatment with and without controls. Evolution of infected patients with CVDs (e) and the tree optimal controls (f)

5.3. Discussion.

Obviously, Figure 3-(a) shows that the controls decrease the number of infected people with HIV. We see also that the evolution curve of AIDS infected (b) with controls increases during the first two years to reach a peak less pronounced than the curve without controls, then tends to decrease over the following years; which explains the good impact of the controls on the evolution of this class.

According to Figure 3-(c) and (d), the number of all HIV and AIDS infected patients under HAART treatment increases significantly when the control measures are adopted; which is explained by the fact that we keep HIV and AIDS infected people under treatment in their state without developing complications, and that the controls preserve more individuals in both campartments without progressing towards cardiovascular diseases.

The curve on Figure 3-(e) illustrates the dynamic of cardiovascular diseases. The evolution of the curve of uncontrolled cardiovascular complications is increasing over time; after 3 years, it reaches a value ten times greater than the initial state. When maintaining controls, we observe a similar increase in the two curves (curve with controls) during the first year, which is due to the uncontrollability of the system at the start, then an increase less significant than the curve without controls, to arrive at a reduction by half in the number of complications after three years of administration of controls.

The curve on Figure 3-(f) represents the curves of the optimal controls u_1, u_2 et u_3, it is assumed that at the beginning there are no controls and that its values increase simultaneously during the first two years, then take values which will subsequently produce following a reduction in the number of cardiovascular complications. We see also, that the u_3 control reaches its maximum value after the second year while preserving it over the years to follow, which explains why the u_3 control, i.e. the diagnosis of traditional risk factors for cardiovascular diseases, must be part of the treatment protocol for HIV infected people.

6. Conclusion

Through this article, we wanted to highlight cardiovascular diseases as a complication due on the one hand to HIV infection, and on the other hand to the effect of HAART treatment. For this we formulated a non-intervention model and presented its results in detail. The study

of the stability of the equilibrium point without control demonstrates that the system is locally asymptotically stable. We calibrated the model using anually confirmed HIV data from Burundi. We have controlled our system through a suite of effective strategies to reduce the number of patients at risk of developing cardiovascular diseases, as well as the number of those infected with complications while minimizing costs.

The optimal control system is generated using three controls which respectively represent prevention efforts that protect susceptible individuals from contracting HIV infection, awareness efforts to educate infected individuals about cardiovascular complications resulting from HIV infection, and the diagnosis and monitoring traditional risk factors for CVDs.
Based on the fitted parameter values as well as several fixed parameter values generated from data bank , Marcrotrends and WHO; based also, on these control strategies; we simulate our system to obtain the comparison of the behavior of each compartment, with and without controls. Certainly, the results indicate that each population targeted by a control benefits from its impact; the reduction of HIV infected people reduces systematically the numbers of individuals in the other compartments. Raising awareness among those infected with AIDS of the need for HAART treatment reduces their progression to complications. And above all the reduction of traditional risk factors reduces these complications.

The combination of these three strategies favorably reduces cardiovascular complications. In conclusion, awareness of the burden of HIV, reduction of behavioral factors such as smoking, alcohol, malnutrition, drugs, obesity; controlling risk factors linked to cardiovascular status such as blood pressure, blood sugar and cholesterol will considerably reduce the risk of developing cardiovascular diseases in people living with HIV; which indicates the effectiveness of the recommended controls.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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