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OPTIMAL CONTROL ANALYSIS OF EFFECT OF HAART ON IMMUNE CELLS AGAINST HIV INFECTION

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ABSTRACT. A non-linear deterministic mathematical model for the transmission dynamics of HIV infection within the body system of an infected individual was formulated for analysis. Multiplication of the virus at the detriment of the immune system of the body (notably the CD4-T-cells and Macrophages) is the effect of introduction of small amount of the virus into the body system of previously susceptible individual. The study aimed at looking into the effect of education, early diagnosis of the infection through proper screening and early treatment of the body as a means of helping the body to stay healthier for a longer period of time. The model developed was analysed for existence of solution, equilibria states (Infection Free Equilibrium I.F.E and Endemic State Equilibrium E.S.E). Local and Global Analysis of the effective reproduction number was done and the result shows that I.F.E is both locally and globally stable if $R_0 < 1$ otherwise the infection spreads in the body. The optimal effect of using Highly Active Anti-Retrovirus Therapy (HAART) as an improved means to ART was considered. The result show that HAART is capable of removing the infected cells quicker thereby reducing the viral burden of the infection in the immune system.

1. INTRODUCTION

Since HIV (Human Immunodeficiency Virus) infection was contracted in 1920, lots of work have been done both by medical practitioners, government agencies etc. to see that it is eradicated but all to no avail. Significant breakthrough in the eradication of this menace is the discovery of Highly Active Anti-Retroviral therapy (HAART) that is capable of suppressing the multiplicative effect of the virus to the possible minimum even though the cost is extremely high for the middle class and almost out of reach to the masses that suffer from the infection. Human Immunodeficiency Virus infection has constitute one of the developmental, health and socio-economic challenges facing the whole world today due to its wide range of infectiousness, strong mortality rate, super-expensive treatment drug (with no amelioration) and outright in-curability [2, 8]. Once the virus gained entry into human blood system either through sexual intercourse, blood transfusion etc., it metamorphosed into AIDS through four clinical stages of infection according to WHO as

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reported by [9]. The first phase known as the acute stage is characterize with strong viral replication which may last for 2-4 weeks [9, 7]. The second phase is the asymptomatic stage which is characterized with no symptoms of HIV and free from major AIDS related opportunistic diseases. The symptomatic stage is the third phase and is characterized with damaged lymph nodes and tissues leading to a massive destruction of defense cells (CD4 cells and Macrophages) thereby exposing the body to opportunistic infections such as tuberculosis, consistent malaria and headache etc. Majorly, the difference between the asymptomatic and the symptomatic stage is the high viral count in the latter. The final stage is full blown AIDS which is a life threatening stage, having a CD4 cells count below 200per ml. [1, 5]
Mathematical epidemiology is a mathematical means of representing infectious disease for the purpose of gaining understanding on the transmission mechanisms of the disease, suggesting the qualitative impact of disease control measures and forecasting disease incidences for both short and long term using mathematical analysis tools [8]. Several researches have been conducted by many researchers worldwide on effective means of preventing, managing and curative approach to deal with HIV/AIDS [5, 4]. It is worthy to mention that the fight against HIV infection and its removal from society was not committed majorly to the health workers as all hands have been, were and still on desk from all circles of life, be it religious, academician, economist etc to see that the menace of HIV/AIDS was eradicated effectively from the society.

2. Model Formulation

Among the researchers that worked on the dynamics of HIV infection within the body is Elaiw [4]. In his paper titled "Global properties of a class of HIV model", he established the criteria under which the infection either increase or sustained once it gained entrance into the body system. The model proposed here modified his model by including the efficacy of HAART in helping the immune systems (CD4 cells and Macrophages) to fight off the infection by (i) removing the infected cells from the body system to ease the viral burden (ii) helping the body to produce more anti bodies to replace the infected ones and (iii) suppressing the multiplicative effect of the virus in the body system. Hence, the model proposed has the state variables describe by the plasma concentrations of: x, the uninfected CD4+ T-cells; x_1, the infected CD4+ T cells; y, the uninfected macrophages; y_1, the infected macrophages; and v, the free virus particles. The populations dynamics of the uninfected CD4+ T cells and macrophages are represented by x and y respectively, where Π_1 and Π_2 represents the rates at which new CD4+ T cell and macrophages are generated from sources within the body; d_1, d_2 are the death rate constants and β_1, β_2 are the infection rate constants. Here, the law of mass action was used. The extension to the original model is the consideration of efficacy of HAART in helping the immune system to produce the uninfected CD4+ T cell and macrophages at the rate of Expression γ_1 and γ_2 and also its impact in removing the infected cells and macrophages at the rate of u_1 respectively. $\dot{x_1}$ and $\dot{y_1}$ describes the population dynamics of the infected CD4+ T cells and Macrophages respectively and shows that they die with rate constant a and δ. The virus particles are produced by the infected CD4+ T cells and infected macrophages with rate constants p_1 and p_2, respectively, and are cleared from plasma with rate constant c, α is the efficacy rate of HAART in clearing the virus from the plasma. All the parameters of the model are supposed to be positive.

Model Assumptions: The following are the basic assumptions for this model:

(1) Early detection of HIV virus is assumed.
(2) We assumed that the production rate of uninfected CD4(or Macrophages) cells before and after infection is constant.
(3) We assumed that infected CD4 cells(or Macrophages) contribute to increment in viral load, hence the more the infected CD4 cells the more the viral count.
(4) We assumed the clearance rate of virus from the infected CD4 cells (or Macrophages) depend on the efficacy of the HAART.
(5) All parameters are assumed non-negative.

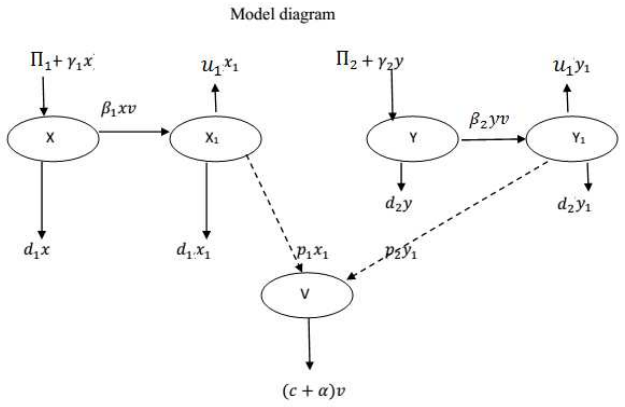

Figure 1: Flow Chart of Extended Model

The system of equations representing the model is given as:

$$
\begin{aligned}
\frac{dx}{dt} &= \Pi_1 - d_1 x - \beta_1 xv + \gamma_1 x \\
\frac{dx_1}{dt} &= \beta_1 xv - (u_1 + d_1)x_1 \\
\frac{dy}{dt} &= \Pi_2 - d_2 y - \beta_2 yv + \gamma_2 y \\
\frac{dy_1}{dt} &= \beta_2 yv - (u_1 + d_2)y_1 \\
\frac{dv}{dt} &= p_1 x_1 + p_2 y_1 - (c+\alpha)v
\end{aligned} \tag{2.1}
$$

Table 1: Parameters and Variables Definition for Model 1

Parameter	Description
$\Pi_i, i = 1, 2$	Normal Production rate of CD4 cells and Macrophages
$\beta_{1,2}$	rate of infection for CD4 cells and Macrophages
$\gamma_{1,2}$	Efficacy of HAART in bolstering production of the cells
$d_{1,2}$	Normal death rate constant of each cells
$p_{1,2}$	Production rate of virus particle in the infected cells
u_1	Efficacy of HAART in removing (killing) infected cells from the body
c	Clearance rate (or death rate) of virus from the body by the body immune system
α	Efficacy of HAART in clearing the virus from the plasma
x	Healthy CD4 cells
x_1	Infected CD4 cells
y	Healthy macrophages
y_1	Infected Macrophages
v	virus particle

3. Model Analysis

This section deals with qualitative analysis of the extended model.

Proposition 3.1. *[Positivity of Solution] There exists positive numbers C_1, C_2 and C_3 such that the compact set:*

$$P_1 = \{(x, x_1, y, y_1, v) \in \Re^5_+ : 0 \leq x, x_1 \leq C_1, 0 \leq y, y_1 \leq C_2, 0 \leq v \leq C_3\}$$

is positively invariant.

Proof. Recall the system of equations governing the extended model and by making the substitution $k_1 = d_1 - \gamma_1$, $k_2 = d_2 - \gamma_2$, $k_3 = u_1 + d_1$, $k_4 = u_1 + d_2$ and $k_5 = c + \alpha$ we obtain:

$$\begin{aligned}
\frac{dx}{dt} &= \Pi_1 - \beta_1 xv - k_1 x \\
\frac{dx_1}{dt} &= \beta_1 xv - k_3 x_1 \\
\frac{dy}{dt} &= \Pi_2 - \beta_2 yv - k_2 y \\
\frac{dy_1}{dt} &= \beta_2 yv - k_4 y_1 \\
\frac{dv}{dt} &= p_1 x_1 + p_2 y_1 - k_5 v
\end{aligned} \tag{3.1}$$

We consider the system of equations governing the model extended by re-grouping each cell (both CD4 cells and Macrophages) by making a new substitution $X = x + x_1$ and $Y = y + y_1$. The time derivatives of both healthy and infected CD4 cell under the new

category is thus given as:

$$\left.\begin{aligned} X(t) &= x(t) + x_1(t) \\ \frac{dX}{dt} &= \frac{dx}{dt} + \frac{dx_1}{dt} \\ \frac{dX}{dt} &= \Pi_1 + \gamma_1 x - d_1(x + x_1) - u_1 x_1 \\ \frac{dX}{dt} &\leq \Pi_1 - d_1 X \end{aligned}\right\}$$

solving the resulting first order O.D.E above, we have:

$$\begin{aligned} &\frac{dX}{dt} + d_1 X \leq \Pi_1 \\ &e^{d_1 t}\left[\frac{dX}{dt} + d_1 X\right] \leq \Pi_1 e^{d_1 t} \\ &\frac{d}{dt}\left[X.e^{d_1 t}\right] \leq \Pi_1 e^{d_1 t} \\ &d\left[X.e^{d_1 t}\right] \leq \left[\Pi_1 e^{d_1 t}\right] dt \\ &X(t) \leq \frac{\Pi_1}{d_1} + ce^{-d_1 t} \end{aligned}$$

which is positive for any time t. Obviously, as $t \to \infty$, the solution $X(t)$ is bounded above by a non-negative number C_1 defined by $\frac{\Pi_1}{d_1}$. Hence $0 \leq X(t) \leq \frac{\Pi_1}{d_1}$, it follows that, $0 \leq x(t), x_1(t) \leq C_1$ where $C_1 = \frac{\Pi_1}{d_1}$ for all $t \geq 0$.
Similarly, the time derivatives of both healthy and infected macrophages cell under the new category is thus given as:

$$\left.\begin{aligned} Y(t) &= y(t) + y_1(t) \\ \frac{dY}{dt} &= \frac{dy}{dt} + \frac{dy_1}{dt} \\ \frac{dY}{dt} &= \Pi_2 + \gamma_1 y - d_1(y + y_1) - u_1 y_1 \\ \frac{dY}{dt} &\leq \Pi_2 - d_2 Y \end{aligned}\right\}$$

solving the resulting first order O.D.E above, we have:

$$\begin{aligned} &\frac{dY}{dt} + d_2 Y \leq \Pi_2 \\ &e^{d_2 t}\left[\frac{dY}{dt} + d_2 Y\right] \leq \Pi_2 e^{d_2 t} \\ &\frac{dY}{dt}\left[Y.e^{d_2 t}\right] \leq \Pi_2 e^{d_2 t} \\ &d\left[Y.e^{d_2 t}\right] \leq \left[\Pi_2 e^{d_2 t}\right] dt \\ &Y(t) \leq \frac{\Pi_2}{d_2} + ce^{-d_2 t} \end{aligned}$$

which is positive for any time t. Obviously, as $t \to \infty$, the solution $Y(t)$ is bounded above by a non-negative number C_2 defined by $\frac{\Pi_2}{d_2}$. Hence $0 \leq Y(t) \leq \frac{\Pi_2}{d_2}$, it follows that, $0 \leq y(t), y_1(t) \leq C_2$ for all $t \geq 0$ where $C_2 = \frac{\Pi_2}{d_2}$.

On the other hand, using the last equation in the system of equations (3.1) by substituting the result from above, we obtained

$$\begin{aligned}
&\frac{dv}{dt} \leq p_1C_1 + p_2C_2 - (c+\alpha)v \\
&\frac{dv}{dt} + (c+\alpha)v \leq p_1C_1 + p_2C_2 \\
&e^{c+\alpha}t\left[\frac{dv}{dt} + (c+\alpha)v\right] \leq e^{c+\alpha}t(p_1C_1 + p_2C_2) \\
&v \leq \frac{p_1C_1 + p_2C_2}{c+\alpha} + ke^{-(c+\alpha)}t
\end{aligned}$$

Thus $v(t) \geq 0$ for all time $t \geq 0$. As $t \to \infty$, the virus population approaches a non-negative constant $C_3 = \frac{p_1C_1+p_2C_2}{c+\alpha}$. This complete the prove. □

Steady States of the Model

Lemma 3.1. *The system of equations* (2.1) *has two unique equilibria states which are denoted as Infection Free Equilibrium (I.F.E) and the Endemic State Equilibrium (E.S.E) states.*

Proof. Applying the elementary knowledge in Calculus by noting that at equilibrium, the rate of change is zero. Thus, using $\frac{dx}{dt} = \frac{dx_1}{dt} = \frac{dy}{dt} = \frac{dy_1}{dt} = \frac{dv}{dt} = 0$, we obtain the system of equations given as:

$$\begin{aligned}
&\Pi_1 - \beta_1 xv - k_1 x = 0 \\
&\beta_1 xv - k_3 x_1 = 0 \\
&\Pi_2 - \beta_2 yv - k_2 y = 0 \\
&\beta_2 yv - k_4 y_1 = 0 \\
&p_1 x_1 + p_2 y_1 - k_5 v = 0
\end{aligned} \tag{3.2}$$

Using the second and fourth equations in the system of equations above to obtain:

$$x_1 = \frac{\beta_1 xv}{k_3},\ y_1 = \frac{\beta_2 yv}{k_4}$$

Substituting the above into the fifth equation in the system gives:

$$\begin{aligned}
&\left[\frac{p_1\beta_1 x}{k_3} + \frac{p_2\beta_2 y}{k_4} - k_5\right] v = 0 \\
&\Rightarrow v = 0,\ or\ \frac{p_1\beta_1 x}{k_3} + \frac{p_2\beta_2 y}{k_4} - k_5 = 0
\end{aligned} \tag{3.3}$$

Thus, from the result above, it is obvious that two unique steady states solutions of the model equations (2.1) exists. This proof the lemma. □

3.1. **Infected Free Equilibrium State,** $v = 0$**.** The unique infection free equilibrium denoted as E^0 of the model exists when $v = 0$ and is given as:

$$E^0 : \{x_0, x_{1,0}, y_0, y_{1,0}, v_0\} = \left\{\frac{\Pi_1}{d_1 - \gamma_1}, 0, \frac{\Pi_2}{d_2 - \gamma_2}, 0, 0\right\}$$

3.2. **Endemic State Equilibrium Point,** $v \neq 0$**.** In the presence of infection, the steady state for the model was obtained as follows: Eliminating v from the first and third equations of (3.2) by multiplying the two equations with $\beta_2 y$ and $\beta_1 x$ respectively and subtracting the resulting expressions, we have:

$$k_6 y - k_7 x + k_8 xy = 0 \tag{3.4}$$

where $k_6 = \beta_2 \Pi_1$, $k_7 = \beta_1 \Pi_2$ and $k_8 = (\beta_2 k_1 - \beta_1 k_2)$. It is obvious to state that k_6 and k_7 are both positive while k_8 may be positive, negative or zero. If k_8 is zero, then the special case of infected equilibrium is given as:

$$x_s^* = \frac{k_3 k_4 k_5 k_6}{(p_2\beta_2 k_3 k_7 + p_1\beta_1 k_4 k_6)},\ y_s^* = \frac{k_3 k_4 k_5 k_7}{(p_2\beta_2 k_3 k_7 + p_1\beta_1 k_4 k_6)}$$
$$x_{1,s}^* = \frac{k_1}{k_3}\left(\frac{x_0}{x_s^*} - 1\right) x_s^*,\ y_{1,s}^* = \frac{k_2}{k_4}\left(\frac{y_0}{y_s^*} - 1\right) y_s^*,\ v_s^* = \frac{k_1}{\beta_1}\left(\frac{x_0}{x_s^*} - 1\right)$$

If $k_8 \neq 0$, by making y the subject of formula in the second expression in (3.3), that is, $\frac{p_1\beta_1 x}{k_3} + \frac{p_2\beta_2 y}{k_4} - k_5 = 0$ to obtain:

$$y = k_9 - k_{10} x \tag{3.5}$$

where $k_9 = \frac{k_4 k_5}{p_2\beta_2}$ and $k_{10} = \frac{k_4 p_1 \beta_1}{p_2\beta_2 k_3}$. Substituting (3.5) into (3.4) gives:

$$k_{11} x^2 + k_{12} x + k_{13}$$

where $k_{11} = -k_8 k_{10}$, $k_{12} = k_8 k_9 - k_6 k_{10} - k_7$ and $k_{13} = k_6 k_9$. The positive solution of the quadratic equation gives the desired infected equilibrium point as:

$$E_\epsilon^* = \left.\begin{array}{l} x_\epsilon^* = \dfrac{-k_{12} + \sqrt{k_{12}^2 - 4k_{11}k_{13}}}{2k_{11}},\ y_\epsilon^* = k_9 - k_{10} x_\epsilon^* \\ x_{1,\epsilon}^* = \dfrac{k_1}{k_3}\left(\dfrac{x_0}{x_\epsilon^*} - 1\right) x_\epsilon^*,\ y_{1,\epsilon}^* = \dfrac{k_2}{k_4}\left(\dfrac{y_0}{y_\epsilon^*} - 1\right) y_\epsilon^*,\ v_\epsilon^* = \dfrac{k_1}{\beta_1}\left(\dfrac{x_0}{x_\epsilon^*} - 1\right) \end{array}\right\}$$

3.3. **Model Reproduction Number.** Following the approach established by Driessche and Watmough, see [6], the basic reproduction number of the model was obtained as:

$$R_0 = \frac{k_4\beta_1 p_1 x_0 + k_3\beta_2 p_2 y_0}{k_3 k_4 k_5}.$$

3.4. **Local Stability Analysis of the Infection Free Equilibrium State.**

Proposition 3.2. *The infection free state is Locally Asymptotically Stable (LAS) in* E^0 *whenever* $R_0 < 1$

Proof. Consider the Jacobian matrix of the system of equations (3.1) given as:

$$J = \begin{pmatrix} -k_1 - \beta_1 v & 0 & 0 & 0 & -\beta_1 x \\ \beta_1 v & -k_3 & 0 & 0 & \beta_1 x \\ 0 & 0 & -k_2 - \beta_2 v & 0 & -\beta_2 y \\ 0 & 0 & \beta_2 v & -k_4 & \beta_2 y \\ 0 & p_1 & 0 & p_2 & -k_5 \end{pmatrix}$$

Evaluating the above matrix at the infection free equilibrium state to obtain;

$$J_{E_0} = \begin{bmatrix} -k_1 & 0 & 0 & 0 & -\beta_1 x_0 \\ 0 & -k_3 & 0 & 0 & \beta_1 x_0 \\ 0 & 0 & -k_2 & 0 & -\beta_2 y_0 \\ 0 & 0 & 0 & -k_4 & \beta_2 y_0 \\ 0 & p_1 & 0 & p_2 & -k_5 \end{bmatrix}$$

With corresponding eigenvalues: $\lambda_1 = -k_1$, $\lambda_2 = -k_2$, $\lambda_3 = -k_4$, $\lambda_4 = -k_4$ and $\lambda_5 = \dfrac{k_4\beta_1 p_1 x_0 + k_3\beta_2 p_2 y_0 - k_3 k_4 k_5}{k_3 k_4}$. It is obvious that that λ_3 and λ_4 are both strictly less than zero. However, it is sufficient that $d_1 > \gamma_1$ and $d_2 > \gamma_2$ for both λ_1 and λ_2 to satisfy the stability criterion. For λ_5 to satisfy the stability condition, then

$$\begin{aligned} &\frac{k_4\beta_1 p_1 x_0 + k_3\beta_2 p_2 y_0 - k_3 k_4 k_5}{k_3 k_4} < 0 \\ &\frac{k_4\beta_1 p_1 x_0 + k_3\beta_2 p_2 y_0}{k_3 k_4} - \frac{k_3 k_4 k_5}{k_3 k_4} < 0 \\ &\Rightarrow \ \frac{k_4\beta_1 p_1 x_0 + k_3\beta_2 p_2 y_0}{k_3 k_4} < k_5 \\ &\Rightarrow \ \frac{k_4\beta_1 p_1 x_0 + k_3\beta_2 p_2 y_0}{k_3 k_4 k_5} < 1 \\ &\Rightarrow \ R_0 < 1 \end{aligned}$$

□

3.5. **Global Stability of the Infection Free Equilibrium State.**

Theorem 3.1. *The infection free state is Globally Asymptotically Stable (GAS) in E_0 whenever $R_0 \leq 1$*

Proof. Consider a well defined, continuous and positive definite Lyapunov function L_{E_0} given as:

$$L_{E_0} = x_0\left[\frac{x}{x_0} - x_0 ln\left(\frac{x}{x_0}\right)\right] + \frac{p_2 k_3 y_0}{p_1 k_4}\left[\frac{y}{y_0} - y_0 ln\left(\frac{y}{y_0}\right)\right] + x_1 + \frac{p_2 k_3}{p_1 k_4} y_1 + \frac{k_3}{p_1} v\,.$$

The time derivative of the above equation is given as:

$$\dot{L}_{E_0} = \left(1 - \frac{x_0}{x}\right)\dot{x} + \frac{p_2 k_3}{p_1 k_4}\left(1 - \frac{y_0}{y}\right)\dot{y} + \dot{x}_1 + \frac{p_2 k_3}{p_1 k_4}\dot{y}_1 + \frac{k_3}{p_1}\dot{v}\,.$$

Substituting the expressions for each time derivative as found in (3.1), the above equation becomes:

$$\begin{aligned} \dot{L}_{E_0} = &\left(1 - \frac{x_0}{x}\right)(\Pi_1 - \beta_1 x v - k_1 x) + \frac{p_2 k_3}{p_1 k_4}\left(1 - \frac{y_0}{y}\right)(\Pi_2 - \beta_2 y v - k_2 y) \\ &+ (\beta_1 x v - k_3 x_1) + \frac{p_2 k_3}{p_1 k_4}(\beta_2 y v - k_4 y_1) + \frac{k_3}{p_1}(p_1 x_1 + p_2 y_1 - k_5 v) \end{aligned}\,.$$

Using $\Pi_1 = \beta_1 x_0 v_0 - d_1 x_0 + \gamma_1 x_0$, $\Pi_2 = \beta_2 y_0 v_0 - d_2 y_0 + \gamma_2 y_0$, $k_3 x_1 = \beta_1 x_0 v_0$, $k_4 y_1 = \beta_2 y_0 v_0$ and $k_5 v = p_1 x_{1,0} + p_2 y_{1,0}$, the above expression we simplify to:

$$\begin{aligned}\dot{L}_{E_0} &= \left(1 - \frac{x_0}{x}\right)(\beta_1 x_0 v_0 - d_1 x_0 + \gamma_1 x_0 - \beta_1 x v + d_1 x - \gamma_1 x) + \\ &\frac{p_2 k_3}{p_1 k_4}\left(1 - \frac{y_0}{y}\right)(\beta_2 y_0 v_0 - d_2 y_0 + \gamma_2 y_0 - \beta_2 y v + d_2 y - \gamma_2 y) \\ &+ (\beta_1 x v - \beta_1 x_0 v_0) + \frac{p_2 k_3}{p_1 k_4}(\beta_2 y v - \beta_2 y_0 v_0) + \frac{k_3}{p_1}(p_1 x_1 + p_2 y_1 - p_1 x_{1,0} - p_2 y_{1,0}).\end{aligned}$$

On further simplification, we obtained:

$$\begin{aligned}\dot{L}_{E_0} &= k_1 x_0\left[2 - \frac{x_0}{x} - \frac{x}{x_0}\right] + \frac{p_2 k_3 k_2}{p_1 k_4} y_0\left[\left(2 - \frac{y_0}{y} - \frac{y}{y_0}\right)\right] - \beta_1 x_0 v_0\left(\frac{x_0}{x} - \frac{v}{v_0}\right) \\ &- \frac{p_2 k_3}{p_1 k_4}\beta_2 y_0 v_0\left[\frac{y_0}{y} - \frac{v}{v_0}\right] + \frac{k_3 k_5}{p_1}(R_{0,1} - 1)\end{aligned} \tag{3.6}$$

It can be observed that the first four terms of equation (3.6) above equals zero whenever $x_0 = x$, $y_0 = y$ and $v_0 = v$. Also, from elementary Mathematics, it is obvious to say that the arithmetical mean is always greater than or equal to the geometrical mean such that the first four terms of (3.6) are less than or equal to zero. Thus, if $R_{0,1} \leq 1$, then $\dot{L}_{E_0} \leq 0$ for all $x, y, v > 0$. Therefore, the maximal compact invariant set in $\left\{(x, x_1, y, y_1, v) \in E_0 : \dot{L}_{E_0} = 0\right\}$ is the singleton $\{E_0\}$ whenever $R_0 \leq 1$. The global stability of E_0 follows from LaSalle's invariance principle. □

3.6. **Analysis of Optimal Control of the Model.** The essence of a controlled system is to ascertain the effect of some measures taken to eradicate/diminish the spread of an infection. Several researchers have worked on optimal control measures to infectious disease, among them are [11], they analyzed cost effectiveness in treating Tuberculosis disease. Also, [10] studied the optimal control strategy of HIV-1 epidemic by incorporating two controls to the HIV-1 recombinant virus model. In order to monitor the effect of HAART on its effect on viral count, three time dependent control measures were proposed as $u_1(t)$, $u_2(t)$ and $u_3(t)$ respectively. Control $u_1(t)$ denotes the efficacy/effectiveness of the drug therapy to resist healthy cells (CD-4 or Macrophages) from getting infected. This is a treatment strategy that builds immunity for the defense cells. The control $u_2(t)$ integrates the effort of the therapy (HAART) in suppressing/reducing the multiplicative effect of the virus by removing consistently the infected cells (CD-4 or Macrophages) away from the body. The third control $u_3(t)$ denotes healthy eating habit that help the immune system to act better. According to [3], healthy eating habit improve overall qualities of life by providing essential nutrients for the body, it keep the immune system stronger for better fight against opportunistic infections and it helps the medication to manage HIV symptoms and its side effect. The control functions introduced are bounded and Lebesque integrable. As a control mechanism, the choice of measurable functions that are defined on a fixed intervals satisfies the condition $0 \leq u_i(t) < 1$ for $i = 1, 2, 3$.
The state variable is the following system of five ordinary differential equations:

$$
\left.\begin{aligned}
\frac{dx}{dt} &= \Pi_1 - d_1x(t) - \beta_1x(t)v(t) + \gamma_1x(t) + u_1(t)x(t) + u_3(t)x(t)\\
\frac{dx_1}{dt} &= \beta_1x(t)v(t) - (\mu_1 + d_1)x_1(t) - u_2(t)x_1(t)\\
\frac{dy}{dt} &= \Pi_2 - d_2y(t) - \beta_2y(t)v(t) + \gamma_2y(t) + u_1(t)y(t) + u_3(t)y(t)\\
\frac{dy_1}{dt} &= \beta_2y(t)v(t) - (\mu_1 + d_2)y_1(t) - u_2(t)y_1(t)\\
\frac{dv}{dt} &= p_1x_1(t) + p_2y_1(t) - (c+\alpha)v(t) - u_2(t)v(t)
\end{aligned}\right\}. \tag{3.7}
$$

The objective is to minimize the spread of the infection to the defense cells (CD-4 and Macrophages) while also maximizing (boosting) the production of more defense cells and maintaining the cost associated to the controls. The proposed optimal control problem with objective functional is derived as:

(3.8)

$$
J(u_1(t), u_2(t), u_3(t)) = \int_0^{t_f} \left(Ax(t) + By(t) - [\frac{S_1}{2}u_1^2(t) + \frac{S_2}{2}u_2^2(t) + \frac{S_3}{2}u_3^2(t)] \right) dt\,.
$$

Where $Ax(t)$ represents the benefit of CD-4 cells derived from taking HAART and eating healthy diet, $By(t)$ represents the benefits of Macrophages that is obtained from taking HAART and eating healthy diet and $S_iu_i^2$ are the systemic costs of the drug treatment and cost of eating healthy meals to help the immune system. The constants S_1, S_2 and S_3 denote the relative weight (weighting constants) attached to the drug and food therapies, u_1, u_2 and u_3 are the control variables. The quadratic terms in the functional justifies the fact that when drugs such as HAART are administered in high dose, they are cyanogenetic to the human body. The goal is to increase the number of immune cells (CD-4 and Macrophages) present at any time by reducing the viral load (the number of free virions) through reducing the infected cells while also minimizing the cost of treatment. Hence, the solution desired is an optimal control solutions u_1^*, u_2^* and u_3^* that maximizes the increment in the defense cells such that:

$$
J(u_1^*(t), u_2^*(t), u_3^*(t)) = max_u J(u_1(t), u_2(t), u_3(t) : u_1(t), u_2(t), u_3(t) \in U)\,.
$$

where $U = \{u_1(t), u_2(t), u_3(t) \in L^1(o, t_f) | 0 \leq u_i(t) < 1, i = 1, 2, 3\}$ is the control set. The state system (3.7) together with the objective functional (3.8) were used to analyzed the optimal control of the model.

Theorem 3.2. *There exists an optimal control u_1^*, u_2^* and u_3^* and corresponding solution x^*, x_1^*, y^*, y_1^* and v^* that maximizes $J(u_1(t), u_2(t), u_3(t))$ over Ω. Furthermore, there exist*

adjoint functions $\lambda_i(t)$ *for* $i = 1, 2, .., 5$ *such that*

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= (\lambda_1 - \lambda_2)\beta_1 v^* + \lambda_1(d_1 - \gamma_1 - u_1^* - u_3^*) - A \\
\frac{d\lambda_2}{dt} &= \lambda_2(\mu_1 + d_1 + u_2^*) - \lambda_5 p_1 \\
\frac{d\lambda_3}{dt} &= (\lambda_3 - \lambda_4)\beta_2 v^* + \lambda_3(d_2 - \gamma_2 - u_1^* - u_3^*) - B \qquad , \\
\frac{d\lambda_4}{dt} &= \lambda_4(\mu_1 + d_2 + u_2^*) - \lambda_5 p_2 \\
\frac{d\lambda_5}{dt} &= (\lambda_1 - \lambda_2)\beta_1 x^* + (\lambda_3 - \lambda_4)\beta_2 y^* + \lambda_5(c + \alpha + u_2^*)
\end{aligned} \tag{3.9}$$

with transversality conditions

$$\lambda_i(t_f) = 0, \ i = 1, 2, 3, 4, 5\,. \tag{3.10}$$

Proof. To prove the existence of optimal control, the Pontryagin Maximum Principle (PMP) established by [12] was employed. The technique was based on obtaining a function H called the Hamiltonian such that:

$$\begin{aligned}
&H(x(t), x_1(t), y(t), y_1(t), v(t), u_1(t), u_2(t), u_3(t), \lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t)) \\
&= Ax(t) + By(t) - [\frac{S_1}{2}u_1^2(t) + \frac{S_2}{2}u_2^2(t) + \frac{S_3}{2}u_3^2(t)] + \sum_{i=1}^{5} \lambda_i g_i(x(t), x_1(t), y(t), y_1(t), v(t))
\end{aligned}$$

where $g_i(x(t), x_1(t), y(t), y_1(t), v(t))$ is the right hand side of the differential equation of state variables x, x_1, y, y_1, v. Inserting the right hand side of the state variables to the equation above gives:

$$\begin{aligned}
&H(x, x_1, y, y_1, v, u_1(t), u_2(t), u_3(t), \lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t)) \\
&= Ax(t) + By(t) - \left[\frac{S_1}{2}u_1^2(t) + \frac{S_2}{2}u_2^2(t) + \frac{S_3}{2}u_3^2(t)\right] + \lambda_1[\Pi_1 - \beta_1 xv - d_1 x \\
&\quad + \gamma_1 x + u_1(t)x + u_3(t)x] + \lambda_2[\beta_1 x(t)v(t) - (\mu_1 + d_1)x_1(t) - u_2(t)x_1(t)] \\
&\quad + \lambda_3[\Pi_2 - d_2 y(t) - \beta_2 y(t)v(t) + \gamma_2 y(t) + u_1(t)y(t) + u_3(t)y(t)] \\
&\quad + \lambda_4[\beta_2 y(t)v(t) - (\mu_1 + d_2)y_1(t) - u_2(t)y_1(t)] + \lambda_5[p_1 x_1(t) + p_2 y_1(t) \\
&\quad - (c + \alpha)v(t) - u_2(t)v(t)]
\end{aligned}$$

Thus, the prove of theorem 3.2 follows from the prove of these two lemma. □

Lemma 3.2. *The optimal control* (u_1^*, u_2^*, u_3^*) *that maximizes* $J(u_1, u_2, u_3)$ *over* Ω *is expressed as:*

$$\begin{aligned}
u_1^*(t) &= max\left\{0, min\left\{\frac{\lambda_1 x^* + \lambda_3 y^*}{S_1}, 1\right\}\right\} \\
u_2^*(t) &= max\left\{0, min\left\{-\frac{\lambda_2 x_1^* + \lambda_4 y_1^* + \lambda_5 v^*}{S_2}, 1\right\}\right\}. \\
u_3^*(t) &= max\left\{0, min\left\{\frac{\lambda_1 x^* + \lambda_3 y^*}{S_1}, 1\right\}\right\}
\end{aligned}$$

Proof. By applying the optimality condition of PMP on the Hamiltonian function H, we obtained:

$$\begin{aligned}\frac{\partial H}{\partial u_1} &= -S_1u_1 + \lambda_1 x + \lambda_3 y\\ \frac{\partial H}{\partial u_2} &= -S_2u_2 - \lambda_2 x_1 - \lambda_4 y_1 - \lambda_5 v\,.\\ \frac{\partial H}{\partial u_3} &= -S_3u_3 + \lambda_1 x + \lambda_3 y\end{aligned}$$

Calculating $\dfrac{\partial H}{\partial u_i} = 0$ for $i = 1, 2, 3$ gives:

$$\begin{aligned}&- S_1u_1 + \lambda_1 x + \lambda_3 y = 0\\ &- S_2u_2 - \lambda_2 x_1 - \lambda_4 y_1 - \lambda_5 v = 0\,.\\ &- S_3u_3 + \lambda_1 x + \lambda_3 y = 0\end{aligned}$$

Simplifying the above result to get

$$\begin{aligned}u_1 &= \frac{\lambda_1 x + \lambda_3 y}{S_1}\\ u_2 &= -\frac{\lambda_2 x_1 + \lambda_4 y_1 + \lambda_5 v}{S_2}\,.\\ u_3 &= \frac{\lambda_1 x + \lambda_3 y}{S_3}\end{aligned} \tag{3.11}$$

The characterization of the optimal control is computed on the set $\{t_f : 0 < u_i^*(t_f) < 1\}$. Thus, by using property of control space, equation (3.11) becomes:

$$u_1^* = \begin{cases} 0,\ if\ \dfrac{\lambda_1 x^* + \lambda_3 y^*}{S_1} \le 0\\ \dfrac{\lambda_1 x^* + \lambda_3 y^*}{S_1}\ if\ 0 < \dfrac{\lambda_1 x^* + \lambda_3 y^*}{S_1} < 1\\ 1\ if\ \dfrac{\lambda_1 x^* + \lambda_3 y^*}{S_1} \ge 1\end{cases} \tag{3.12}$$

$$u_2^* = \begin{cases} 0,\ if\ -\dfrac{\lambda_2 x_1^* + \lambda_4 y_1^* + \lambda_5 v^*}{S_2} \le 0\\ -\dfrac{\lambda_2 x_1^* + \lambda_4 y_1^* + \lambda_5 v^*}{S_2}\ if\ 0 < -\dfrac{\lambda_2 x_1^* + \lambda_4 y_1^* + \lambda_5 v^*}{S_2} < 1\\ 1\ if\ -\dfrac{\lambda_2 x_1^* + \lambda_4 y_1^* + \lambda_5 v^*}{S_2} \ge 1\end{cases} \tag{3.13}$$

$$u_3^* = \begin{cases} 0,\ if\ \dfrac{\lambda_1 x^* + \lambda_3 y^*}{S_3} \le 0\\ \dfrac{\lambda_1 x^* + \lambda_3 y^*}{S_3}\ if\ 0 < \dfrac{\lambda_1 x^* + \lambda_3 y^*}{S_3} < 1\\ 1\ if\ \dfrac{\lambda_1 x^* + \lambda_3 y^*}{S_3} \ge 1\end{cases} \tag{3.14}$$

Equations (3.12), (3.13) and (3.14) can be written in compact form as:

$$u_1^*(t) = max\left\{0, min\left\{\frac{\lambda_1 x^* + \lambda_3 y^*}{S_1}, 1\right\}\right\}$$
$$u_2^*(t) = max\left\{0, min\left\{-\frac{\lambda_2 x_1^* + \lambda_4 y_1^* + \lambda_5 v^*}{S_2}, 1\right\}\right\}$$
$$u_3^*(t) = max\left\{0, min\left\{\frac{\lambda_1 x^* + \lambda_3 y^*}{S_1}, 1\right\}\right\}$$

This complete the proof of the lemma. □

Lemma 3.3. *Suppose $u_1^*(t), u_2^*(t), u_3^*(t)$ are optimal control and x^*, x_1^*, y^*, y_1^*, v^* t are the corresponding solutions of state system (3.9), then there exist adjoint functions $\lambda_i(t)$ for $i = 1, 2, .., 5$ such that*

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= (\lambda_1 - \lambda_2)\beta_1 v^* + \lambda_1(d_1 - \gamma_1 - u_1^* - u_3^*) - A \\
\frac{d\lambda_2}{dt} &= \lambda_2(\mu_1 + d_1 + u_2^*) - \lambda_5 p_1 \\
\frac{d\lambda_3}{dt} &= (\lambda_3 - \lambda_4)\beta_2 v^* + \lambda_3(d_2 - \gamma_2 - u_1^* - u_3^*) - B \qquad , \\
\frac{d\lambda_4}{dt} &= \lambda_4(\mu_1 + d_2 + u_2^*) - \lambda_5 p_2 \\
\frac{d\lambda_5}{dt} &= (\lambda_1 - \lambda_2)\beta_1 x^* + (\lambda_3 - \lambda_4)\beta_2 y^* + \lambda_5(c + \alpha + u_2^*)
\end{aligned}$$

with transversality conditions

$$\lambda_i(t_f) = 0,\ i = 1, 2, 3, 4, 5\,.$$

Proof. By applying adjoint equation criterion of Pontryagin's Maximum Principle (PMP) on the Hamiltonian function, we differentiate the Hamiltonian with respect to each state variables x, x_1, y, y_1, v, to obtain the following system of equations:

$$\begin{aligned}
\frac{\partial H}{\partial x} &= A + \lambda_1(-\beta_1 v - d_1 + \gamma_1 + u_1 + u_3) + \lambda_2\beta_1 v \\
\frac{\partial H}{\partial x_1} &= -\lambda_2(\mu_1 + d_1 + u_2) + \lambda_5 p_1 \\
\frac{\partial H}{\partial y} &= B + \lambda_3(-\beta_2 v - d_2 + \gamma_2 + u_1 + u_3) + \lambda_4\beta_2 v \\
\frac{\partial H}{\partial y_1} &= -\lambda_4(\mu_1 + d_2 + u_2) + \lambda_5 p_2 \\
\frac{\partial H}{\partial v} &= -\lambda_1\beta_1 x + \lambda_2\beta_1 x - \lambda_3\beta_2 y + \lambda_4\beta_2 y - \lambda_5(c + \alpha + u_2)
\end{aligned}$$

As stated by PMP, $\frac{\partial\lambda_1}{\partial t} = -\frac{\partial H}{\partial x}$, $\frac{\partial\lambda_2}{\partial t} = -\frac{\partial H}{\partial x_1}$, $\frac{\partial\lambda_3}{\partial t} = -\frac{\partial H}{\partial y}$, $\frac{\partial\lambda_4}{\partial t} = -\frac{\partial H}{\partial y_1}$, $\frac{\partial\lambda_5}{\partial t} = -\frac{\partial H}{\partial v}$. Substituting these into the above system of equation and simplifying to get (3.9) and (3.10) respectively. This complete the proof of the Lemma 3.3 and hence Theorem 3.2 □

4. NUMERICAL EXAMPLES OF OPTIMAL CONTROL

Quantitative analysis of the optimal control problem was done in this section. The optimal strategy was obtained by solving the thirteen ODEs resulting from the state variables, adjoint equations and co-state equations. The well known Rung-Kutta order four method was used to simulate the effect of the control with time effect. In order to present a numerical result, the parameter in parameter Table 1 together with the initial conditions $x(0) = 500, x_1(0) = 10, y(0) = 500, y_1(0) = 10, v(0) = 10^{-6}$ were used to obtained the graph presented below.

The first five graphs, figures $2 - 6$ depicts the case of applying all the three controls to the model for each state variables. All controlled model were plotted against no control and the figures below were obtained.

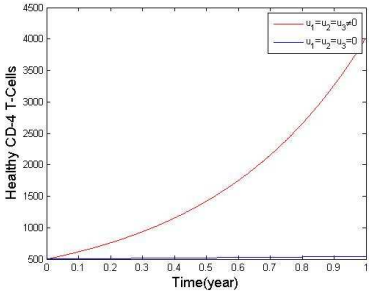

Figure 2: The graph represent the density of the uninfected CD-4 cells with and without control

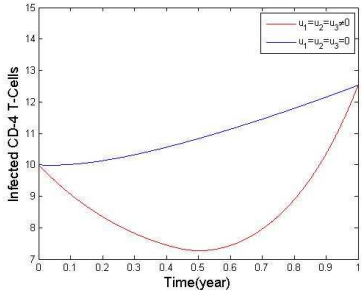

Figure 3: The graph represent the density of the infected CD-4 cells with and without control

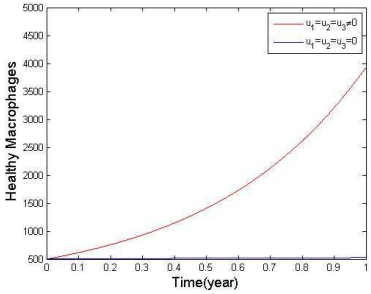

Figure 4: The graph represent the density of the uninfected Macrophages cells with and without control

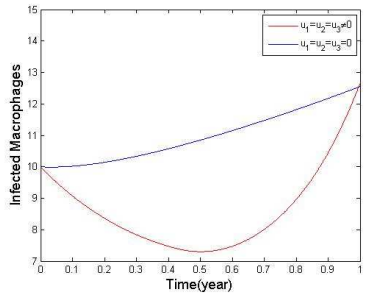

Figure 5: The graph represent the density of the infected Macrophages cells with and without control

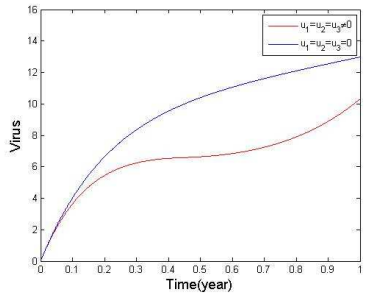

Figure 6: The graph represent the density of the Virus cells with and without control

The figures $7-11$ represents the effect of using only one control (u_1) on the model as against no control. The figure depicts the effectiveness of HAART in shielding the immune systems from being infected thereby helping the body system to maintain constant production of defense cells. This explained the reason why people that started the therapy early tend to leave a longer healthy life despite the infection.

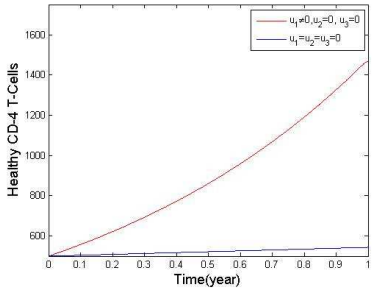

Figure 7: The graph represent the density of the uninfected CD-4 cells with one control Strategy u_1 and without control

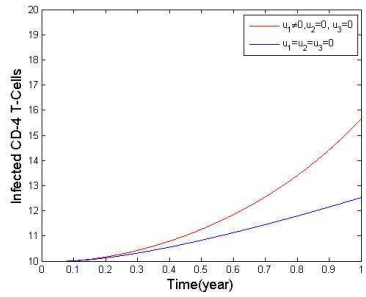

Figure 8: The graph represent the density of the infected CD-4 cells with one control Strategy u_1 and without control

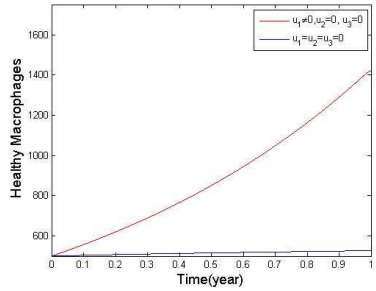

Figure 9: The graph represent the density of the uninfected Macrophages cells with one control Strategy u_1 and without control

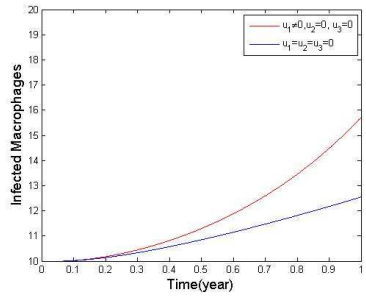

Figure 10: The graph represent the density of the infected Macrophages cells with one control Strategy u_1 and without control

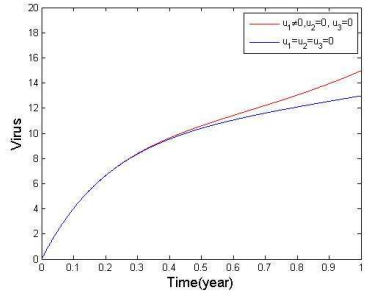

Figure 11: The graph represent the density of the Virus cells with one control Strategy u_1 and without control

The figures $12-16$ represent the profile of using two controls (u_1, u_2) to established their effects on the model system. It was observed that two controls performed better with compartments x_1, y_1 and v_1. Its impact on the other two compartments is small compared with those three. This is in agreement as to the fact that reducing the infected/infectious defense cells reduce the viral burden and hence lower the viral count.

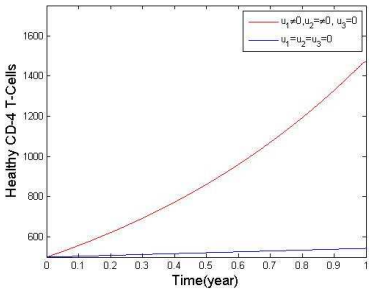

Figure 12: The graph represent the density of the uninfected CD-4 cells with two control Strategies $u_1 \& u_2$ and without control

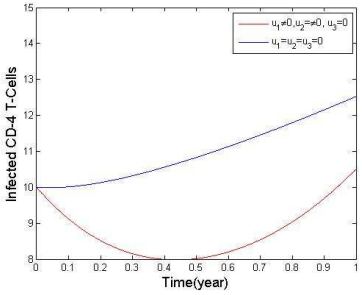

Figure 13: The graph represent the density of the infected CD-4 cells with two control Strategies $u_1 \& u_2$ and without control

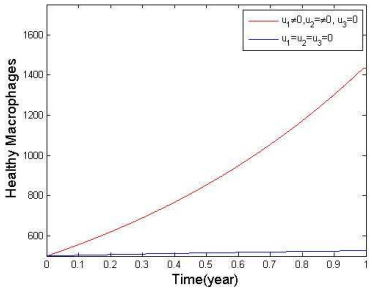

Figure 14: The graph represent the density of the uninfected Macrophages cells with two control Strategies $u_1 \& u_2$ and without control

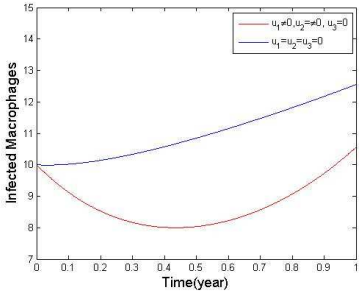

Figure 15: The graph represent the density of the infected Macrophages cells with two control Strategies $u_1 \& u_2$ and without control

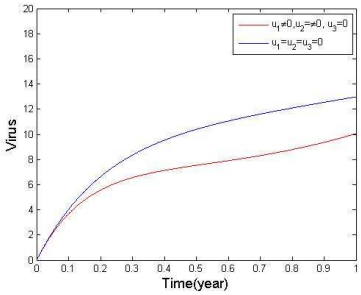

Figure 16: The graph represent the density of the Virus cells with two control Strategies $u_1 \& u_2$ and without control

5. CONCLUSION

Based on the outcome of both the qualitative and optimal control analysis of the extended model, the result showcased the efficacy of Highly Active Anti-Retrovirus Therapy (HAART) in helping the immune systems (which include but not limited to CD4-cells and Macrophages) to fight off the multiplicative effect of the virus. It was observed from the analysis of the effective reproduction number of the model that the higher the effectiveness of HAART in cleaning the system of the virus, the lower the reproduction number. Thus, clearance rate $'c'$ of the virus from the immune system is a highly sensitive parameter that must be increased if we want to take a shot at eradication of HIV infection. Also from the result obtained, the effectiveness of HAART in boosting the production rate of more immune system (CD4 cells and Macrophages) resulted in a prolong healthier life of the infected provided that the infected also maintain a good healthy habit. It was observed from the optimal control analysis that good dietary attitude coupled with cleansing power of HAART can reduce the viral burden to an infinitesimally small amount.

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