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THERAPEUTIC RESPONSE OF OPTIMIZED THERMODYNAMIC CONTROL MODEL IN HIV DYNAMICS

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Abstract: **In a continued quest to permanently have a cure to HIV infection, a thermodynamic optimized control infectivity model was introduced in an adopted basic viral dynamics model. The ensued model, an Ordinary Differential Equation (ODE) was solved at two instances. First under the condition of uninfected cell (CD4+) proliferation with saturation response and secondly when there was no uninfected cell (CD4+) proliferation and saturation response with each having two series of controlled and uncontrolled dynamics. The Ordinary Differential Equation (ODE) solution method was a numerical integration that utilized explicit Runge-Kutta method in MATLAB™ function ode 23. Historical drug parameters for the model were introduced to the model for simulation of the infection dynamics from day 20 to 300 for cure. The infection time course showed that in the first instant for the controlled brown series, both infected cell count (y) and viral load (v) were forced to die out and converge to equilibrium of 0 $\left(cells/_{\mu L}\right)$ and 0 $\left(copies/_{mL}\right)$ respectively, at about five (5) days after introduction of the drug control parameters that is about the twenty fifth (25th) day of infection. The uninfected cell converges to equilibrium average supply rate from thymus and taking cognizance of proliferation to about 1200($cells\mu L^{-1}$) at about thirtieth (35th) day after introduction of control that is about the fifty fifth (55th) day of infection. The uncontrolled blue series progressed as expected. In the second instant for the controlled green series, both infected cell count (y) and viral load (v) were again forced to die out and converge to equilibrium of 0 $\left(cells/_{\mu L}\right)$ and 0 $\left(copies/_{mL}\right)$ respectively, at about five (5) days after introduction of the optimized control drug parameters that is about the twenty fifth (25th) day of infection. The uninfected cell converges to equilibrium average supply rate from thymus to have $\lambda/\delta\left(cells/_{\mu L}\right)$, 1000($cells\mu L^{-1}$) at about thirtieth (35th) day after introduction of control that is about the fifty fifth (55th) day of infection hence validating the model. The uncontrolled red series progressed as expected. This explains recovery and making up of the depreciated uninfected cell count. Combined front of interfacial energetic approach of Hamaker coefficient and spectrophotometric approach have proved effective at optimized condition in the fight against HIV. Clinical management as well as the pharmaceutical industries should adopt the method for a clinical extinction of the disease.**

Keywords: **Human immunodeficiency virus, Interfacial energetics, Control Infectivity, Absorbance, Hamaker coefficient.**

1. INTRODUCTION

Although the burden of the epidemic continues to vary considerably between countries and regions an estimated 0.6% (0.6-0.7%) of adults aged 15-49 years worldwide are living with HIV. Again, 39.9 million (36.1-44.6) people were living with HIV at the end of 2023 (WHO, 2024). UNAIDS, (2013) documented that the solutions for the global increasing rate of Human Immunodeficiency Virus **(**HIV) infection are continuously being sought for, for its elimination. 88. 4 million (71-3-112.8million) people have been infected with the HIV virus and about 42.3 million (35.7-51.1) million people have died of HIV since the beginning of the epidemic (WHO, 2024).

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Clinical solution to the problem of HIV is hampered by the rapid genetic mutation of HIV. About ten billion new viral particles of HIV can be generated daily, in chronic cases (Omenyi, 2005). Variability in response to therapy has made some individuals experience virologic failure on therapy that is highly effective on others. Under the use of Highly Active Anti Retroviral Therapy (HAART), transient rebounds of plasma viremia have also remained a problem (Jeffry, 2006). Most viral diseases have the ability to develop resistance. Ronsard *et al.*, in (Santoro & Perno, 2013), noted that a rate-limiting factor in the management of HIV infections, is the plethora of genetic variations in infectivity leading to failure of clinical trials. HIV, as one of the most intensively studied viral infections, now has massive drug development efforts starting soon after identification of the virus with twenty seven (27) different antiretroviral drugs (Hill, Rosenbloom, Nowark, & Siliciano, 2018), capable of halting viral replication and preventing transmission and progression to AIDS but still without a cure. Virus infectivity in HIV infection is observed to vary (Ganusov, Neher & Perelson, 2012).

Ilo, (2024a) had developed a validated model through concepts of thermodynamics implementation to unravel the mystery of transcriptional bifurcation in HIV dynamics. Ilo, (2024b) had also established HIV adhesion driven infectivity through electrostatics interaction mechanism. Ilo, (2022) through thermodynamics spectrophotometry gave an insight control infectivity in HIV dynamics. Ani, (2015) through the study of interfacial energetics been established that the lymphocyte is the target of the virus. Ilo, Omenyi, and Dim, (2021a) had applied thermodynamics in the dynamics of HIV. Ilo, Omenyi and Ani, (2021b) had quantified drug primary mechanism of action through thermodynamics Hamaker concept. Thermodynamic optimization of HIV drugs in this study, drove its impetus from all these successes recorded in the thermodynamic approach to HIV infection analysis.

2. PREVIOUS WORK/LITERATURE SURVEY

Control model of HIV dynamics

Costanza *et al.* cited in Rivadeneira, *et al.*, (2014) showed a control aggregate parameter which is a function of drug amount gave aggregate control parameter β_C, under therapy as

$$\beta_C = (\beta_0 - \beta_1 u - \beta_2 u^2) \quad (1)$$

β_0 is probability of infection, the second term is the drug primary (dominant) mechanism of action term while the third term is the drug secondary mechanism of action term with β_2 being identified as a function of β_1. β_1 drug primary mechanism of action parameter and has value greater than one, β_2 is drug secondary mechanism of action parameter and has maximum value of one, u represent drug amount.

Bonhoeffer, *et al.*, (1997), also proposed a basic model of viral dynamics at therapeutic condition as equation (2) which come from their HIV immunological analysis rooted on the fact that uninfected target cells and free virus experience mass action with some probability β_0 for infection to be established. This is according to a simple mass action term, that is $\beta_0 xv$ which generates infected cells, y, that are lost at rate, a, larger than d to reflect viral effects in shortening the infected cell lifespan and free viruses are produced by infected cells at constant rate $k$per cell and cleared from circulation at rate u per virus.

$$\begin{aligned} \dot{x} &= \lambda - dx - (1-\eta)\beta_0 xv \\ \dot{y} &= (1-\eta)\beta_0 xv - ay, \\ \dot{v} &= ky - uv. \end{aligned} \quad (2)$$

Where x is susceptible cells, y is infected cells, v is virus particle, λ is rate of production of susceptible cells, d is death rate of susceptible cells, β_0 probability of infection, a is death rate of infected cells, k is rate of virus production, u is clearance rate of virus particles and η is drug response.

In the quest for infection control the above model is a fall out of their model equation (3) and that of so many notable researchers which is a representation of the disease immunology.

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta xv, \\ \dot{y} &= \beta xv - ay, \\ \dot{v} &= ky - uv. \end{aligned} \quad (3)$$

A solution of model (3) was provided by (Pantaleo, Graziosi and Fauci, 1993) where three (3) main stages, namely the acute HIV infection (primary infection), asymptomatic and the advanced – aids are clearly shown in a typical HIV infection course of figure 1.

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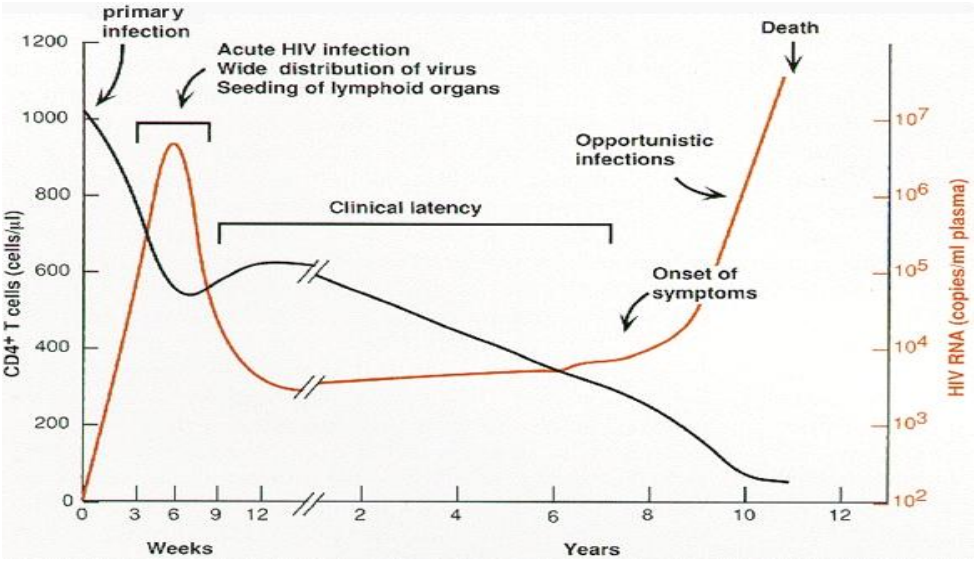

Figure 1: Approximate Time-Course of HIV Infection. (Pantaleo, Graziosi and Fauci, 1993)

When infection is not yet established, normal $CD4^+$ T cell counts range from five hundred (500) to one thousand six hundred (1600) cells per cubic micro litre, on the average (1000) cells per cubic micro litre and drops to less than hundred (500) cells per μL (cells mm^{-3}) if infection is fully established.

Materials in interaction peak absorbance surface effects

Peak absorbance in particles involved in HIV infection were analyzed by (Ani, 2015). He came up that if blood component surface is completely covered or coated by the drug film, $\tilde{a}_d = \tilde{a}_{bd}$ meaning one hundred percent efficacy. He also concluded that when coating is not complete, $(\tilde{a}_{bd} - \tilde{a}_b)$ is less than $(\tilde{a}_d - \tilde{a}_b)$ as also experienced when $\tilde{a}_{bd} = \tilde{a}_b$. Where is $\tilde{a}_d$ peak absorbance for drug film only, $\tilde{a}_b$ is peak absorbance for blood component only and $\tilde{a}_{bd}$ is peak absorbance for drug film coated given blood component.

Coefficient of adhesion

Ilo, (2022) had come with adhesion coefficient β_{0T}, a thermodynamic expression for HIV infectivity,

$$\beta_{0T} = \varepsilon\left(\frac{\psi(\gamma_{PS})}{\gamma_{PL}+\gamma_{SL}}\right) \quad (4)$$

Where γ_{SL}, γ_{PL} and γ_{PS} are interfacial energetics between susceptible cell and serum, virus and serum and virus and susceptible cell respectively, ψ static dynamic factor, ε the genetic factor.

3. METHODOLOGY

Aggregate control adhesion parameter model had been thermodynamically optimized using linear optimization technique by (Ilo, 2022). The model is introduced in an adopted basic viral dynamics model and the ensued model an Ordinary Differential Equation (ODE) was solved at the first instance of two series: brown for therapy and blue for untreated both for condition of uninfected cell (CD4+) proliferation and saturation response while at the second instance also of two series: green for therapy and red for untreated there was no uninfected cell (CD4+) proliferation and saturation response. The solution approach of the Ordinary Differential Equation (ODE) was numerical integration that utilized explicit Runge-Kutta method in MATLAB™ function ode 23. Imported historical drug parameters were introduced from day twenty to day three hundred at both the first and second instances to actually showcase that the optimized model was capable of curing permanently the HIV infection by primarily forcing down the viral load to $0(copies mL^{-1})$, infected cell count to $0(cells\mu L^{-1})$ and same time optimizing the uninfected cell (CD4+) count to thymus average supply rate of $1000(cells\mu L^{-1})$ for model 5 and $1200(cells\mu L^{-1})$ for model 6, when proliferation and saturation of uninfected cell (CD4+) are experienced. The control model was tested on a worst-case scenario where the infection is maximally ravaging the patient with the maximum genetic factor. The imported drug parameters were introduced from day 20 to day 300 for the two scenario that is a situation of both uninfected cell (CD4+) proliferation and saturation response and no uninfected cell (CD4+) proliferation and saturation response to showcase therapeutic effects of the optimized model for disease extinction.

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Thermodynamics optimized control model of HIV dynamics

Optimized model equation (5) incorporating uninfected cell (CD4+) proliferation and saturation response had been proposed by (Ilo, 2022) to extinct the HIV infection.

$$\dot{x} = \lambda - dx + rx\left(1 - \frac{x}{x_{max}}\right) - \left(\varepsilon\left(\frac{\psi(\gamma_{PS})}{\gamma_{PL}+\gamma_{SL}}\right) - \left(\frac{(A_{PL}+A_{SL})}{(A_{PS}+A_{LL})} \Big/ \left(\frac{\tilde{a}_{bd}-\tilde{a}_b}{\tilde{a}_d-\tilde{a}_b}\right)\right)\omega - \beta_{2T(100\%\eta_a)}\omega^2\right)\frac{xv}{1+\alpha v},$$

$$\dot{y} = \left(\varepsilon\left(\frac{\psi(\gamma_{PS})}{\gamma_{PL}+\gamma_{SL}}\right) - \left(\frac{(A_{PL}+A_{SL})}{(A_{PS}+A_{LL})} \Big/ \left(\frac{\tilde{a}_{bd}-\tilde{a}_b}{\tilde{a}_d-\tilde{a}_b}\right)\right)\omega - \beta_{2T(100\%\eta_a)}\omega^2\right)\frac{xv}{1+\alpha v} - ay,$$

$$\dot{v} = ky - uv. \qquad (5)$$

But, when there was no uninfected cell (CD4+) proliferation and saturation response, the model reduced to equation (6),

$$\dot{x} = \lambda - dx - \left(\varepsilon\left(\frac{\psi(\gamma_{PS})}{\gamma_{PL}+\gamma_{SL}}\right) - \left(\frac{(A_{PL}+A_{SL})}{(A_{PS}+A_{LL})} \Big/ \left(\frac{\tilde{a}_{bd}-\tilde{a}_b}{\tilde{a}_d-\tilde{a}_b}\right)\right)\omega - \beta_{2T(100\%\eta_a)}\omega^2\right)xv,$$

$$\dot{y} = \left(\varepsilon\left(\frac{\psi(\gamma_{PS})}{\gamma_{PL}+\gamma_{SL}}\right) - \left(\frac{(A_{PL}+A_{SL})}{(A_{PS}+A_{LL})} \Big/ \left(\frac{\tilde{a}_{bd}-\tilde{a}_b}{\tilde{a}_d-\tilde{a}_b}\right)\right)\omega - \beta_{2T(100\%\eta_a)}\omega^2\right)xv - ay,$$

$$\dot{v} = ky - uv. \qquad (6)$$

Where $\tilde{a}_d$ is peak absorbance for drug film only, $\tilde{a}_b$ is peak absorbance for blood component only, $\tilde{a}_{bd}$ is peak absorbance for drug film coated given blood component, ω is amount of drug, x_{max} is the population density at which proliferation cuts off, $\beta_{2T(100\%\eta_a)}$is secondary drug mechanism of action parameter at hundred percent efficiency, r is maximum proliferation factor, α is the saturation response, A_{PS} is hamaker constant for both particles of virus (p) and lymphocyte (s), A_{LL} is hamaker constant for serum (plasma) (L), A_{PL} is hamaker constant for both particles of virus (p) and serum (L) and A_{SL} is hamaker constant for both particles of lymphocyte (s) and serum (L).

4. RESULTS AND DISCUSSIONS

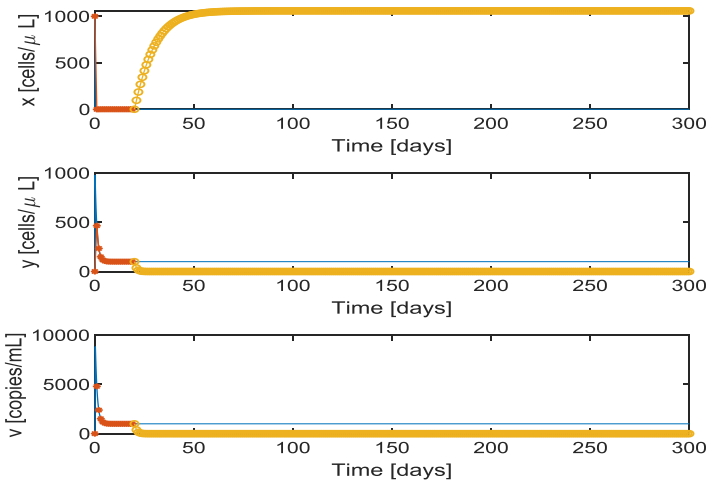

Fig 1: Simulation with optimized drug parameters with uninfected cell (CD4+) proliferation and saturation response.

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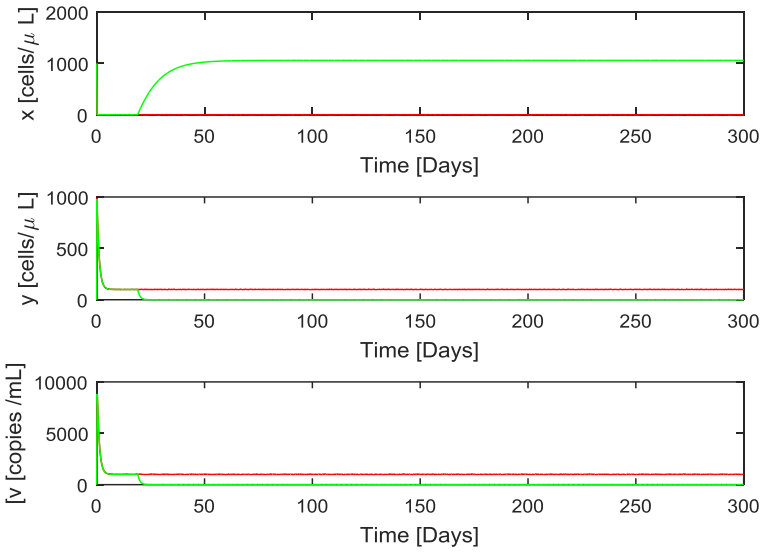

Fig 2: Simulation with optimized drug parameters without uninfected cell (CD4+) proliferation and saturation response.

Upon the introduction of the optimized drug parameters, dynamics of each plot for every series comprised subplot of uninfected cell (CD4+) count (x) ($cells\mu L^{-1}$), infected cell count (y) ($cells\mu L^{-1}$) and Viral load (v) ($copiesmL^{-1}$) infection time-course. Figure 2 and 3 show actually that the optimized thermodynamics control model changed disease dynamics to extinctive. Dynamics of figure 2 revealed disease extinctive ability of the model (3) which has uninfected cell (CD4+) proliferation and saturation response. Figure 2 shows two series blue and brown both of worst case scenario, of each sub-plot, that is uninfected cell (CD4+) count (x) ($cells\mu L^{-1}$), infected cell count (y) ($cells\mu L^{-1}$) and viral load (v) ($copiesmL^{-1}$) infection time-course of dynamics equation (3) for 300 days. Series blue was uncontrolled for all the 300 days with ω value set to zero (0) amount of drug for the three hundred days. Series brown was initially uncontrolled with value for ω set to zero (0) from day 0 to day 19, but controlled with optimized drug parameter introduction from day 20 to 300. Both infected cell count (y) and viral load (v) were forced to die out and converge to equilibrium of 0 $\left({}^{cells}/_{\mu L}\right)$ and 0 $\left({}^{copies}/_{mL}\right)$ respectively, at about five (5) days after introduction of the optimized control drug parameters that is about the twenty fifth (25th) day of infection. The uninfected cell converges to equilibrium average supply rate from thymus and taking cognizance of proliferation to about 1200($cells\mu L^{-1}$) at about thirtieth (35th) day after introduction of control that is about the fifty fifth (55th) day of infection. This explains recovery and making up of the depreciated uninfected cell count. The blue series progressed as expected without control.

In the second instance, model (6) also showed a similar dynamic in figure (3) except that uninfected cell (CD4+) proliferation and saturation response were not observed. Both infected cell count (y) and viral load (v) were forced to die out and converge to equilibrium of 0 $\left({}^{cells}/_{\mu L}\right)$ and 0 $\left({}^{copies}/_{mL}\right)$ respectively, at about five (5) days after introduction of the optimized control drug parameters that is about the twenty fifth (25th) day of infection. The uninfected cell converges to equilibrium average supply rate from thymus to about $\lambda/\delta\left({}^{cells}/_{\mu L}\right)$, 1000($cells\mu L^{-1}$) at about thirtieth (35th) day after introduction of control that is about the fifty fifth (55th) day of infection. This also explains recovery and making up of the depreciated uninfected cell count. The red series progressed as expected without control.

Interfacial energetic approach of Hamaker coefficient and spectrophotometric approach have proved effective at optimized condition in the fight against HIV. Clinical management as well as the pharmaceutical industries should adopt the method for a clinical extinction of the disease.

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