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CLINICAL IMPLICATIONS OF DRUG THERMODYNAMIC CONTROL IN HIV DYNAMICS

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Abstract: **To solve continued HIV menace proposed thermodynamics HIV control model which is an Ordinary Differential Equation (ODE) was solved with imported historical experimental data for: green series D1 representing Lamivudine, Nevirapine & Zidovudine combination therapy; blue series D2 representing Tenofovir, Lamivudine & Efavirenz combination therapy; mauve series D3 representing Nevirapine single therapy, and non-therapeutic red series representing when $\tilde{a}_{bd} = \tilde{a}_b$ to distinguish untreated infection dynamics from the treated. The solution method is numerical integration that utilized explicit Runge-Kutta method in MATLAB™ function ode 23. Imported historical drug parameters were introduced from day twenty to both day three hundred in the first instance and to day ninety int the second instance to reveal if the dynamics generated by the thermodynamics expressed model is in accordance with what obtains in clinical experience of the utilized drugs parameters with reference to comparison between combination therapy and single therapy drugs. Results show actually that the thermodynamics control model is capable of changing the disease dynamics. Dynamics of each plot for every series which comprised subplot of uninfected cell (CD4+) count (x) ($cells\mu L^{-1}$), infected cell count (y) ($cells\mu L^{-1}$) and Viral load (v) ($copies mL^{-1}$) infection time-course responded accordingly. The solution at drug intervention from the plot shows that green series D1 representing Lamivudine, Nevirapine & Zidovudine combination therapy had the best response to therapy achieving over 900 ($cells\mu L^{-1}$), this is closely followed by blue series D2 representing Tenofovir, Lamivudine & Efavirenz combination therapy and finally mauve series D3 representing Nevirapine single therapy that attained 500 ($cells\mu L^{-1}$). These are in line with both clinical experience where Lamivudine, Nevirapine & Zidovudine combination therapy had best efficacy as reported in the literature. Out of the trio mauve series D3 representing Nevirapine single therapy has also the least performance. Recall that D3 is not a combination therapy hence quite reasonable for the least performance. Results show that actually combination therapy had a higher response than the single therapy. The result is acutely validated by clinical experience from historical data. The red series represented when $\tilde{a}_{bd} = \tilde{a}_b$, a situation of untreated infection. It shows a demarcation indicating that all controlled series for uninfected cells have higher values of uninfected cell (CD4+) count (x) ($cells\mu L^{-1}$) as well as lower values of both infected cell count (y) ($cells\mu L^{-1}$) and viral load (v) ($copies mL^{-1}$). These are expected and are quite evident in the simulated infection time course. The spectroscopic technique yielded a clue to surface properties of the interaction with drug and application of this study in pharmaceutical industries, in the area of drug design and in clinical studies cannot be overemphasized.**

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

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1. INTRODUCTION

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. 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 (WHO, 2024). 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. Again, 39.9 million (36.1-44.6) people were living with HIV at the end of 2023 (WHO, 2024).

Spectroscopic techniques yield a variety of surface properties of materials that are situated anywhere between 1.0 and more than 10 nm of their surfaces (Etzler, 2001). Brady, (1996) noted a wealth of spectroscopic and other analytical techniques for probing the surface properties of solid materials. Giese and van Oss (2002) reported that contact angle technique has been reported as being capable of yielding the actual surface or interfacial properties at the precise surfaces of solids that are relevant to their interaction with other condensed phase materials. Dzyaloshinskii, Lifshiftz, and Pitaevskii, (1961) had proposed Lifshiftz theory which relates energy of an interacting system with Hamaker coefficients based on their appropriate spectrophotometric data. Good, (1979) noted that the term surface energy is used because a change in the surface area of a solid cannot be accomplished without doing work against the elastic forces and plastic resistance of the solid.

It has not been easy to identify the actual mechanism of virus and blood interaction parameters within the existing mathematical models. This is also as a result of unavailability of experimental data on HIV/blood interactions. The impetus to unravel interfacial energetics and genetics in HIV discordant couples is rooted on the following successes in HIV through thermodynamics. 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. Ilo, (2024a) had developed a validated model through concepts of thermodynamics implementation to unravel the mystery of transcriptional bifurcation in HIV dynamics. Recall also Ilo, (2024b) had also established HIV adhesion driven infectivity through electrostatics interaction mechanism. In this paper, dynamics of thermodynamic control infectivity sought through thermodynamic spectrophotometric absorbance of both drugs and susceptible cells were compared with the clinical experience of some selected HIV drugs.

2. PREVIOUS WORK/LITERATURE SURVEY

Historical Viral Dynamics

Healthy cells are infected by the virus at a rate that is proportional to the product of their population size and the amount of free virus particles in HIV infection, (Bonhoeffer, May, Shaw, and Nowak, 1997). This rate constant is an indication of the effectiveness of the infection process, (Hill, Rosenbloom, Nowark, and Siliciano, 2018). In the virus life cycle (replication cycle), a stage without which the HIV life cycle would be cut short is the first stage, the binding (attachment) stage. The viral particle is attracted to a cell (lymphocyte) with the appropriate CD4 receptor molecules where it attaches (binds) and by fusion to a susceptible cell membrane or by endocytosis (an energy using up process) and then enters the cell during entry to the body. With these reasonings researchers, notably Bonhoeffer, *et al.*, (1997), proposed a basic model of viral dynamics as:

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

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 is infectivity (interaction parameter), a is death rate of infected cells, k is rate of virus production and u is clearance rate of virus particles.

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Three (3) main stages, namely the acute HIV infection (primary infection), asymptomatic and the advanced – aids as clearly shown in a typical HIV infection course Fig. 1 have been identified in HIV infection dynamics.

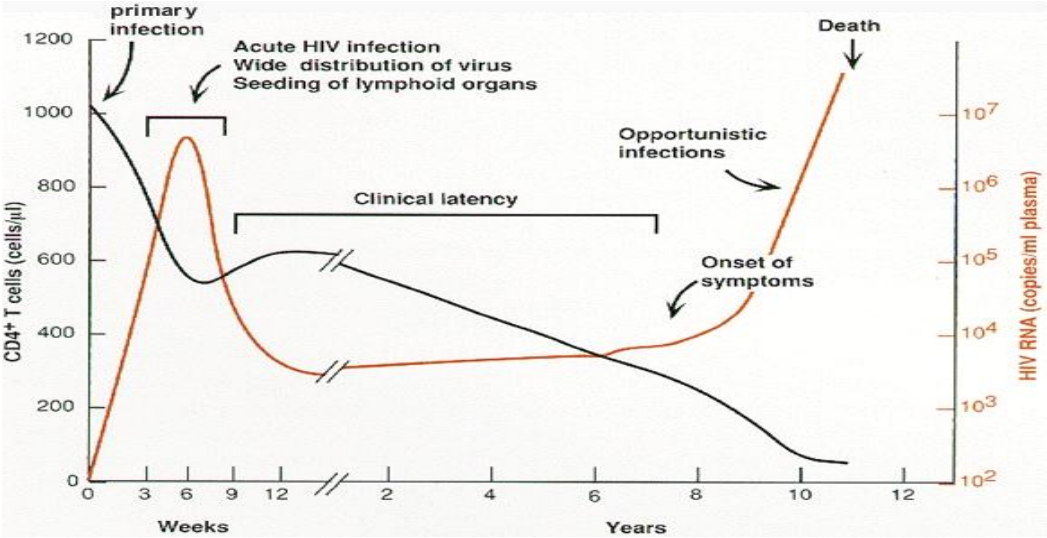

Figure 1: Approximate Time-Course of HIV Infection. (Pantaleo, Graziosi and Fauci, 1993)

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.

Therapeutic model of HIV dynamics

Bonhoeffer, *et al.*, (1997), also proposed a basic model of viral dynamics at therapeutic condition as equation (2).

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

η is drug (response) efficiency and β_0 is the interaction parameter.

Absorbance values of drugs and blood samples in HIV dynamics

Ani, (2015) analyzed absorbance parameters of the interaction between HIV particles, susceptible cell and the drugs as $\tilde{a}_d$ peak absorbance for drug film only, $\tilde{a}_b$ peak absorbance for blood component only and $\tilde{a}_{bd}$ peak absorbance for drug film coated given blood component and came up that if the blood component surface is completely covered or coated/blocked by the drug film which is desirable, $\tilde{a}_{bd} = \tilde{a}_d$ and one would in principle expect 100% effective drug. When coating is not complete, $(\tilde{a}_d - \tilde{a}_b)$ will be greater than $(\tilde{a}_{bd} - \tilde{a}_b)$ likewise when there is no coating at all, $\tilde{a}_{bd} = \tilde{a}_b$.

3. METHODOLOGY

Proposed thermodynamics HIV control model which is an Ordinary Differential Equation (ODE) was solved with imported historical experimental data for: green series D1 representing Lamivudine, Nevirapine & Zidovudine combination therapy; blue series D2 representing Tenofovir, Lamivudine & Efavirenz combination therapy; mauve series D3 representing Nevirapine single therapy, and non-therapeutic red series representing when $\tilde{a}_{bd} = \tilde{a}_b$ to x-ray situation of untreated infection. The solution method is numerical integration that utilized explicit Runge-Kutta method in MATLAB™ function ode 23. Imported historical drug parameters were introduced from day twenty to both day three hundred and day ninety to reveal if the dynamics generated by the thermodynamics expressed model is in accordance with what obtains in clinical experience of the utilized drugs parameters with reference to combination therapy and single therapy.

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HIV dynamics thermodynamics control model

(Ilo, 2022), to utilize spectroscopic technique had proposed thermodynamic model (3).

$$\dot{x} = \lambda - dx - \beta_0 xv + \beta_0 \left(\frac{\tilde{a}_{bd} - \tilde{a}_b}{\tilde{a}_d - \tilde{a}_b}\right) xv,$$

$$\dot{y} = \beta_0 xv - \beta_0 \left(\frac{\tilde{a}_{bd} - \tilde{a}_b}{\tilde{a}_d - \tilde{a}_b}\right) xv - ay,$$

$$\dot{v} = ky - uv. \qquad (3)$$

Where β_0 is the mass action parameter $\tilde{a}_d$ 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 and ω is amount of drug.

4. RESULTS AND DISCUSSIONS

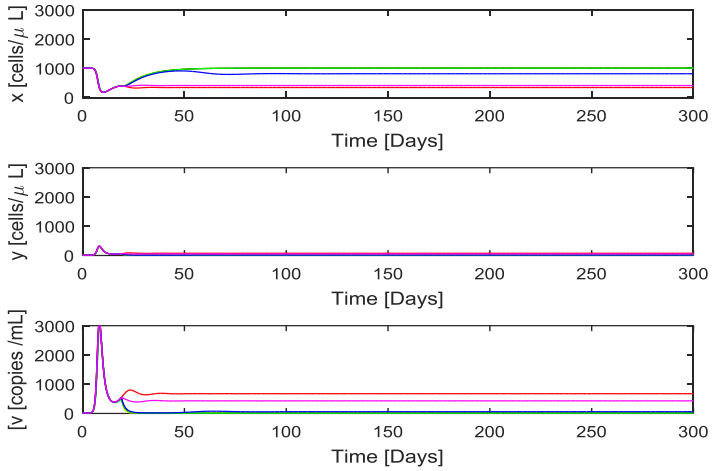

Fig 1: Simulation with D1, D2 and D3 from day twenty to day three hundred.

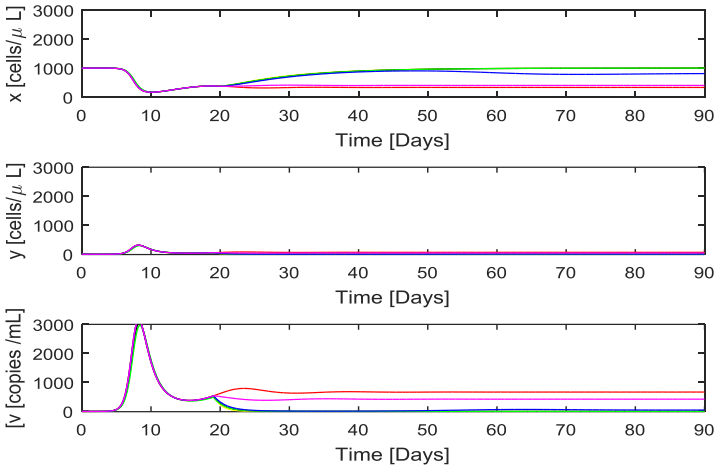

Fig 2: Simulation with D1, D2 and D3 from day twenty to day ninety.

Figure 2 and 3 show actually the thermodynamics control model is capable of changing the disease dynamics. 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. The solution at drug intervention from the plot shows that green series D1 representing Lamivudine, Nevirapine & Zidovudine combination therapy had the best response to therapy achieving over 900 ($cells\mu L^{-1}$), this is closely followed by blue series D2 representing Tenofovir, Lamivudine &

Efavirenz combination therapy and finally mauve series D3 representing Nevirapine single therapy that attained 500 ($cells\mu L^{-1}$). These are in line with both clinical experience where Lamivudine, Nevirapine & Zidovudine combination therapy had best efficacy as reported. Out of the trio mauve series D3 representing Nevirapine single therapy has also the least performance. Recall that D3 is not a combination therapy hence quite reasonable the least performance. Results show that actually combination therapy had a higher response than the single therapy. The result is acutely validated by clinical experience. The red series represented when $\tilde{a}_{bd} = \tilde{a}_b$, a situation of normal untreated infection. It shows a demarcation indicating that all controlled series for uninfected cells have higher values of uninfected cell (CD4+) count (x) ($cells\mu L^{-1}$) as well as lower values of both infected cell count (y) ($cells\mu L^{-1}$) and viral load (v) ($copies mL^{-1}$). These are expected and are quite evident in figures 2 and 3.

Spectroscopic techniques yield a clue to surface properties of the drug and application of this study in pharmaceutical industries, in the area of drug design and in clinical studies cannot be overemphasized.

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