

# Modelling the Long-term HIV Immune Viral Dynamics and Medical Treatment of HIV Infection

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## ABSTRACT

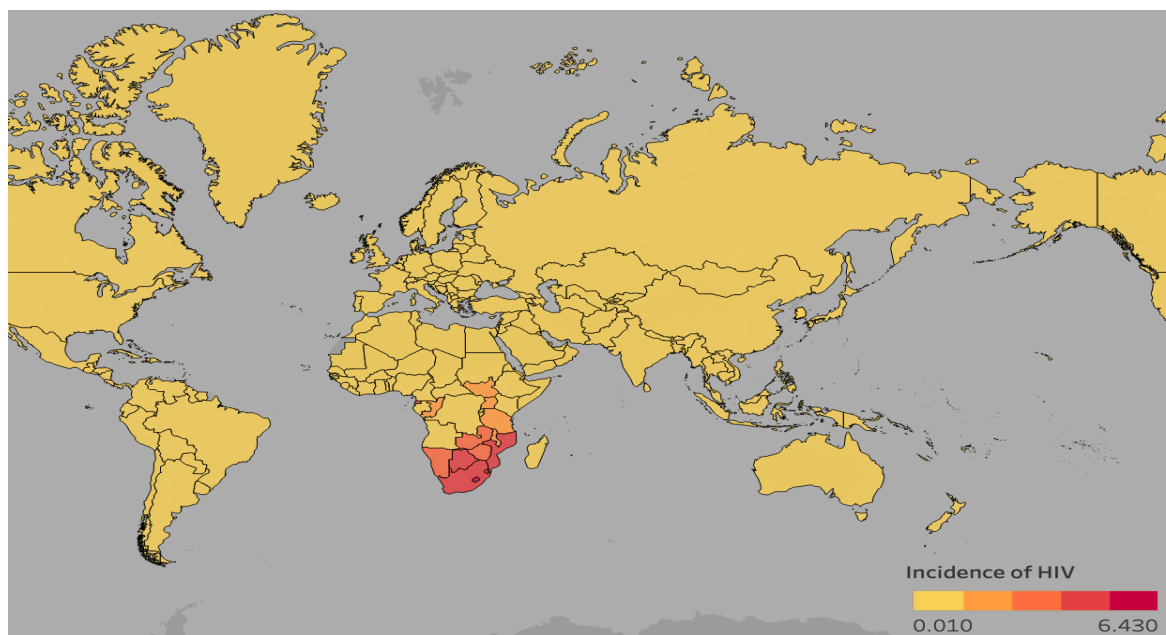
*This biomedical work centers on applying system dynamics methodology to studying the long-term HIV immune viral dynamics in terms of feedback theory. The objective is to enhance understanding of the typical development path from HIV to AIDS as well as to explore various outcomes owing to varied ART adherence in real setting. Moreover, it is projected to nudge HIV patients better to adhere to ART through an interactive learning environment built upon the underlying system dynamics model. It is found that the underlying model structure is capable of reproducing the general patterns of human immune system failure and HIV viral explosion by synthesizing existing clinical evidence and by calibrating model parameters. In addition, model analysis indicates that three decomposed dynamics of immune cells and HIV virus over the whole infecting cycle can be interpreted from the perspective of loop dominance – interactions between positive and negative loops. Although there is no cure for HIV/AIDS infection at present, high adherence to ART can suppress HIV virus successfully for a long period as has been validated in policy scenario analysis. In combination with real-world evidence, this modelling work echoes and highlights the importance of ART adherence in real environment. In order to cope with challenges caused by HIV epidemic in the future, it is recommended that public health policymakers should implement effective strategies to stimulate ART adoption and promote adherence to ART treatment among HIV patients.*

## KEYWORDS

*Biomedical model, HIV virus, ART treatment, System dynamics.*

## 1. INTRODUCTION

HIV/AIDS is one of the major global public health issues that we face today. It is estimated that there were 37.7 million (95% confidence interval: 30.2–45.1 million) people living with HIV at the end of 2020 (WHO, 2021), most of whom are in the African regions, as illustrated in Figure 1. Given the context of current Covid-19 pandemic, HIV epidemic in Africa may get even worse (UNAIDS, 2021c) owing to disturbed health care system and medicine supply chain. If not treated on time, HIV patients will gradually move towards acquired immunodeficiency syndrome (AIDS) and die with a variety of opportunistic infections or cancers. Although medicine is progressing fast, there is still no cure for HIV infection at present. The best practice for HIV treatment is called antiretroviral therapy (ART), which involves taking a combination of antiretroviral drugs daily. Therefore, adherence to ART plays a key role to manage HIV virus load and to make HIV patients live well in reality (Kim et al., 2018).



**Figure 1: Incidence of HIV per 1,000 uninfected population in 2019**

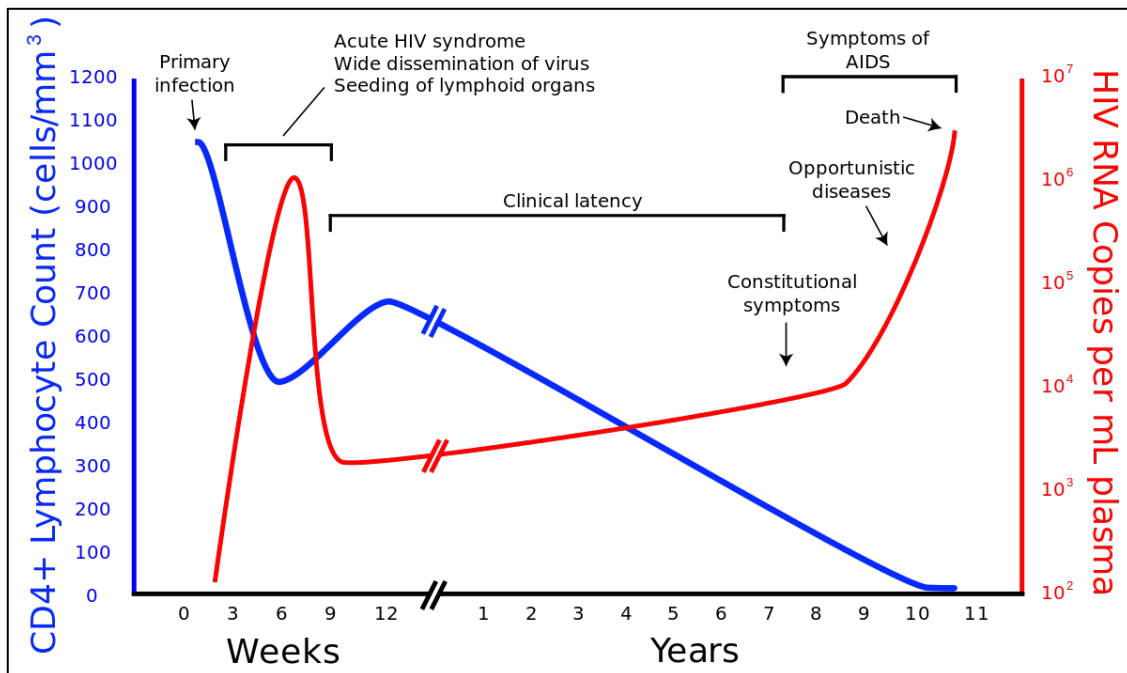
Because of complex interactions between individuals, healthcare facilities, and society in health-related issues, system dynamics (SD) has been broadly adopted in the fields of healthcare and medicine (Darabi & Hosseinichimeh, 2020; Davahli et al., 2020). With respect to HIV/AIDS epidemic, many SD works focused on modelling how HIV virus spread between individuals within a population (e.g., Dangerfield & Roberts, 1989; Lounsbury et al., 2015; Morgan et al., 2020; Sterman, 2000, ch. 9). Most of these so-called “between-host” models are based on the classic SIR or SEIR epidemiological model structure, as has been widely used to model the Covid-19 pandemic (Ghaffarzadegan & Rahmandad, 2020; Rahmandad et al., 2021; Struben, 2020). By contrast, “within-host” or broadly named “biophysical” models (Sajid et al., 2020; Sturis et al., 1991) are relatively rare in SD domain. In particular, N. (2016) developed a detailed SD model to investigate immune activation for HIV patients when they are attacked by Tuberculosis and Malaria.

Beyond the SD domain, there have been a number of mathematical models that study HIV/AIDS dynamics in the traditional medicine research, according to a systematic review (Dorratoltaj et al., 2017). These great works lay a solid foundation for applied SD modelling methodology. However, most of these models cannot depict the whole three stages observed in the long-term HIV infection, except for M. Hadjiandreou (2007) and Hernandez-Vargas and Middleton (2013). Besides, the ART treatment is not taken into account in some modeling studies such as Hernandez-Vargas and Middleton (2013) to further investigate the policy impact. As is highlighted by Hill et al. (2018), the application of mathematical models not only helps understand the underlying HIV viral dynamics, but can inform better decisions or policies about how to treat HIV infection effectively.

## 2. PROBLEM STATEMENT

Typically, HIV infected patients will experience three distinguishing phases (Fauci, 2003): (i) an acute infection phase; (ii) a chronic asymptomatic period; and (iii) a final AIDS stage. The

reference modes of CD4+ T cells (left axis) and HIV viral loads (right axis, in power of 10) are illustrated in Figure 2:



**Figure 2: Reference modes of CD4+ T cells and HIV viral RNA<sup>1</sup>**

Given the primary work done by Hernandez-Vargas and Middleton (2013), the long-term HIV immune viral dynamics is going to be principally investigated in this SD modelling work. To be more exact, the underlying model structure will try to capture the fundamental interactions between immune cells (CD4+ T cells & macrophages) and HIV virus so as to reproduce the three main phases during the HIV infection. In addition, achieving the 2020 targets (UNAIDS, 2021a) for sustained antiretroviral therapy and viral suppression is a key challenge for many HIV prevalent nations, such as South Africa (Johnson et al., 2017; van Schalkwyk et al., 2021). Therefore, two antiretroviral treatment regimens (Reverse transcriptase inhibitor drug & Protease inhibitor drug) have been incorporated into the fundamental HIV viral dynamics model to evaluate the impacts of a wide range of ART adherence scenarios.

### 3. KEY RESEARCH OBJECTIVES

First of all, this research intends to apply SD modelling methodology to gain useful insights into the HIV immune viral dynamics through feedback theory. It will focus on explaining how the patterns of immune cells and HIV virus evolve in the long run owing to the interactions between them at a systems level.

<sup>1</sup> Graph is taken from: [https://upload.wikimedia.org/wikipedia/commons/thumb/0/0e/Hiv-timecourse\\_copy.svg/1200px-Hiv-timecourse\\_copy.svg.png](https://upload.wikimedia.org/wikipedia/commons/thumb/0/0e/Hiv-timecourse_copy.svg/1200px-Hiv-timecourse_copy.svg.png)

Then, a SD model-based interactive learning environment is designed with the purpose of better educational campaign for the benefits of public health. It is expected that HIV patients or laypeople can explore HIV viral dynamics easily without the knowledge of complicated mathematical equations behind the scene through the simulation game. As a result, it hopes to enhance public understanding of the dynamics of HIV virus infection and to promote adherence to ART treatment in practice.

Since UNAIDS (2021b) has set a 95–95–95<sup>2</sup> testing and treatment target by 2025 in order to end HIV epidemic as soon as possible. It is believed that the research objectives identified above align with the vision of UNAIDS for a healthier and better world.

#### 4. SYSTEM ANALYSIS

The real human immune system is undoubtedly complex, but the backbone of most “within-host” models is the basic viral dynamics model, which is comprised of uninfected target cells, infected cells, and virus (Hill et al., 2018). The fundamental causal relationships between cells and virus are that initially infected cells will produce HIV viruses, which then infect more uninfected target cells (i.e., CD4+ T cells here) and turn them into infected cells that can produce even more viruses. In system dynamics language, a causal loop diagram (CLD) can be drawn, as shown in Figure 3. As we see, there is a positive feedback loop (R) and a negative feedback loop (B) in the basic viral dynamics model. The positive loop drives the virus to produce more and more if uncontrolled, but the negative loop can limit the growth of virus as uninfected target cells deplete over the time.

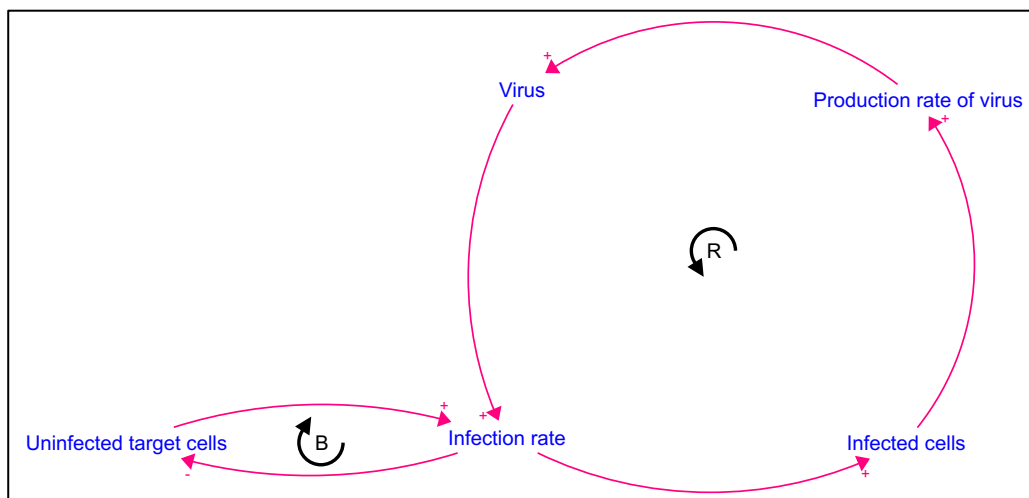


Figure 3: Causal loop diagram of basic viral dynamics model

<sup>2</sup> 95–95–95: 95% of people within the sub-population who are living with HIV know their HIV status; 95% of people within the sub-population who are living with HIV who know their HIV status are on antiretroviral therapy; 95% of people within the sub-population who are on antiretroviral therapy have suppressed viral loads.

However, it has been validated that this basic viral dynamics model is not sufficient to explain the entire progression to AIDS (Hill et al., 2018). Hence, Hernandez-Vargas and Middleton (2013) took another distinct immune cell subset – macrophages into consideration so as to expand the basic HIV viral model boundary. A completer CLD is illustrated in Figure 4, including 3 balancing and 4 reinforcing feedback loops in total. From the perspective of Hernandez-Vargas and Middleton (2013), the acute stage of HIV infection mainly results from the fast infection of CD4+ T cells (loop R1), while the positive feedback loop – R4 contributes to the long-term slow infection process and the final viral explosion in the AIDS phase as macrophages survive much longer than CD4+ T cells and get infected more slowly. This conclusion ought to be subject for further clinical examination.

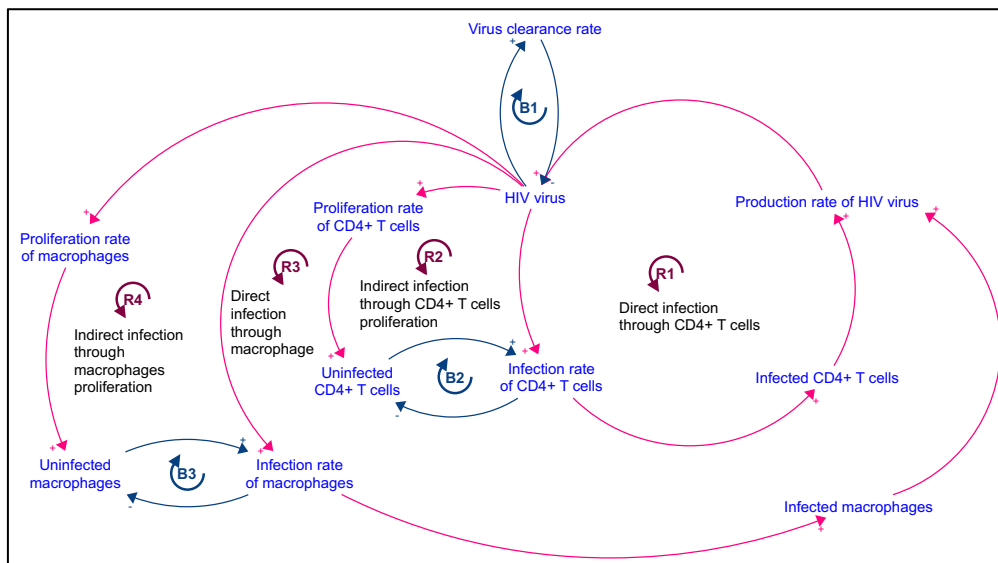


Figure 4: Causal loop diagram of detailed HIV infection

Although CLD is helpful to identify the interactions between key variables in a system, correctly distinguishing stocks from flows is important for developing a simulation model further. By incorporating available data, we can then run the model and test the model behaviours.

## 5. MODEL STRUCTURE AND VALIDATION

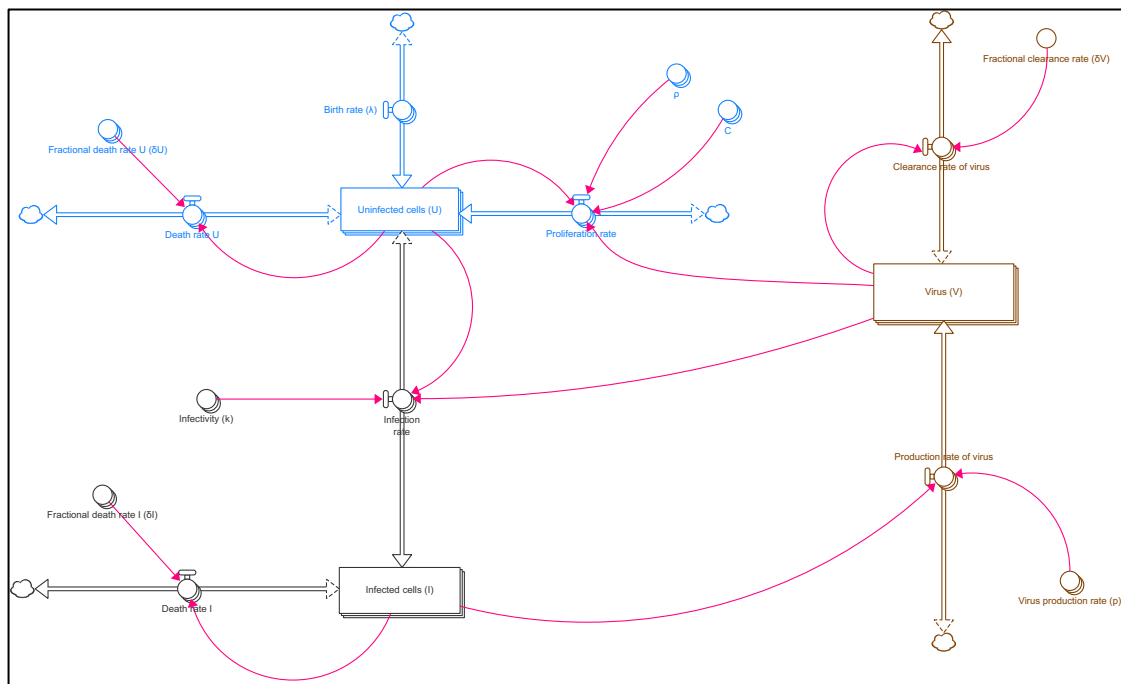
Based on a set of ordinary differential equations that have been well studied (Dorratoltaj et al., 2017; Hernandez-Vargas & Middleton, 2013; Hill et al., 2018), the key stocks – uninfected CD4+ T cells and macrophages, infected CD4+ T cells and macrophages, and HIV virus as well as their corresponding inflows and outflows can be easily identified.

$$\frac{dU}{dt} = \lambda + \frac{\rho V}{c+V}U - kUV - \delta_U U \quad (1)$$

$$\frac{dI}{dt} = kUV - \delta_I I \quad (2)$$

$$\frac{dV}{dt} = pI - \delta_V V \quad (3)$$

According to Equation (1)-(3), uninfected target cells ( $U$ ) are assumed to be born at a constant rate  $\lambda$  in the immune system and die with a fractional death rate  $\delta_U$ . Infected cells ( $I$ ) are produced when uninfected cells are infected by viruses ( $V$ ) at the level of infectivity  $k$  and die with a rate  $\delta_I$ , in proportion to the level of infected cells. The production rate of virus is determined by the level of infected cells and the virus production rate ( $p$ ). As with immune cells, viruses are cleared at a fractional rate of  $\delta_V$ . However, virus can also trigger the proliferation of uninfected immune cells (antigen stimulated proliferation), as emphasized in M. Hadjiandreou (2007). These mathematical equations are the foundation for the stock and flow diagram (SFD), which is depicted in Figure 5. As there are two distinct immune cells (CD4+ T cells & macrophages) considered in the model, an array of the same model structure applies to both of them.



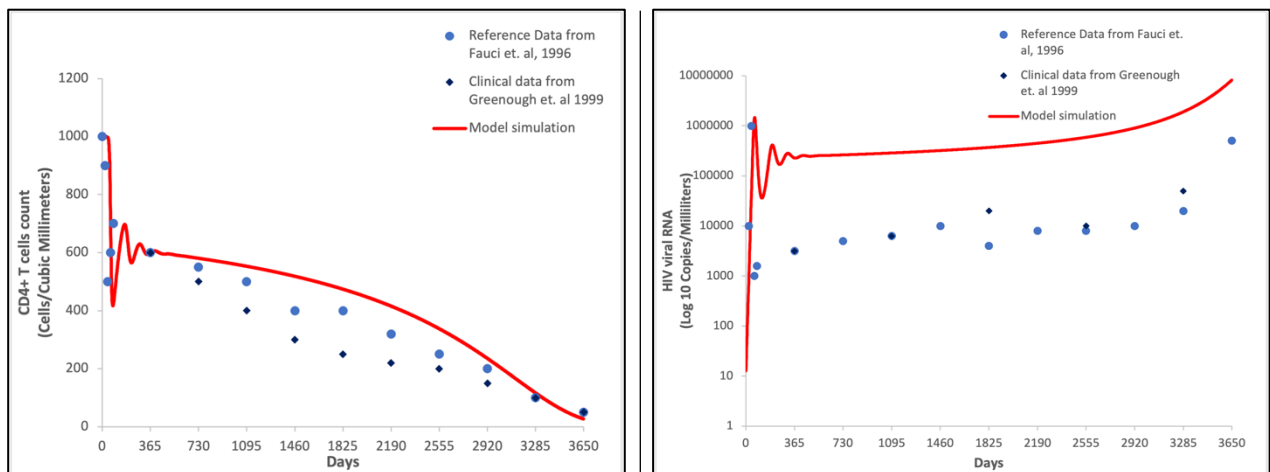
**Figure 5: Stock and flow diagram of HIV infection model**

Given the complexity of biological system, it is worth noting that this HIV immune viral dynamics model does include some unrealistic assumptions. For example, firstly it assumes that there is no delay during the production of HIV virus, but in fact it takes time for a cell to pass through multiple stages of the viral lifecycle (Hill et al., 2018). Secondly, the immune system is not modelled explicitly, so Cytotoxic T lymphocytes (CTL) response is not taken into account (Hernandez-Vargas & Middleton, 2013). Moreover, latently infected cells and drug resistance mentioned in Hill et al. (2018) are not considered too. Regarding ART, it simply uses single parameters to represent drug efficacy rather than model the whole drug absorption process within human body.

Since structure determines behaviour, the dynamic hypothesis for HIV immune system is that infected immune cells produce HIV viruses, which then infect more normal immune cells (CD4+ T cells and macrophages). As we see in Figure 2, the overall behaviour of CD4+ T cells is a declining pattern in the long term, whereas HIV viral loads grow almost exponentially at the acute infection and final AIDS phases. However, there are some oscillations of both CD4+ T cells and HIV virus over the first 12 weeks.

Model testing is critical in SD practice. Sterman (2000, p. 859) listed a series of comprehensive tests for assessment of dynamic models in Table 21-4. Dimensional consistency has been checked within the modelling software – Stella Architecture (isee systems inc., 2021). With respect to parameter assessment, most variables have concrete names and realistic counterparts, except for two proliferation parameters – ( $\rho$  & C) used to represent the non-linear relationship between uninfected cells and virus (Hernandez-Vargas & Middleton, 2013). More importantly, we are very interested in testing the previous hypothesis and knowing whether such a simple model can reproduce the problematic behaviours of key variables like CD4+ T cells and HIV virus, as shown in Figure 2.

Firstly, the model behaviour of CD4+ T cells is compared to both reference data (Fauci, 1996) and clinical data (Greenough et al., 1999), shown in Figure 6 (left one). In general, the model simulation replicates three distinct stages of a typical HIV infection process and calibrates with empirical data well. Next, we compare simulated HIV viral loads with empirical data (Figure 6, right one), and it is found that there is a remarkable gap between them in the order of magnitude even though the patterns resemble each other.



**Figure 6: Comparative behaviour graphs of CD4+ T cells and HIV viral RNA**

In the analysis of Hernandez-Vargas and Middleton (2013), they only considered two feedback systems. However, in fact, the whole dynamics are determined by a few more feedback loops. Using the state-of-the-art algorithm - “Loops That Matter” built in Stella Architect, it is convenient to analyse loop dominance during the whole-time scale. At the initial 12 weeks (around 84 days), Figure 7 (upper left) shows that Loop R1 (matching with the CLD in Figure 4) dominates the whole system, so the HIV viral RNA soars and CD4+ T cells fall sharply in such a very short period. During the clinical latency period (Figure 7 upper right), Loop R2 grows stronger and stronger and begins to dominate the system at the second year. Since it takes much longer time for CD4+ T cells to get infected through Loop R2 than R1, the decreasing rate of CD4+ T immune cells gets much smaller and the growth of HIV virus also slows down. Finally, the strength of Loop R2 gets weakened because of the extremely small number of CD4+ T cells at the AIDS phase, shown in Figure 7 (bottom). However, many macrophages can still stimulate the proliferation of HIV virus (Loop R3), which further infects the remaining CD4+ T immune cells through Loop R1 and makes the immune system completely break down. Over the whole phases, the balancing feedback loop B1 mainly limits the growth of HIV virus.



To summarize, this simple model structure can reproduce the problematic patterns of both CD4+ T cells and HIV virus over a long period. Since the simulation results cannot meet with reference data or clinical data exactly, it is possible to refine the model by expanding the current model boundary in order to relax a number of unrealistic assumptions highlighted earlier.

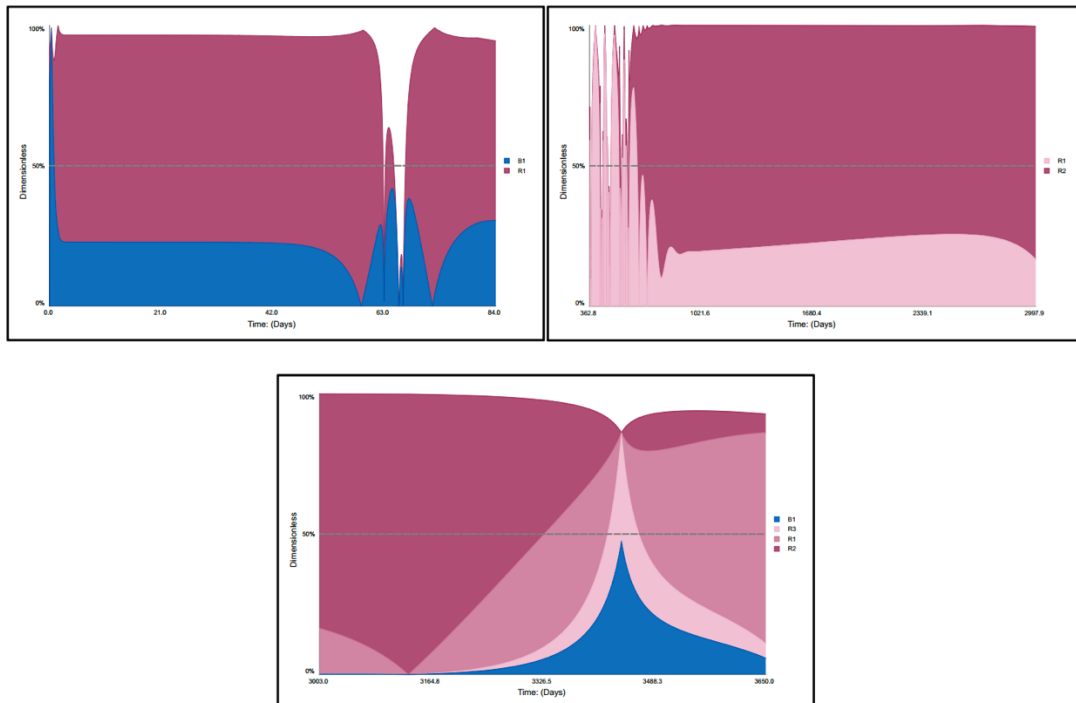


Figure 7: Calculated loop dominance information over the whole HIV infection process

## 6. SCENARIO AND POLICY ANALYSIS

Following the basic model analysis, it is necessary to conduct policy scenario analysis to evaluate the effectiveness of different intervening strategies. Since ART is the only effective treatment for HIV/AIDS patients, three distinguishing ART scenarios (shown in Figure 8) are compared so as to illustrate the vital role of treatment adherence in practice. Basically, it supposes that inhibitor drugs' efficacies are the same and equal to 0.4. In addition, the first ART is assumed to begin at 90 days after infection as there is significant delay between infection, diagnosis, and treatment.

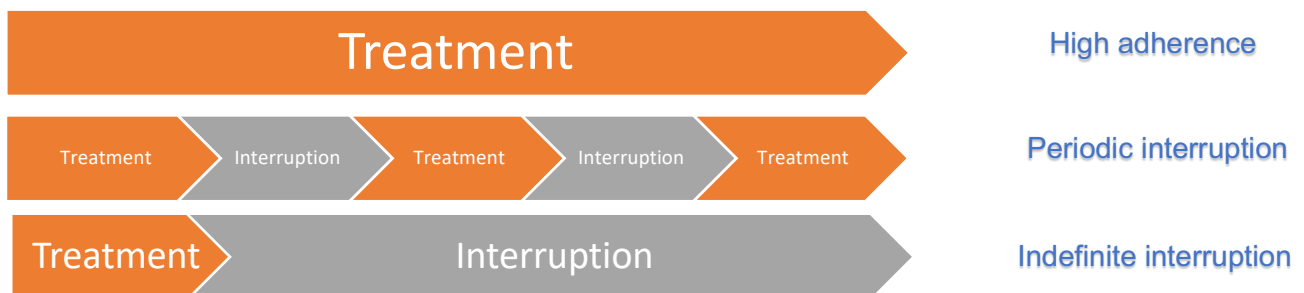


Figure 8: Three representative treatment adherence scenarios



## 6.1 SCENARIO 1: HIGH ADHERENCE

High adherence (Figure 8, top) refers to long-term adherence to ART without any interruption, which is the best-case scenario. Following the basic assumption, it indicates that if HIV patients can adhere to the prescribed drug regime without considering latent drug resistance, CD4+ T immune cells can recover from the decline trend, as shown in Figure 9 (line 1, green). This is called “viral suppression” in clinical terminology. Normally, patients living with successful HIV viral suppression can have a lifespan as long as healthy people.

## 6.2 SCENARIO 2: PERIODIC INTERRUPTION

Periodic interruption (Figure 8, middle) indicates that HIV patients receive ART from time to time and the treatment is interrupted at some middle periods. Since there can be a wide range of combinations in this scenario, each treatment or interruption period is presumed to last for 2 years. Not surprisingly, we see a strong oscillating pattern of CD4+ T cells in Figure 9 (line 2, blue) in contrast to that in Scenario 1.

## 6.3 SCENARIO 3: INDEFINITE INTERRUPTION

Indefinite interruption (Figure 8, bottom) means that HIV patients stick to ART for some time at the beginning but then withdraw from the treatment forever. In the last scenario, we assume that HIV patients adhere to ART for the first two years and then drop out of the treatment until the end. This is dangerous because HIV patients without continuing ART treatment can still develop into AIDS after some years, illustrated in Figure 9 (line 3, pink). It follows almost the same pattern as base run (line 4, red) – No ART.

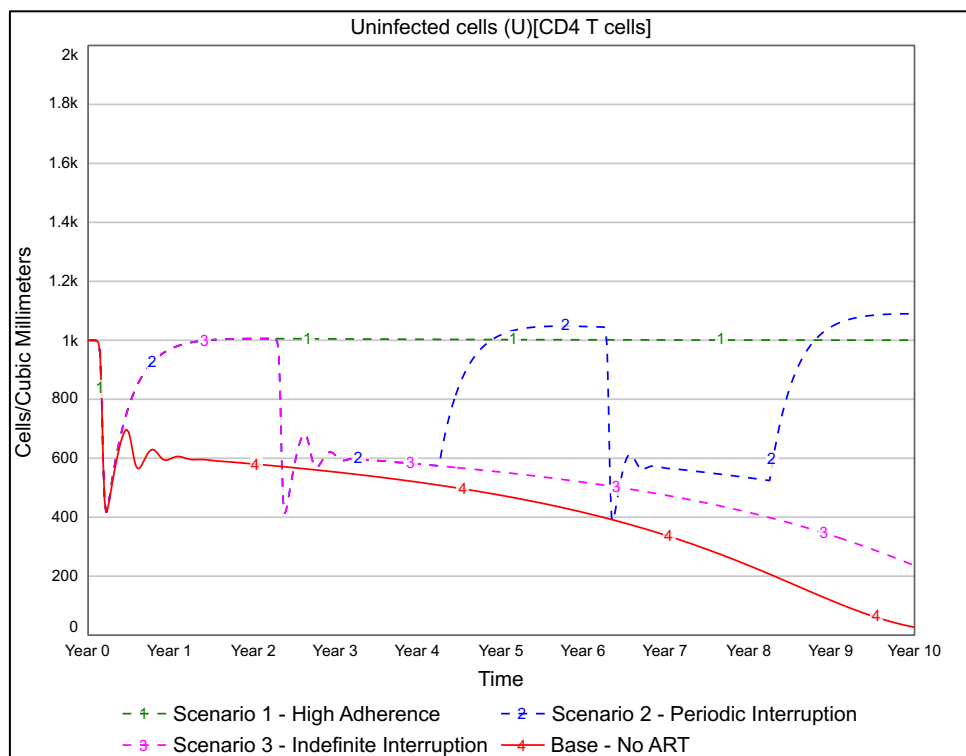


Figure 9: Comparative graph of three different treatment scenarios with base run

## 7. RECOMMENDATIONS AND POLICY DESIGN

According to policy scenario analysis above, we find that ART is effective to suppress HIV virus, but it cannot cure the disease at all. This maybe one of the main reasons that HIV epidemic has sustained for so many years globally. Therefore, it is critical for HIV patients to adhere to ART strictly in reality. Without long-term adherence to treatment, HIV patient's immune system is so fragile that they get susceptible to a multiplicity of devastating infections, as CD4+ T cells in their bodies will reduce gradually over time. In summary, simulation results imply that, the earlier patients start ART treatment and the higher adherence to treatment, it takes longer time for HIV prognosis to the final AIDS stage.

As there is a variety of ART adherence scenarios in real context, the three representative scenarios are definitely not able to exhaust all possible outcomes for each HIV patient. Hence, an interactive learning environment aiming to promote ART treatment adherence is developed and published online. Hopefully, relevant stakeholders, especially HIV patients, can not only explore HIV immune viral dynamics interactively through "game" simulation, but test their own assumptions or treatment behaviours during the Covid-19 pandemic and learn useful insights on ART adherence. It is expected that they will feel it inside and act for real change in their life later.

## 8. CONCLUSION

Building upon professional knowledge and experimental data in other disciplines, SD is a useful methodology that can be applied to enhance understanding of complex systems through feedback theory. By integrating SD modelling method with the newest clinical and medical evidence, this study explores the dynamics of HIV immune cells and virus in the long run. As a result, the developed SD model can reproduce the problematic behaviours over the long-term HIV infection in general, though there are some differences between simulation results and reference data, which lay ground for further clinical research and model development in the future. Traditionally, SD is widely used to model HIV prevalence within a community or area, including regional HIV prevention and treatment policy assessment. By contrast, this research focuses on "within-host" infection dynamics and tries to expand SD application to biomedical issues. In short, the cross-disciplinary approach opens a new door for researchers to understand HIV infection within human body and builds consensus on the importance of ART adherence.

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