Dynamics of HIV/AIDS Infection and Antiretroviral Treatment

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Abstract – **Human Immunodeficiency Virus (HIV) attacks the immune systems, making it harder for the body to fight infection and disease. Over time a HIV infection will progress into Acquired Immunodeficiency Syndrome (AIDS) at which point one's immune system is severely crippled. While there currently is no cure for the HIV virus, it can be treated through antiretroviral medication in order to halt its progression to AIDS. Thus, the main goal of this paper is to develop a model of the dynamics of a HIV infection and subsequently introduce antiretroviral treatment. After creating a mathematical model of the infection dynamics, Simulink is utilized to simulate the system and any perturbations to it.**

I. Introduction

HIV affects over 37 million individuals around the world. Left untreated, HIV leads to loss of CD4+ T cells and increased risk of infections and cancers (1). HIV is a highly infectious virus, with transmission occurring through exchange of bodily fluids with an infected individual. Common modes of transmission include sexual intercourse, sharing infected needles, and Perinatal transmission. Once in the body, HIV enters the lymphoid tissues and infects the abundant CD4+ T cells (2). At this stage, rapid replication of the virus begins, with the virus becoming detectable by day 10 of infection. HIV continues to proliferate throughout the body reaching peak levels at day 30 (1). After this, the viral levels within the host body drop to a set point where it remains at an equilibrium due to complex viral-host interactions. In healthy individuals, concentration of CD4+ T cells should be between 500-1200 cells/µl (3). As HIV-mediated CD4+ T cell death continues, CD4 T cell counts continue to drop. CD4+ T cell levels under 350 cells/µl lead to increased risk of several infections and cancers such as Kaposi Sarcoma. If CD4+ T cell counts below 200 cells/µl or an individual has an AIDs defining complication, the individual is deemed to have AIDS (1).

HIV replication occurs in seven stages: 1) Binding, 2) Fusion, 3) Reverse Transcription, 4) Integration, 5) Replication, 6) Assembly, 7) Budding. In the binding stage, the HIV virus attaches to the surface of the CD4+ T cell. In the fusion stage, the envelope of HIV fuses with the cell membrane, allowing HIV to enter the CD4+ cell. HIV releases reverse transcriptase to convert its RNA into DNA allowing it to be able to combine with the cell's DNA. During integration, the HIV enzyme integrase inserts the viral DNA into the host cells DNA. Once integrated, replication makes new chains of HIV proteins from the host cell's mechanisms. In the assembly stage, the newly formed HIV proteins and HIV RNA form immature HIV at the surface of the cell. During budding, long chains of immature HIV are pushed out from the surface of the host cell, the HIV enzyme protease breaks up the chain and releases the mature, infectious, virus into the body (4).

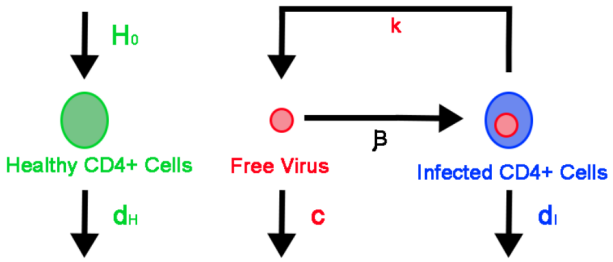


Figure 1. Diagram of HIV infection. Based on Reference 5.

Viral dynamics are well understood and equations modeling a viral infection can be found in literature (6,7,8). To model a HIV infection, there are three main states: Healthy CD4+ T cells (H), Infected CD4+ T cells (I), and free virus (or virions) (V). These three stages interact as shown in Figure 1 and can be represented by the equations below:

$$\frac{dH}{dt} = H_0 - d_H H - \beta HV \qquad (1)$$

$$\frac{dI}{dt} = \beta HV - d_I I \qquad (2)$$

$$\frac{dV}{dt} = kI - cV \qquad (3)$$

H_0	CD4+ cell production rate = 10 mm^3/day
k	Virus production rate= 100 counts/infected T cell
d_H	Death rate of healthy cells=0.02 cells/day
d_I	Death rate of infected cells=0.24 cells/day
c	Virus clearance rate=2.4/day
β	Efficiency of Infection=$2.4 \times 10^{-5} mm^{-3}$/day

Table 1. Parameters of HIV Infection Model (7,8)

HIV replication is reliant on three enzymes properly functioning: reverse-transcriptase, integrase, and protease (9). As a result, in order to treat HIV, many drugs target these enzymes, particularly reverse transcriptase and protease. Reverse Transcription inhibitors (RTIs) inhibit the reverse

transcription stage of HIV replication and Protease inhibitors (PIs) inhibit the budding stage. Clinically, once the count of virions/free virus is under 50 per ml of plasma, HIV is considered suppressed successfully (10). In order to model antiretroviral treatment and investigate the effects of RTI and PI drugs we incorporated treatment into the model. Since RTIs affect the reverse transcription stage, the initial infection of a CD4+ T cell is slowed, thus the effect of RTIs is only on T cell counts. Since PIs affect budding, it slows the viral production rate, and thus only has an effect on free virus counts. Considering efficacy of RTI medication as u_1, $(1 - u_1) * \beta$ represents the new efficiency of infection. Similarly, taking the efficacy of PI medication as u_2, $(1 - u_2) * k$ represents the new viral production rate. HIV dynamics with antiretroviral treatment can be modeled by the equations below:

$$\frac{dH}{dt} = H_0 - d_H H - (1 - u_1)\beta HV \quad (4)$$

$$\frac{dI}{dt} = (1 - u_1)\beta HV - d_I I \quad (5)$$

$$\frac{dV}{dt} = (1 - u_2)kI - cV \quad (6)$$

In this model, efficacy is a value between 0 and 1, with 1 representing a 100% effective drug. Typical drugs do not exceed 60% due to being toxic to the patient from the high dosage needed to achieve such efficacy. Instead a high efficacy value can be shown as 0.5, a medium efficacy as 0.25, and a low efficacy value as 0.1.

II. METHODS

Due to the complexity and many biological processes involved in viral infections the following assumptions were made in order to simplify our model:

1. Infected CD4+ cells immediately produce virus.
2. Rates are constant, i.e., virus production, CD4+ T cell production, death rates, efficiency of infection, and virus clearance rate.
3. The virus does not undergo any mutations, including the development of drug resistance.
4. The individual does not have any underlying health conditions.

In order to investigate the stability of our model for HIV infection we linearized equations 1-3 by solving for the steady-state conditions. There were equilibrium points at (500,0,0) and (240.00,21.67,902.78). The linearized equations at the (240.00,21.67,902.78) equilibrium point can be shown as:

$$\frac{dH}{dt} = -0.0417H - 0.0058V \quad (7)$$

$$\frac{dI}{dt} = 0.0217H - 0.24I + 0.0058V \quad (8)$$

$$\frac{dV}{dt} = 100I - 2.4V \quad (9)$$

Stability can be determined through eigenvalue analysis. At equilibrium point (500,0,0), the eigenvalues have positive and negative real parts indicating it is unstable at that point. At (240.00,21.67,902.78), the eigenvalues have negative real parts, indicating that the system is stable around that point.

Combining our assumptions and equations 1-3 that were derived prior, we can assemble the following Simulink model:

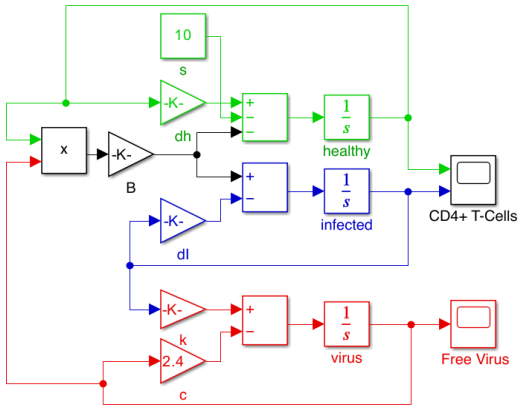


Figure 2. Simulink model of HIV infection with no treatment.

In order to simulate different patient conditions, the initial conditions of the integrators are changed. Firstly, to simulate a healthy individual with no HIV virus in their body we use 1000 healthy CD4+ T cells, no infected T cells, and zero virus. The next step is to introduce a HIV infection and simulate the dynamics of that. In order to do so we simply change the initial condition of the virus integrator to 1, this represents 1 free virus per ml of plasma.

We then had to amend the Simulink model in order to represent the introduction of antiretroviral treatment. Doing so by using equations 4-6, we updated the simulink to the following model:

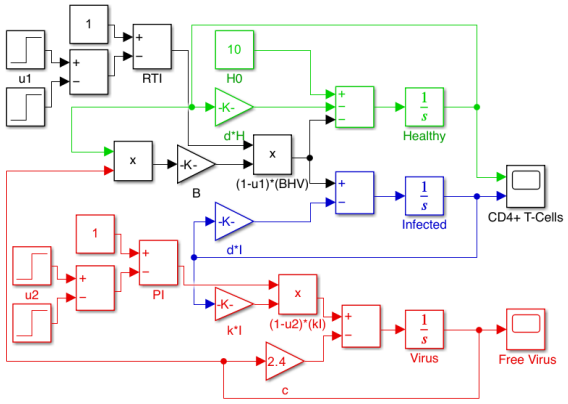


Figure 3. Simulink model of HIV infection with antiretroviral treatment.

For an infected individual the initial conditions of the integrators remain unchanged from the previous Simulink model of HIV infection. Here we are simply introducing antiretroviral medication taken daily for a set amount of days. The parameter u1 is changed to vary the efficacy of PI medication and u2 is changed to vary the efficacy of RTI medication. As mentioned above, for low efficacy the parameter would be 0.1, 0.25 for medium, and 0.5 for high.

III. RESULTS

As outlined prior in the methods, we first used our Simulink model to simulate an individual with no virions in their body. We started with an initial condition of 1000 healthy CD4+ T cells.

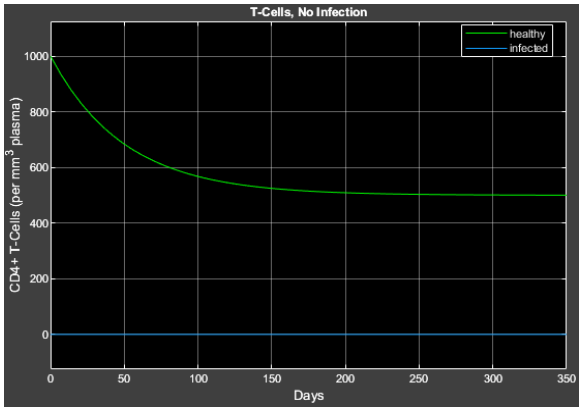
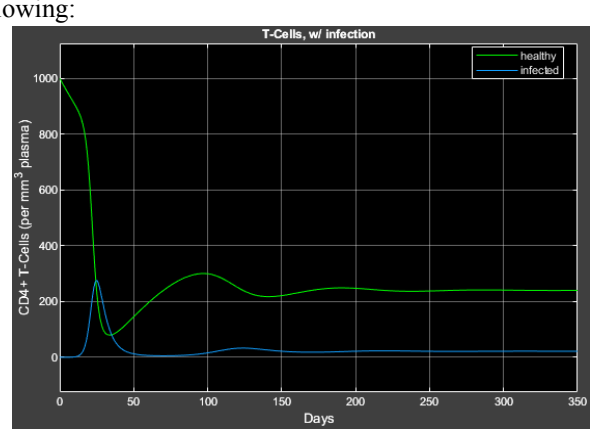


Figure 4. Healthy and infected CD4+ T cells overtime of a healthy individual.

Upon simulation, the number of healthy CD4+ T cells decline over time until they stabilize to 500 per mm^3 of plasma by 250 days as seen in Figure 4. Both infected T cells and free virus (not pictured) do not deviate from zero for the duration of the simulation.

After altering the initial conditions to represent an individual who was recently infected with HIV we observe the following:



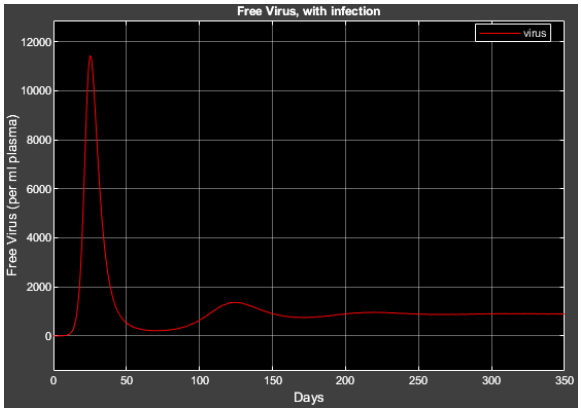
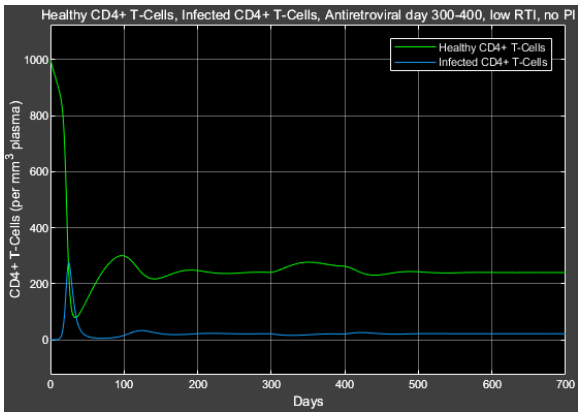


Figure 5. Healthy, infected CD4+ T cells, and free virus of an individual who developed a HIV infection on day 0, no treatment.

As seen above in Figure 5, there is a spike in virions around 30 days at which the number of virions per ml plasma exceeds 11,000 before stabilizing to about 902. There is a simultaneous spike in the number of infected CD4+ T cells that rise from 0 to above 200 cells per mm^3 of plasma before stabilizing to 21. Lastly, we see a steep decline in healthy CD4+ cells during the same days as the spikes in the other measurements. The healthy T cell count drops all the way down to about 100 per mm^3 of plasma before stabilizing to about 240.

At this point we introduced the second iteration of our Simulink model that considered antiretroviral treatment. We began by applying low efficacy RTY daily treatment from day 300 to 400:



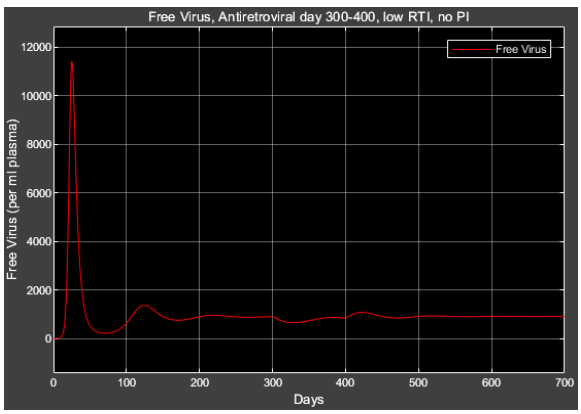


Figure 6. Healthy, infected CD4+ T cells, and free virus of an individual who developed a HIV infection on day 0, low efficacy RTI therapy taken day 300-400 .

Day 0-300 is identical to that of Figure 5. Once medication begins on day 300, there are small decreases in the number of virions and infected T cells, as well as an increase in the number of healthy T cells. Once medication is halted on day 400, there are spikes in free virus and infected T cells as well as a drop in healthy T cells prior to all three stabilizing in the same fashion as Figure 5.

Next we simulated every possibility of low, medium, and high efficacies as well as all the combinations of RTIs and PIs (see table 2 in the Appendix). Anytime a high efficacy is used we very quickly get the number of virions under 50 per ml of plasma. High efficacies also have the highest spike in virions after medication is ceased. Based on the results of these simulations we concluded combination therapy including medium efficacy RTI and PI drugs is most effective (see Discussion for reasoning):

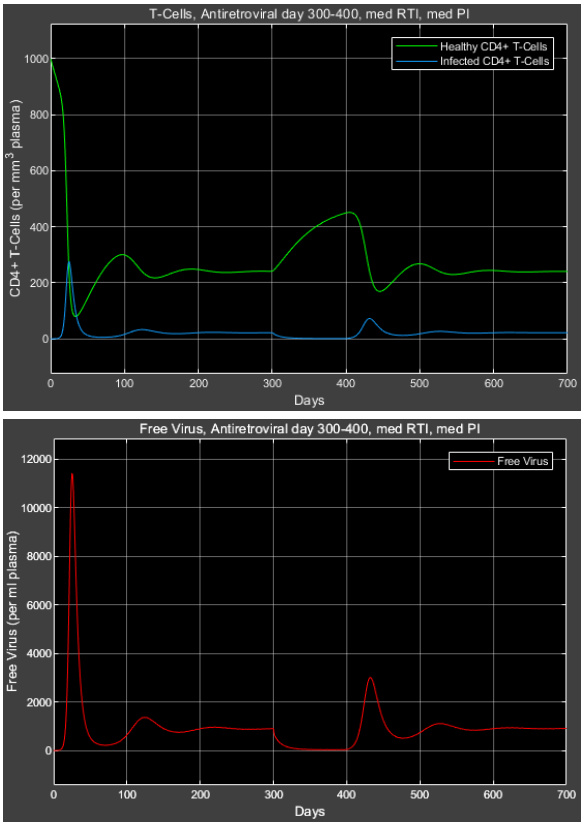


Figure 7. Healthy, infected CD4+ T cells, and free virus of an individual who developed a HIV infection on day 0, medium efficacy combination therapy taken day 300-400 .

For the combination of medium efficacy RTIs and PIs as seen in figure 7, both virions and infected CD4+ T cells are reduced, virions per ml plasma reaching below 50 in only 42 days. During the entire duration of the medication, healthy T cell count rises quickly. Once medication is halted on day 400, virions spike to about 3000 per ml plasma. Additionally, there is a small drop in healthy T cells and a small increase in infected T cells before all three once again stabilize.

IV. Discussion

Analysis of results:

We began by simulating a healthy individual with no HIV infection using the simulink model in Figure 2 and this resulted in the plot in Figure 4. Overtime, due to the relationship between T cell death rate and production rate the number of healthy CD4+ T cells decreased from the initial 1000 and stabilized to 500 per mm^3 plasma. Due to there being no virions in the system, neither infected T cells nor free virus can move from 0. With these conditions we see that the system stabilizes to one of the two equilibrium points we found prior, (500,0,0). As determined by our eigenvalue analysis, this point is unstable. To test both the instability of this point and model a HIV infection we changed the initial conditions to have 1 virion per ml plasma. As seen in Figure 5 this resulted in spikes in both free virus and infected T cells during the most obvious phase of HIV infection. Oer time this system also stabilized, but this time, to the second equilibrium point of (240.00,21.67,902.78). As determined prior, this point is stable. Once the model stabilizes to this point it is representative of the patient advancing from HIV to AIDS where the virus is still present, but more dormant and there are consistently low numbers of healthy CD4+ T cells. In summary, if the system is perturbed from the first equilibrium point by either infected T cells or virus it will eventually stabilize to the second at which point one has AIDS.

Next, we used the Simulink model in figure 3 to incorporate antiretroviral treatment. Using this model we were able to generate table 2 by testing all possibilities of efficacies and combinations of RTIs and PIs. It is immediately noticeable that whenever a low efficacy drug is used by itself or in combination with another low or medium efficacy drug, the virion count never reaches the target. This is understandable because it is rare that medication is effective at extremely low dosage. Anytime a high efficacy drug is used, whether it is a RTI, PI, or both in combination, the virus is suppressed quickly, at best in only 14 days. While this seems appealing, the spike in virions in the situation that medication is stopped is very high for high efficacy treatment. This is important because while not desirable, stoppage of medication for a variety of reasons sometimes has to occur, and if it does we want to minimize the resurgence in infection.

Based on these factors, we decided medium efficacy combination therapy was best. The reasoning for this is because that combination successfully reaches the target of less than 50 virions per ml plasma in a respectable amount of time, 42 days. While this is about two weeks slower than some of the high efficacy options, two weeks isn't critical in the long timeframe of a HIV infection. Additionally, in the situation that medication had to be ceased, the spike in virus is lower than any of the high efficacy options.

Future steps:

It is important to note that while this model provides a valuable starting point for understanding the dynamics of HIV/AIDS and its antiretroviral treatment, it is not perfect. Based on our simulation, RTIs and PIs have similar effects on viral suppression, but in vivo, RTIs are observed to be more effective (11). This is likely due to the simplicity of our model not fully encapsulating the complexity of the biological interactions between the virus and the drugs. In the future, more work is needed to improve the biological accuracy of the antiretroviral model in hopes of aligning more closely with in vivo results.

Additionally, our current model doesn't reflect the different dosages needed for different medications to reach desired efficacy levels. Future steps could involve incorporating dosage as a variable when modeling HIV dynamics.

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Appendix

Table 2

	Viral Low During Antiretroviral (virions/ml)	Peak of viral resurgence after stoppage of medication (virions/ml)	Days to reach <50 virions per ml plasma (Days)
No RTI, Low PI	595	1076	NA
No RTI, Med PI	238	1710	NA
No RTI, High PI	6.6	3145	26
Low RTI, No PI	649	1083	NA
Med RTI, No PI	307	1720	NA
High RTI, No PI	0	3151	32
Low RTI, Low PI	403	1357	NA
Med RTI, Low PI	153	2332	NA
High RTI, Low PI	0	3252	28
Low RTI, Med PI	133	2330	NA
Med RTI, Med PI	30	3013	42
High RTI, Med PI	0	3334	24
Low RTI, High PI	0	3169	26
Med RTI, High PI	1.9	3301	21
High RTI, High PI	0.4	3379	14