HIV-1 dynamics in vivo and models for proposed treatments

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Abstract

The work of Perelson et al. on modeling HIV-1 dynamics in vivo, specifically when a protease inhibitor treatment was administered to observed patients with HIV-1 infection, is analyzed and extended to other forms of treatment. In particular, the hypothetical dynamics of a theoretical CCR5 receptor mutagen is applied to the compartment model developed by Perelson. When viral load under this new treatment type is plotted against time, the curve shape is different from that of the protease inhibitor treatment. This may suggest alternative real-world outcomes (e.g. a CCR5 receptor mutagen may be able to eliminate HIV-1 from a patient in practice, unlike protease inhibitors), however development and testing of this form of treatment is necessary in order to come to this conclusion. Additionally, the CCR5 receptor mutagen treatment takes more time to drop a patient's viral load to a value below one than the protease inhibitor treatment does. A notable property of the CCR5 receptor mutagen, however, is that its efficiency increases as the patient's viral load at the time of initiation of treatment increases. Further research utilizing other modes of combating HIV infection, including the implementation of CRISPR-CAS9, are considered mathematically. This paper demonstrates a method of applying Perelson's model to a particular method of treatment, and this method can be applied to other types of treatment as well.

1 Biological Context

HIV/AIDS

HIV (human immunodeficiency virus) is a highly mutative retrovirus that can cause acute HIV infection and, over time, cause AIDS (acquired immunodeficiency syndrome). The virus hijacks the host's immune system in order to replicate and survive. Long-term subjection to this hijacking causes the host's immune system to deteriorate; a certain level of deterioration designates the host to be suffering from AIDS. Unlike most viruses, the genetic material of HIV is RNA (ribonucleic acid). This RNA is comprised of 9 genes that encodes 15 proteins that HIV utilizes to target and hijack the host's immune system.

Immune System

The immune system is a set of organs and molecules that work together in the human body as a defense against disease. Nonspecific and specific lines of defense help protect the body from pathogens. The non-specific line of defense includes the mechanical barriers such as mucous, hairs and cilia, skin oils, and chemicals in perspiration and gastric juices. If a pathogen happens to get past this first line of defense, it is then subject to the body's specific line of defense. This specific line of defense utilizes various subsets of antigen-specific lymphocytes to eradicate antigens from the body. B cells provide immunity to antigens that are circulating in the blood. T cells provide immunity to antigens inside or associated with cells. There are many types of T cells including cytotoxic T cells (T_C) that lyse cells displaying foreign antigens, and helper T cells (T_H) that facilitate the response of T_C and B cells. T cells can be differentiated, in part, based on certain proteins on their surfaces. Helper T cells, which are often called T4 cells, have an integral protein, CD4, on their surfaces. T_H cells are important conductors of the immune system that make sure that the antigen-specific cell response is increased throughout the immune system. Without these important mediators of increased system response, the immune system is at the mercy of the antigens that have invaded.

Viral Life Cycle

HIV encodes 15 proteins used when infecting a host's immune system. These proteins include a glycoprotein (gp120), reverse transcriptase, integrase, and protease. Infection of a host cell starts when gp120 on HIV binds to the CCR5 receptors on CD4+ T cells. It then uses reverse transcriptase to transcribe its RNA material into DNA (deoxyribonucleic acid) that is then integrated into the host cell's genome with an integrase protein. The virus's genetic material is now incorporated into the genome of the host cell and will be transcribed as the cell replicates. The final stage of the infection is after the assembly and exocytosis of the virus: the protease cleaves the immature polypeptide into the mature (infectious) form of the virus. When enough viruses have been synthesized in the host cell, the budding can lyse and kill the host cell. These mature viruses can now go on and infect, replicate, and lyse other host cells.[2,9]

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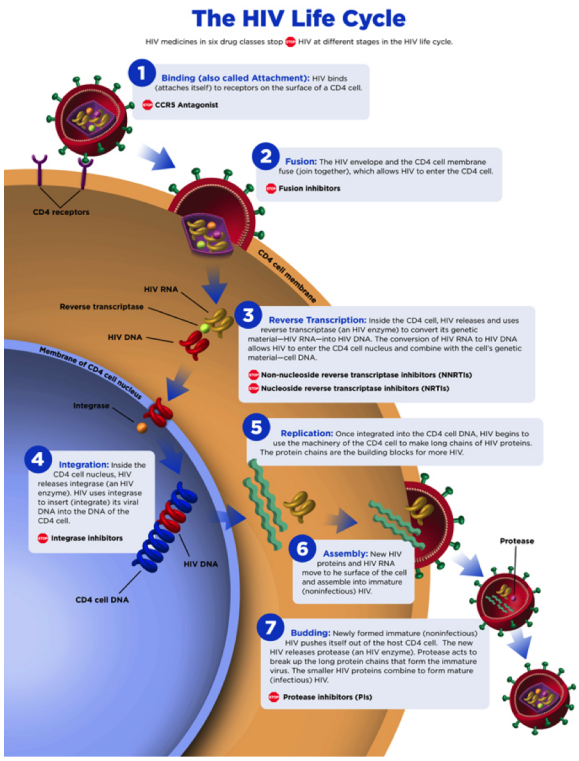

Stages of Infection

Acute HIV Infection

Acute HIV Infection characterizes the first stage of infection. Acute HIV Infection occurs approximately within 2 to 6 weeks after a person is infected with HIV. Symptoms often present as those of the flu, including fever, headache, and rashes. During this stage, HIV is quickly multiplying and spreading throughout the body. The virus infects and kills the CD4+ T cells of the immune system. Due to this rapid multiplication, the viral load in an individual is the highest and the individual is the most infectious.

Clinical Latency

The second stage of HIV infection is the latent stage (also called chronic HIV infection or asymptomatic HIV infection). During this stage of the disease, the virus continues to multiply and destroy the infected individual's immune system., but at a very low sustained level. People in the latent stage of HIV infection often do not show symptoms but can still infect others with the virus. This latent stage lasts on average 10 years.

AIDS

AIDS characterizes the last stage of HIV infection. It is the result of the fact that HIV has deteriorated the immune system to the point that it cannot fight of certain rare cancers and opportunistic infections. AIDS is diagnosed when a person with HIV has a CD4 count of less than 200 cells/mm^3 and/or one or more opportunistic infections.

HIV Treatments

Current

Due to the fact that the virus exhibits a very high mutation rate, and that HIV can hide out in the body in very low levels, there is no cure to HIV. However, the various stages in the life cycle of the virus can be targeted for treatment. In the past few decades these treatments have become simple and effective enough to allow patients to live approximately the same lifespan of those who are HIV negative. These

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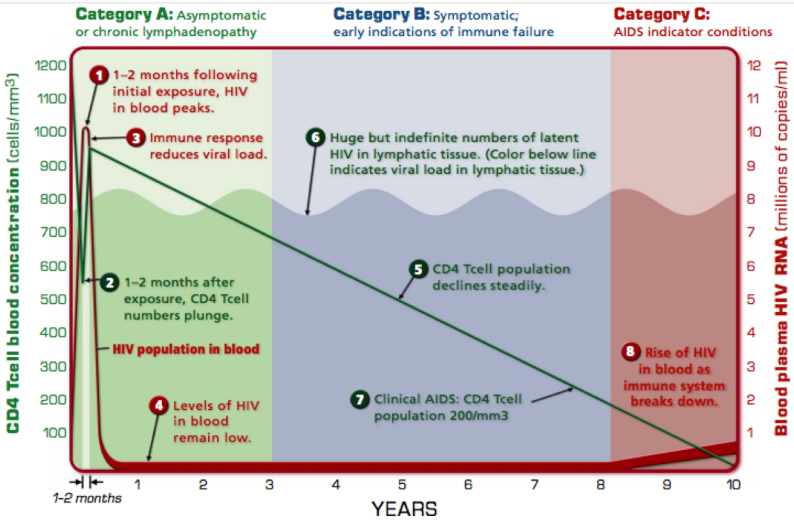


treatments include drugs that affect the various parts of the viral life cycle. Ritonavir, for example, is a protease inhibitor that stops the cleavage of immature viral protein into mature (infectious) protein.

Proposed

Proposed treatment involves the administration of a drug that takes of the bone marrow and other stem cells creating CD4+ T cells and affects their synthesis so that these cells do not exhibit these receptors. CD4- T cells in an infected individual will no longer be susceptible to binding by HIV.

2 Historical Background

HIV/AIDS History

The inception of HIV is thought to be from chimpanzees that were infected with SIV (simian immunodeficiency virus). Biologists propose that the virus mutated and infected the humans that were hunting these chimpanzees in Africa. The virus disseminated throughout Africa and caused widespread death, panic and fear in the 1970s due to trade, travel, and increased sex work during this period. The first few cases of HIV occurred in the U.S in 1981, when homosexual men were dying of pneumonia-like infections. Soon, AIDS Clinics opened and the virus was discovered in 1984. Once the disease was identified, it quickly became an epidemic, as AIDS was the leading cause of death in 1994 of peoples ages 25 to 44.

The first protease inhibitor was created in 1995, and other drugs were manufactured and that were taken in tandem to fight the infection. Drugs companies and clinical trials then perfected the various types of medications to one pill that can be taken daily to treat the infection. Campaigns for HIV testing became more widespread and the epidemic soon died down and remains endemic in the U.S.

3 Mathematical Model

Current Model and Extension

Perelson et al. modeled HIV-1 dynamics in the body by assuming the virus infects target cells (T) with a rate constant β, which describes the mass-action kinetics of this reaction. The authors also defined a parameter δ^*, representing the rate of loss of virus producing cells, and a parameter N, representing the number of new virions produced per infected cell during its lifetime. The value c corresponds to the rate constant for virion clearance.[6]

For the purpose of extending this model to multiple classes of treatments, λ is defined as the rate of production of new, healthy CD4 target cells and (delta) is defined as the rate of loss of these healthy CD4 cells. The resulting model is the following system of three differential equations:

$$\frac{dT}{dt} = \lambda - \delta T - \beta VT$$
$$\frac{dT^*}{dt} = \beta VT - \delta^* T^*$$
$$\frac{dV}{dt} = N\delta^* T^* - cV$$

The resulting steady state values are:

$$T_0 = \frac{\lambda}{(\delta + \beta V_0)}$$
$$T_0^* = \frac{\beta V_0 T_0}{\delta^*}$$
$$V_0 = \frac{N\delta^* T_0^*}{c}$$

These steady state values represent the latent stage of HIV.

Using this as the baseline model, the authors then introduced a protease inhibitor, Ritonavir, to this model. Using the mechanism described above, the protease inhibitor effectively makes all virions non-infective at and after the time the drug is administered. This results in the following system:

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - \delta T - \beta V_1 T \\
\frac{dT^*}{dt} &= \beta V_1 T - \delta^* T^* \\
\frac{dV_1}{dt} &= -cV_1 \\
\frac{dV_{NI}}{dt} &= N\delta^* T^* - cV_{NI}
\end{aligned}$$

where V_I represents infectious virions and V_{NI} represents non-infectious virions. Assuming $v(t) = v(t)ni + v(t)i$, an equation for viral load as a function of time can be solved for:

$$V(t) = V_0 e^{-ct} + \frac{cV_0}{(c-\delta^*)}\left(\frac{c}{(c-\delta^*)}(e^{-\delta^* t} - e^{-ct}) - \delta^* t e^{-ct}\right)$$

Perelson et al. estimated c and δ^* using a nonlinear regression analysis. Five patients (three with AIDS, two in the latent stage of HIV-1 infection) were given Ritonavir as treatment, and their HIV-1 RNA levels were tracked over the course of one week. The authors generated of viral RNA copies/mL versus time in days, and used best-fit values to determine c and δ^* for each individual in the study. The mean c value was found to be 3.07 days^{-1} and the mean δ^* value was found to be 0.49 days^{-1}. The result of these parameter values is an average half-life of 0.24 days amongst the five participants.

The authors make two notable assumptions when deriving this model. One is that the protease is completely and universally effective. That is, it always executes its mechanism in its entirety at every relevant point in the body. It also assumes no viruses develop or inherently have a resistance to the protease. Finally, it assumes the system is at the steady state described above, which is fairly unrealistic for patients with AIDS (patients 102, 103 and 105).

What Perelson et al. did not analyze, however, are the effects of other HIV-1 treatments. Due to the fact that HIV has a high mutation rate, the efficacy of utilizing protease inhibitors to fight the infection declines over time, and is one of the reasons that HIV is incurable. Further research suggests that changes in the host's immune cells may be a better avenue for research, as the 'Berlin patient' who was transiently "cured" of HIV had all of his T cells replaced with a bone marrow transplant as part of his cancer treatment. Consideration of HIV treatments affecting the patient's innate physiology rather than altering the viral replication cycle may lead to more positive clinical outcomes. In this paper, we alter Perelson's model to view the effect of altering the expression of CCR5, the receptor that HIV-1 uses to dock to the CD4 cell. In the model, it is now assumed that the virus cannot infect all newly synthesized T cells, but the current population of T cells can be infected. We alter the above model to reflect this new treatment, and obtain the following system:

$$\begin{aligned}
\frac{dT_I}{dt} &= -\delta T_I - \beta V T_I \\
\frac{dT_R}{dt} &= \lambda - \beta T_R \\
\frac{dT^*}{dt} &= \beta V T_I - \delta^* T^* \\
\frac{dV}{dt} &= N\delta^* T^* - cV
\end{aligned}$$

where T_I represents T cells that can be infected while T_R represents resistant T cells. Using steady state values, the equation describing the dynamics of free virions can be rewritten as:

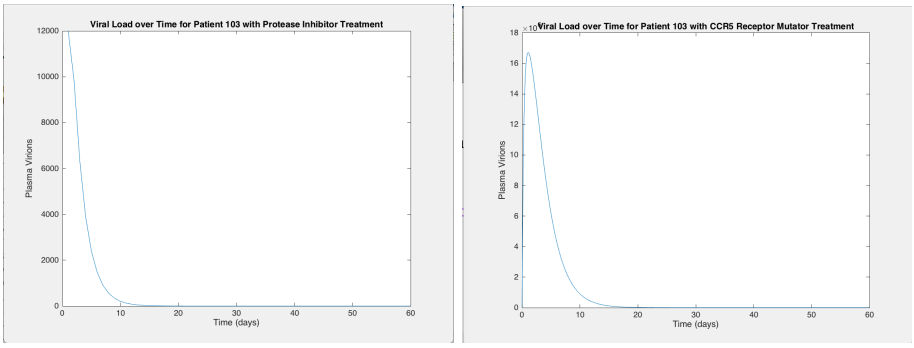
$$\frac{dV}{dt} = \frac{c\delta^* T^*}{\beta T_0} - cV$$

The parameter values β and δ were obtained from previous work on CD4 and HIV-1 dynamics by Perelson et al. and Hellerstein et al.

Solving this system of equations results in dynamics that mimic the cycle of HIV-1 in the body when a patient first becomes infected; there is a spike in viral load just after administration of the drug, followed

by an exponential decrease in viral load. However, the treatment model has the viral load decaying to near zero, while in untreated HIV-1 infection, viral load moves towards some steady state.

parameter	value
c	3.07 $days^{-1}$
δ^*	0.49 $days^{-1}$
δ	0.007967 $days^{-1}$
β	0.000000024 mL/day



4 Results

To compare the effectiveness of a protease inhibitor and a drug that affects expression of CCR5, viral load with respect to time was plotted for each scenario, and the number of days required for viral load to reach a value below one was determined. This method was used due to the fact that the shape of the virion versus time plot was a different shape for each treatment. This process was performed for all participants in the study, assuming half of the CD4 cells in their body were infected at any given time. The results are given in the table below.

Patient	CD4 cells (per mL)	Plasma Virions (10^3 per mL)	Protease Inhibitor Treatment (days to viral load < 1)	CCR5 Receptor Mutator Treatment (days to viral load < 1)
102 (AIDS)	.016	294	27	45.05
103 (latent)	.408	12	20	45.46
104 (AIDS)	.002	52	23	45.47
105 (AIDS)	.011	643	29	44.63
107 (latent)	.412	77	24	45.05

For all patients, the protease inhibitor treatment reduced the theoretical viral load to a value below one faster than the CCR5 receptor mutagen treatment. However, we see that the latter treatment is less variable in its effectiveness. That is, there is little difference between how quickly it drops the viral load to a value below one in individuals with AIDS and in individuals in the latent stage. In terms of clinical research, this shows promise as treatments that have large variation for different individuals often have other complicating factors that change the efficacy or variability in the treatment. The CCR5 receptor mutagen's days to viral load <1 suggests, with their low variability, that the mutagen is not affected by many other factors in the patient's immune system or body and perhaps may have higher efficacy in terms of treatment overall. For example, it would take 35% longer for a protease inhibitor to theoretically clear the virus from patient 102 (who has AIDS) as opposed to patient 103 (who is in the latent stage). On the other hand, it would only take about 4% longer for the CCR5 receptor mutagen to theoretically clear the virus from patient 102 as opposed to patient 103. However, it is evident that our model shows protease inhibitors to be more effective at reducing viral load as opposed to the proposed CCR5 receptor mutagen, so research should be focused on developing HIV-1 treatments with a mechanism of action that mimics the dynamics of the former.

An interesting correlation can also be detected: efficiency of the protease inhibitor treatment decreases as the initial viral load increases. The opposite is true of the CCR5 receptor mutagen. As initial viral load increases, the efficiency of this treatment increases.

5 Outlook

Further Research

The ongoing research on treatments for HIV include the CRISPR-CAS9 gene editing system. CRISPR-CAS9 is a system that makes a double-stranded cut in the host cell's DNA and then can insert a customizable segment of DNA into the genome for replication. This system was found by a yogurt manufacturer in order to protect the bacteria cultures from infections by viruses. Researchers have sought to edit genes made by the CD4+ T cells so that they cannot be infected by HIV while others have thoughts to insert this gene editing system into the T cells so that they can make the appropriate edits to the HIV's genome and protect themselves from infection. When HIV infects a CD4+ T cell, its genome is integrated into the host cell's genomes so that it can be replicated by the host and multiply the number of viruses in the immune system. If a person's were equipped with the DNA cleaving technology of the CRISPR-CAS9 system that includes a DNA cleaving enzyme, and the customizable portion of DNA that seeks the HIV genome, the T cell could find and cut the HIV and prevent infection.

The mathematical models that could be used to analyze this "cure" could include the change in amount of CD4+ T Cells that have incorporated CRISPR-CAS9 system over time, and the change in viral load, and change in number of healthy CD4+ T cells. The mass action coefficient of the CRISPR-CAS9 system would have to be found experimentally in vitro and then analyzed in vivo.[3,4] The amount of cell-to-cell transmission of the components of the CRISPR-CAS9 system can also be assessed as the amount of cell-to-cell transmission of HIV is often higher than the virus-to-cell transmission.[12] The amount of integration of this gene editing technology can further be analyzed using parallel systems of antibody drug therapy adherence.[1,11] The remaining variables would remain the same in the analysis of the healthy CD4+ cells and viral load.

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