HIV-1 Replication Rate

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Abstract

Antiviral drugs have been known to prolong the lives of HIV infected patients. However, it is still uncertain if antiviral drugs affect the rate of virion clearance, the loss of target cells, or both. In this study, we used mathematical models to measure the effects of a protease inhibitor on three infected patients. After analysis of this data, we were able to calculate the lifespans of free virions and infected cells. We found that the antiviral drug decreased not only the number of free virions in the plasma but also the loss of infected target cells. Although this antiviral drug is not a cure for this disease, it can provide insight into creating an effective treatment program for HIV patients.

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1 Introduction

Researchers have been trying to understand why the *human immunodeficiency virus* (HIV) leads to the collapse of the immune system. One hypothesis is that HIV destroys target cells that have CD4 receptors. These target cells, or white blood cells, are crucial to the immune system. Once infected, a target cell becomes a virus-producing cell. After about seven hours, the target cell releases free virions into the plasma either by budding or erupting.

In a recent study, plasma levels of HIV-1 were shown to decrease exponentially after an antiviral drug was administered to five patients (Ho *et al.* 1996). The antiviral drug, known as Ritonavir, is a protease inhibitor that prevents the virus from producing core proteins necessary for viral infection. These core proteins include RNA, gag, and pol proteins (Schupbach 1990). Ritonavir has only been on the market since 1996. Since Ritonavir's lifespan is only 8-10 hours, HIV patients need to take the drug consistently; the recommended dosage is 600mg twice a day (Ad).

Our project initially studied the dynamics of HIV-1 replication rate using what we will refer to as the P-Model (Ho *et al.* 1996). Our main purpose was to estimate the clearance rate and the lifespan of free virions and infected T cells on simulated data from three patients over a ten-day period. By analyzing the derivation of the P-Model, we were able to determine its efficiency for explaining the behavior of HIV replication. We realized that the P-Model's efficiency depends upon many unrealistic assumptions, and decided to take our research further. We came up with a model that takes into account the drug's efficiency, the fact that T cells replicate, and that there is an immune response.

What we call the L-Model is

Before treatment
$$dT/dt = \Lambda - kVT/P - \mu T + qkVT/P \tag{1}$$
$$dT^*/dt = (1-q)kVT/P - \delta T^* \tag{2}$$
$$dV/dt = N\delta T^* - cV - qNkVT/P \tag{3}$$

After treatment
$$dT/dt = \Lambda - kV_1T/P - \mu T + qkV_1T/P \tag{4}$$
$$dT^*/dt = (1-q)kV_1T/P - (r+\delta)T^* \tag{5}$$
$$dV_1/dt = \phi N\delta T^* - cV_1 - q\tilde{N}kV_1T/P \tag{6}$$

$$dV_{NI}/dt = (1 - \phi)N\delta T^* - cV_{NI}, \qquad (7)$$

where the total concentration of virions in the plasma is $V(t) = V_I(t) + V_{NI}(t)$. $V_I(t)$ is the plasma concentration of virions in the infectious pool and $V_{NI}(t)$ is the concentration of virions in the noninfected pool. At the beginning of the treatment, when time is zero, $V_I(0) = V_0$ and $V_{NI}(0) = 0$.

Variables

$V(t)$	$=$	the concentration of viral particles in plasma at time t.
$V_1(t)$	$=$	the plasma concentrations of virions in the infectious pool. produced before the drug's application, $V_i(0) = V_0$.
$V_{NI}(t)$	$=$	the concentration of viral particles in the noninfectious pool. produced after the drug's application, $V_{ni}(0) = 0$.
T	$=$	target cells.
T^*	$=$	virus-producing cells.

Unknown

N	$=$	number of new virions produced per infected cell during its lifetime.
$\tilde{N}$	$=$	virions killed by each T,

Parameters

q	$=$	proportion of successful attacks by the T cells.
T/P	$=$	probability of T cell infection.
Λ	$=$	constant recruitment rate.
μ	$=$	per capita death rate.
ϕ	$=$	drug efficiency.
P	$=$	total population of T cells.
k	$=$	the rate at which HIV infects target cells.
c	$=$	the viral clearance rate.
δ	$=$	the loss rate of infected cells.

In this paper we find a solution in terms of V_0, c, and δ for the total concentration of virions in the plasma at time t. We then use this solution

and the data to estimate c and δ. Next, we compute the half life of free virions and interpret the average lifespan of a virion, an infected cell, and the average generation time of the virus. In the following section we estimate parameters and compare the predictions of a different model with results from the average lifespan of a virion, an infected cell, and the average generation time. We conclude with remarks on the biological implications of our results.

2   Interpretation of the L-Model

What we have named the L-Model is an extension of our initial project. It takes into account the T cells' dynamics and the immune system's defense reaction; therefore, it includes such factors as the rate of change of T cells, the recruitment rate, the mortality rate of T cells, and the number of successful attacks by T cells on the virions. These important elements, omitted in the P-Model, are now taken into account to provide a more accurate analysis. Like the P-Model, the L-Model contains two parts: before and after treatment. As we analyze the change of T cells with respect to time, before treatment we see that there is a recruitment rate as well as a result of the interaction between the virions and the T cells. There is also a mortality rate, reducing the number of T cells. Successful attacks by the immune system on the virus reduce the number of infected T cells. Changes in the number of infected T cells relative to time are also affected by the loss rate of infected T cells. As the number of infected T cells increases, so does the number of virions, but as the population of virions grows there is a portion of virions being eliminated by the clearance rate and by the immune system's successful attacks. Similarly, the "after-treatment" portion of the L-Model includes an analysis of changes in the number of T cells with respect to time. This change is almost identical to the one before treatment, except that this time only the infectious virions affect the normal T cells. This is because the only virions that the T cells recognize are the initial ones. Likewise, the change in the number of infected T cells after treatment is similar to that of before treatment except that the mortality rate of T cells influences the number of infected T cells. There are two types of virions, the infectious and the noninfectious. The change in the number of infectious virions relative to time is related to the drug's effectiveness since the drug is not 100% effective. The term $\phi N \delta T^*$ represents infectious virions that the T cells continue to

attack after treatment. The number of noninfectious T cells is related to the drug's effectiveness and the clearance rate.

In comparison to the P-Model, the L-Model is a better fit for reality because it relaxes most of the assumptions made in the P-Model. The L-Model makes only three assumptions: it assumes that the drug is administered once and that its effectiveness is a constant function of time; it also assumes low initial estimates for the number of new virions produced per infected T cell during its lifetime, and for the number of virions killed by one T cell.

3 Solving for the Concentration of Virions

By simplifying the L-Model and utilizing a few mathematical methods of approximation, we were able to find appropriate estimates for the viral clearance rate, denoted by c, and the loss rate of infected T cells, denoted by δ. In order to simplify the L-Model, we considered the situation when we have a 100% effective drug (i.e., $\phi = 0$) and when the T cells are unable to attack the virus (i.e., $q = 0$). In addition, we must also make the following assumption for simplification purposes: T cells are initially at a quasi-steady state. This implies that the replication rate of T cells relative to time, in comparison to the replication rate of HIV-1 relative to time, is negligible (i.e., $dT/dt = 0$). Thus the number of T cells is considered to be constant throughout the steady period. In dealing with such a small-time interval (T_0), we can also neglect the mortality rate of normally producing T cells (i.e., $\mu T = 0$).

Given these assumptions, we can eliminate equations (1) and (4) from the system, as well as any component containing ϕ or q to obtain:

$$\text{Before treatment} \quad \begin{aligned} dT^*/dt &= kVT - \delta T^* & (8) \\ dV/dt &= N\delta T^* - cV & (9) \end{aligned}$$

$$\text{After treatment} \quad \begin{aligned} dT^*/dt &= kV_I T - \delta T^* & (10) \\ dV_I/dt &= -cV_I & (11) \\ dV_{NI}/dt &= N\delta T^* - cV_{NI}, & (12) \end{aligned}$$

As a result of this elimination process, we are able to derive the P-Model from the L-Model. With this system of five nonlinear differential equations

and a few assumptions, we can derive a solution for the number of virions in the plasma at time t.

Several assumptions are included in this model to simplify the analysis of HIV's behavior under drug treatment. First of all, we assume that the HIV-1 virus infects a target cell at a constant rate k, at which time it takes on the role of a productively infected cell, T^*. Second, we assume the drug is 100% effective and that the number of target cells remains constant. Furthermore, we assume infected cells do not recover during the treatment period, to reduce the complications on the estimation of c and d. We also assume that the system describing the dynamics of HIV-1's reproduction rate is at a quasi-steady state, that is, that $dT^*/dt = 0$ and $dV/dt = 0$ before the drug treatment. This assumption may be reasonable if the uninfected cell concentration stays at its steady state level for approximately a week after the administration of Ritonavir. Given these assumptions, the model becomes simple enough that an interpretation of the dynamics of the virus is possible (a caricature).

Using the P-Model, we were able to derive a mathematical expression for the total concentration of virions at time t that depends only on the initial number of virions, V_0, the rate of virion clearance, c, and the loss rate of infected cells δ. To analyze the replication rate of HIV-1 under drug treatment, we assume that (at the moment we start the treatment) the replication rate of infected T cells and of virions is zero. Thus $dT/dt = 0$ and $dV/dt = 0$. We also assume that the level, T_0, remains constant for the first week after the drug is administered. In other words, we assume that T remains at a steady state for one week after the drug is administered.

Then we obtain the number of infectious virions $V(t)$ by using separation of variables to integrate equation (11):

$$\int_{V_0}^{V_I(t)} \frac{dV_I}{V_I} = \int_0^t -c\,dt$$

$$\ln|V_I| \Big|_{V_0}^{V_I(t)} = -ct \Big|_0^t$$

$$\Rightarrow \quad \ln|V_I(t)| - \ln|V_0| = -ct$$

$$\ln\left|\frac{V_I(t)}{V_0}\right| = -ct \qquad (13)$$

$$e^{\ln\left|\frac{V_I(t)}{V_0}\right|} = e^{ct}$$

$$\left|\frac{V_I(t)}{V_0}\right| = e^{ct}$$

$$V_I(t) = V_0 e^{-ct}.$$

Next, in order to find the number of noninfectious virions in the plasma, we solve equations (10) and (12). First we solve for T^* after we substitute our last result for $V_I(t)$ into equation (10)

$$\frac{dT^*}{dt} = kV_0 e^{-ct}T - \delta T,$$

and since T is constant then

$$\frac{dT^*}{dt} = kV_0 e^{-ct}T_0 - \delta T^*.$$

Using the integrating factor technique yields

$$e^{\delta t}\frac{dT^*}{dt} + \delta e^{\delta t}T^* = kV_0 e^{\delta - ct}T_0.$$

This expression can be written

$$\Rightarrow \quad \frac{d}{dt}(T^* e^{\delta t}) = kV_0 T_0 e^{\delta - ct}.$$

Changing the variable of integration we get

$$\int_0^t \frac{d}{ds}(T^* e^{\delta t})ds = \int_0^t kV_0 T_0 e^{(\delta - c)s}ds$$

$$T^*(t)e^{\delta t} - T^*(0) = \frac{kV_0 T_0}{\delta - c}\left(e^{t(\delta - c)} - 1\right)$$

$$T^*(t)e^{\delta t} = \frac{kV_0 T_0}{\delta - c}\left(e^{t(\delta - c)} - 1\right) + T^*(0)$$

$$T^*(t) = \left[\frac{kV_0 T_0}{\delta - c}\left(e^{t(\delta - c)} - 1\right) + T_0^*\right]e^{-\delta t} \qquad (14)$$

$$T^*(t) = \left[\frac{kV_0 T_0\left(e^{t(\delta - c)} - 1\right) + (\delta - c)T_0^*}{\delta - c}\right]e^{\delta t},$$

where T_0^* is the initial value of $T^*(t)$.

Assuming that we are in a quasi steady-state so that $dT^*/dt = 0$, it follows from equation (8) that if T_0^*, V_0, and T_0 are the initial conditions of T^*, V, and T, respectively, then $kdV_0T_0 = \delta T_0^*$. Making this substitution, equation (14) becomes

$$T^*(t) = \left[\frac{[T_0^*\delta\left(e^{t(\delta-c)} - 1\right) + (\delta - c)T_0^*)]}{\delta - c}\right] e^{-\delta t}, \qquad (15)$$

$$= \frac{T_0^*\delta e^{-ct} - T_0^* c e^{-\delta t}}{\delta - c}$$

$$= \frac{T_0^*}{\delta - c}\left(\delta e^{-ct} - ce^{-\delta t}\right).$$

Next we substitute this expression for $T^*(t)$ into equation (12) and solve for $V_{NI}(t)$, obtaining the number of noninfectious virions in the plasma:

$$\frac{dV_{NI}}{dt} = N\delta\left(\frac{T_0^*}{\delta - c}(\delta e^{-\delta t} - ce^{-\delta t})\right) - cV_{NI}$$

$$= \frac{N\delta T_0^*}{\delta - c}(\delta e^{-ct}) - \frac{N\delta T_0^*}{\delta - c}(ce^{-\delta t}) - cV_{NI}$$

$$\frac{dV_{NI}}{dt} + cV_{NI} = \frac{N\delta T_0^*}{\delta - c}(\delta e^{-ct}) - \frac{N\delta T_0^*}{\delta - c}(ce^{-\delta t}).$$

Using the integrating factor technique yields

$$e^{ct}\frac{dV_{NI}}{dt} + ce^{ct}V_{NI} = \frac{N\delta^2 T_0^*}{\delta - c} - \frac{N\delta^2 T_0^*}{\delta - c}ce^{ct}e^{-\delta t}$$

$$\int_0^t \frac{d}{ds}(e^{cs}V_{NI}) = \int_0^t \frac{N\delta^2 T_0^*}{\delta - c}ds - \int_0^t \frac{N\delta T_0^*}{\delta - c}ce^{(c-\delta)t}ds \qquad (16)$$

$V_{NI}e^{ct} = \frac{N\delta^2 T_0^* t}{\delta - c}\left(\frac{1}{c-\delta}\right)e^{(c-\delta)t}$, since $V_{NI}(0) = 0$.

Now equation (9) and $dV/dt = 0$ implies $N\delta T_0^* = cV_0$, and with this substitution equation (16) can be rewritten as

$$\Rightarrow \quad V_{NI}(t) = \frac{N\delta T_0^*}{\delta - c}\left(\delta t e^{-ct} - \frac{ce^{-\delta t}}{\delta - c} + \frac{ce^{-ct}}{c - \delta}\right)$$

8

$$= \frac{N\delta T_0^*}{\delta - c}\left(\delta t e^{-ct} - \frac{c}{\delta - c}\left(e^{-\delta t}e^{-ct}\right)\right) \qquad (17)$$

$$= \frac{N\delta T_0^*}{c - \delta}\left(\frac{c}{\delta - c}(e^{-\delta t} - e^{-ct}) - \delta t e^{ct}\right)$$

$$V_{NI}(t) = \frac{cV_0}{c - \delta}\left(\frac{c}{c - \delta}(e^{-\delta t} - e^{-ct}) - \delta t e^{-ct}\right).$$

Hence, using equations (13) and (17) the total number of virions in the plasma at time t

$$V(t) = V_I(t) + V_{NI}(t)$$

can be expressed as

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

Given this solution, we can obtain appropriate values for the parameters for c and δ using various mathematical techniques. This work is described below.

4   Estimation of c and δ

We estimated the clearance rate of virions and the loss rate of infected cells by using the *Mathematica*'s packages NonlinearFit, Statistica Nonlinear Regression Analysis, Least Squares Method, and Find Minimum Program.

The *Mathematica* NonlinearFit Package applies internally to Quasi Newton's Method, which gives the best approximations for the parameters of nonlinear multivariable equations. Here we entered the data of virions produced for all three patients. For each patient, we found estimates for V_0, c, and δ, using the solution of $V(t)$ and giving initial estimates to these parameters. We then computed the average estimates for V_0, c, and δ. These approximations enabled us to graph the P-Model by plotting the average predicted values. Finally, we used Mathematica to compute the relative error of the P-Model with respect to the data observed, applying the relative error formula to the data of each patient. Thus, we obtained converging values for every parameter with a minimum error. Similarly, the Statistica Nonlinear Regression analysis package provided these minimum estimates, but for a more complicated case. The Regression Analysis Package, unlike the

NonlinearFit, applied the Quasi Newton's Method to the observed data for all patients simultaneously. As a result, it yielded the average estimates of the parameters. The FindMinimum program, unlike the two aforementioned methods, takes much longer and incorporates more steps to compute the best parameter approximations.

5 Graphical Analysis of the Latino and Perelsom Models

The decline that occurs in the number of virions in the plasma after the drug is administered to the three patients can be interpreted graphically. By graphing the solution to the P-Model $V(t)$ and using the obtained average parameter values of c, δ, and the initial number of virions, V_0, we observe an exponential decay in the number of virons as time progresses (see Figure 1).

Initially we see a delay in the decline of virions, followed by a rapid, then a slower, decline. The delay that occurs in the first few hours is due to the amount of time needed for the drug's absorption, distribution, and penetration. The slow rate of decay in the number of virions during the last hours of the treatment period results from the dissipation of the drug's concentration.

By comparing the predicted data with the observed data we can conclude that the P-Model, under the assumptions made, accurately describes the replication dynamics of HIV-1. This model provides a well-fitting curve for the observed data of each of the patients (Figures 2a-2c). The deviation from the curve to the observed data is almost insignificant, yet as we approach the end of the 10-day trial period this deviation increases. The efficiency of this model for all three cases under study is reflected in the relative error rate of each patient. As time goes by, the relative error for each patient increases (Table 1).

We used *Matlab* to simulate our model. We created a program to find the best number of parameters for k, ϕ, and q, then we graphed the functions of V_I, T, T^*, and V_{NI} to see the behavior of the graphs. Finally, we analyzed the graphs to see if these behaviors are consistent with biological behavior.

6 Comparison of the P-Model to the Wei *et al.* Model

$$V(t; c, \delta) = [V_0/(c - \delta)] \left(c e^{-\delta t} - \delta e^{-ct} \right) \qquad (18)$$

This model was introduced by Wei *et al.* (1995) and its symmetrical formulation does not allow us to distinguish between the viral clearance rate and the loss rate of infected T cells. In addition to this ambiguity involved in finding parametric values for c and δ, we find that the nonlinear regression analysis utilized in finding estimates for c and d in the P-Model is not suitable for this model. Consequently, use of this data-fitting procedure in the Wei *et al.* (1995) model only establishes the fact that it is sensitive to the initial conditions chosen; that is, a slight alteration of the initial conditions for c and δ yields entirely different results for their minimum values as processed by the NonlinearFit package.

In order to demonstrate the limitations of equation (18) for distinguishing the parameters c and δ, we observe that $V(t; c, \delta) = V(t; \delta, c)$. Therefore, if we tried to compute values for c and δ we would not be able to distinguish between them.

7 Analysis of the Drug's Effectiveness (ϕ) According to the L-Model

When the drug is 100% effective $\phi = 0$, and when the drug is completely ineffective $\phi = 1$. Therefore, as ϕ approaches 1 (i.e., as the drug loses its efficiency), the number of noninfectious virions approaches zero. This implies that at $\phi = 1$ the drug's effectiveness has ceased, thereby causing the patients to revert to their condition before treatment.

The drug's effectiveness eventually diminishes (i.e., $\phi \to 1$). With time the virus builds resistance and the drug's concentration in the blood stream vanishes. In order for the patients not to return to their condition before treatment, we must administer the drug periodically. Since the drug's effectiveness changes periodically with time, it must contain a periodic component accounting for the resistance it encounters, ϕ.

11

After administering a protease inhibitor drug Ritonavir in two different strengths, the percentages of infectious virions (V_1), noninfectious virions (V_{NI}), T cells (T), and infectious viron-producing T-cells (T^*) change. This variation is directly affected by the strength of the drug. Histograms allow us to approximate the percentages of virions and cells, and also explain Graph 1.

Analyzing the number of virions before treatment (Histogram 1), we observe that all of the virions produced before the drug's administration are infectious (V_1). In analyzing the number of infected and noninfected T cells before the drug, we assume that 100% of the cells before treatment are producing only infectious virions. After the drug is administered, we divide our observations into two categories: the first one is when we have a drug that is 99% effective, and the second one is when the drug is 10% effective. When we use a 99% effective drug, we observe the percentage of healthy T-cells is greater. This is because the drug is stopping the production of infectious virions; therefore, there are not enough virions to infect T-cells.

In Histogram 2a, we use an extremely efficient drug (99% effective). A drug this efficient will transform cells from infectious virion-producing (T^*) to noninfectious viron-producing cells (T). The greater number of T will show a large population of V_{NI}. On the other hand, in Histogram 2b, when the drug is only 10% effective, the percentage of infected virions will be higher than the noninfected ones (mainly because of the drug's inefficency in protecting cells from becoming T^*). By using a less effective drug, we have a tremendous production of infectious virions (V_i); these virions will infect a greater number of T-cells, consequenly converting them into infectious T-cells (T^*) at a fast rate.

Results

Figure 1 measures the predicted values for the number of free virions in the plasma over a 10-day period. If we use the P-Model, we expect to see an initial delay followed by a rapid then a slow decrease in the number of free virions. This initial delay is less than a day. The number of virions decreases to zero at the end of 10 days.

In Figures 2a-2c, the observed and predicted values are plotted for the three patients. The number of free virions does decrease over time. These results are consistent with our predicted values (refer to Figure 1 for the predicted values).

Figure 3 measures the predicted number of infected virions when the drug's efficiency is 10%, 50%, and 99%. The dashed curve represents the drug's efficiency when it is 99%, the middle curve when it is 50%, and the top curve when it is 10%. Q represents the number of successful attacks by T cells when the T cell count is 1%. When the drug's efficiency is 99%, the number of infected virions approaches zero after two days. The number of infected virions is significantly higher when the drug's efficiency is 10

Figure 4 measures the predicted number of noninfectious virions for drug efficiencies of 10%, 50%, and 99%. When the drug is 99% effective, the number of noninfectious virions reaches a peak of 15 virions 1.5 days after treatment. Then there is a slow decline in the number of noninfectious virions over the 10-day period. The peak only reaches eight noninfectious virions for a drug efficiency of 50%, and two noninfectious virions for a drug efficiency of 10%.

Figure 5 measures the predicted number of T cells using the same drug. When the drug's efficiency is 99%, the T cell count remains constant at a value of 1.3295×10^4 cells.

Figure 6 measures the predicted number of infected T cells. When the drug is 99% efficient, the number of infected T cells approaches zero. This occurs six days after drug treatment. When the drug is 50% effective, there is a gradual decrease in the number of infected T cells. However, there are still 10 infected T cells remaining after 10 days of drug treatment. The number of infected T cells increases when the drug is 10% effective.

8   Conclusion

We look upon the work done here as only the beginning of an on-going learning process. Thus our work is not entirely conclusive. With this in mind, we offer to those individuals interested in expanding on our work some suggestions for improving the accuracy of our model. First, it is important to consider the long-term effects and treatment process for the antiviral drug. A long-term model would focus on the dynamics of HIV and include HIV's density, mutation rate, and drug resistance. Since HIV becomes resistant to Ritonavir, it is important to continue applying the drug. Reapplication can be modeled as a periodic funtion of time for the drug's effectiveness.

Graphically, we would expect to get a cyclic function which repeats itself every time the drug is applied. Over time, the total number of virions and infected T cells declines, but as soon as HIV builds resistance, the number of virions will increase dramatically. Therefore, if we consider a long-term effect we will expect a cyclic funtion which initially decreases then increases rapidly.

To bring this model closer to reality, it is also essential to increase the sample size. Another suggestion for further research would be to administer more than one drug during the period of study. Although the list of ideas for further study is not exhaustive, we leave the generation of more interesting additions to our list up to the curious scientist in all of us.

Acknowledgements

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Figure 1

Number of Free Virions (model)
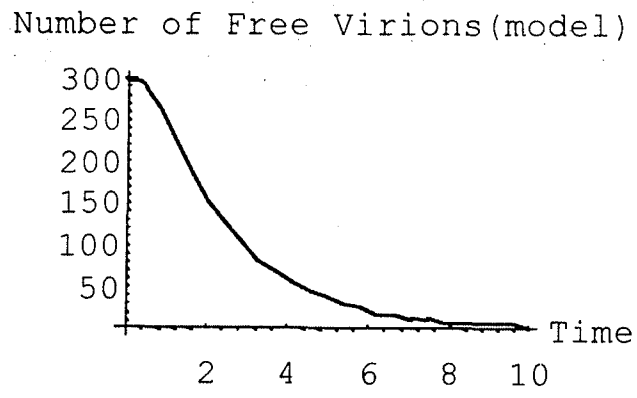
Figures 2a - 2c

Number of free virions as a function of time for each of the three patients.
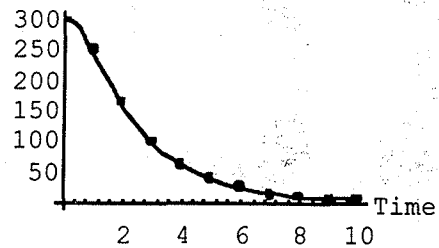
Figure 2a:

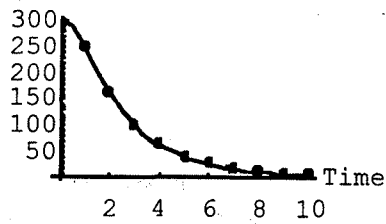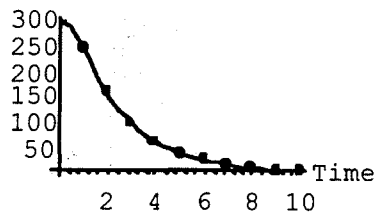Number of Free Virions in Plasma(1)

Figure 2b

Number of Free Virions in Plasma(2)

Figure 2c:

Number of Free Virions in Plasma(3)

Histograms

Effect of the drug on Virions and on T-cells.
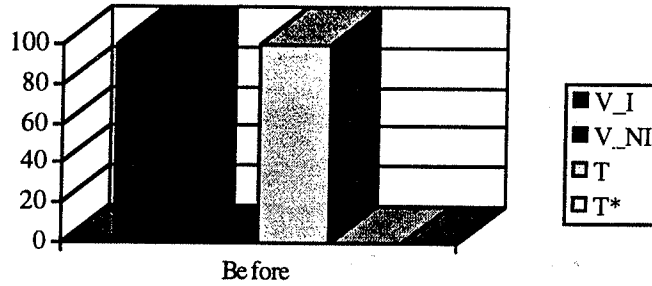
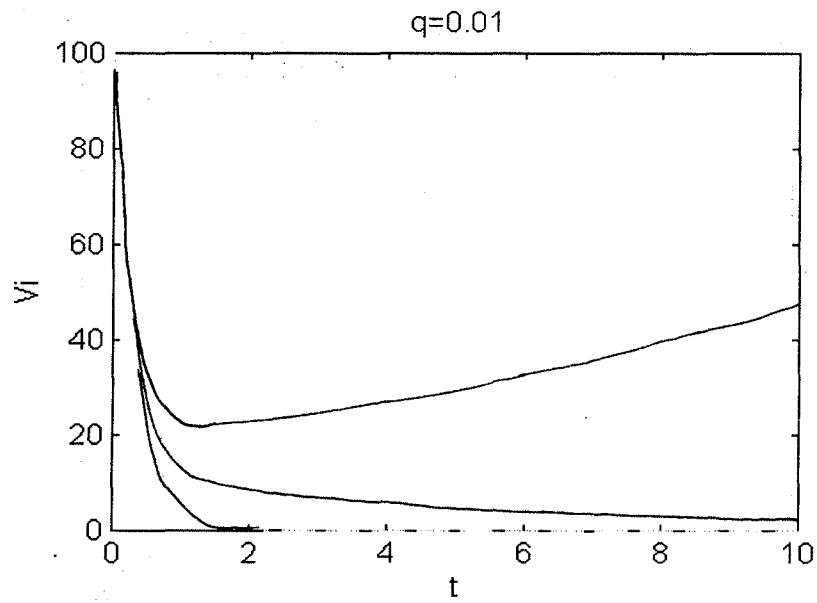**Histogram 1**
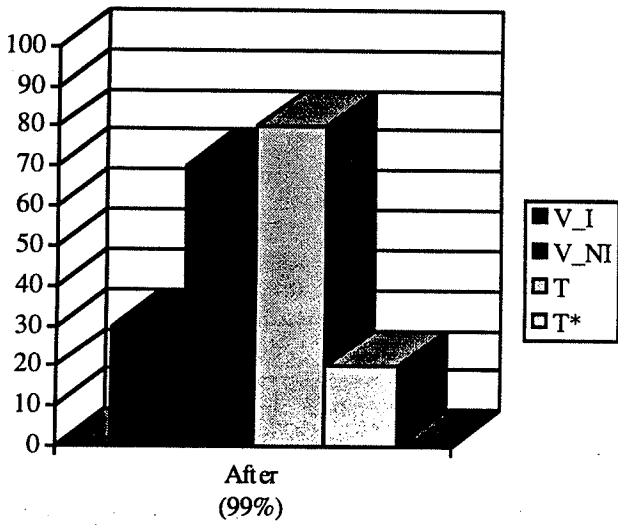
Histogram 2a
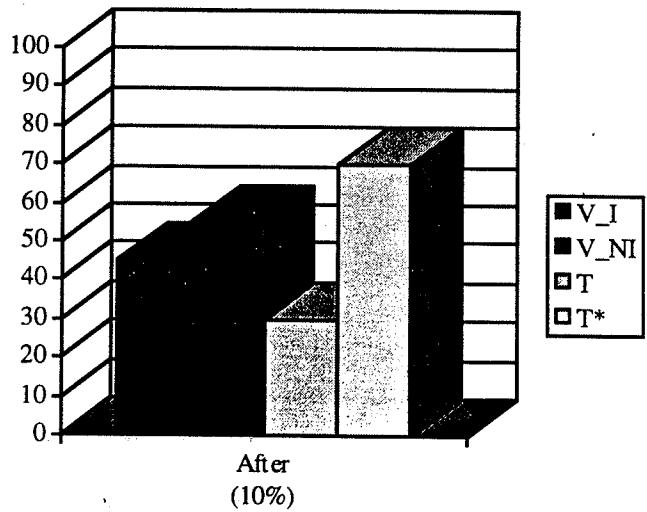
Histogram 2b

HIV-1 Replication Rate

q=0.01

Figure 3

q = 0.01
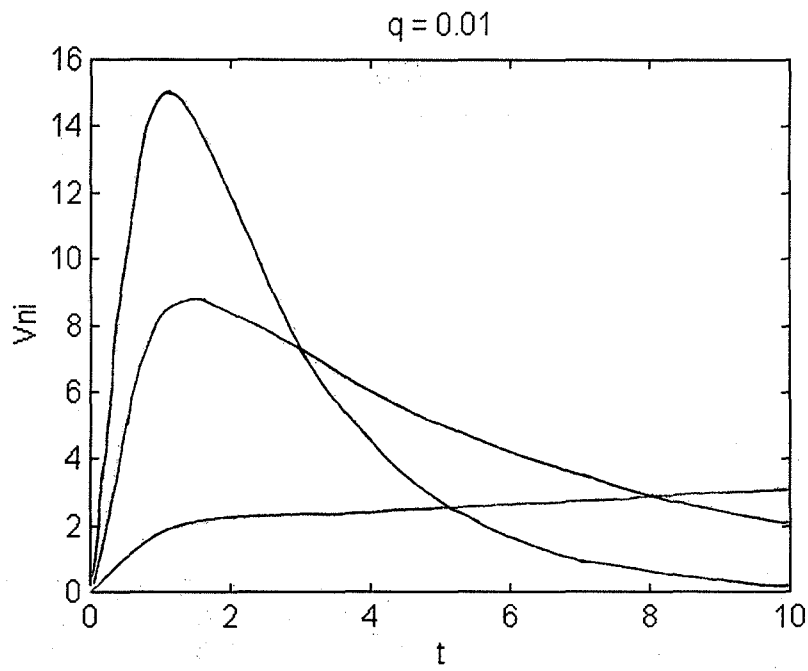
Figure 4

HIV-1 Replication Rate

q = 0.01

Figure 5

q = 0.01

Figure 6