On a Mathematical Model of HAART

B. D. Aggarwala

Abstract — **We develop a mathematical model to chart the progression of the virus in an HIV positive patient. The model gives realistic results. We also discuss what happens when the treatment is stopped.**

I. Introduction

HIV is the latest frontier of virus' attack on humanity. This virus has already killed more than 30 million people all over the world and there is no end in sight. So far, there is no drug that can give you immunity against this virus and no such drug is on the anvil. Only some attempts of questionable value have been made by the drug companies. This is perhaps because this virus is extremely mutable. In the presence of any antiretroviral (ARV) drug, it mutates to become resistant to the drug before the drug is able to eliminate it. If you stop the treatment, it starts multiplying again. If you develop a drug that gives you immunity against the wild type HIV virus, there would be little or no immunity against various kinds of drug resistant viruses which are developing rapidly, most notably in the developed countries, where the ARV treatment is relatively more common. It is estimated that in the U.S., about 50% of patients receiving antiretroviral therapy are infected with HIV viruses that express resistance to at least one of the available antiretroviral drugs [1]. This implies the necessity of developing more and more new drugs to which different strains of resistant viruses are susceptible. As this virus resistance reaches the countries where even the present day ARV's are not affordable, one can expect a new wave of potentially untreatable HIV prevalence. In today's environment, it is imperative to test a newly infected patient for any resistant viruses before starting an optimal treatment [1]. Any suboptimal treatment will lead to early drug failure and further development of resistant viruses. The main causes of development of resistance are suboptimal treatment and incomplete adherence to therapy. This is because, if the treatment is interrupted (or not optimal), the virus starts to multiply and to mutate. It should be emphasized that resistance is both the cause and the consequence of virus replication. The virus needs to replicate in order for it to mutate and to develop resistance, and if the prescribed drug is suboptimal, it replicates in the presence of that drug and develops further resistance to it. The relationship between drug resistance and antiretroviral activity would appear to be Bell- shaped in as much as little or no drug pressure would result in no resistance development and very strong antiretroviral activity would result in no replication and therefore no resistance development as well [2,8]. In this paper, we shall use the terms 'drug failure' and 'propagation of resistant virus' interchangeably. It is a challenge to develop drugs that will give you immunity against ALL kinds of resistant viruses. Elimination of HIV is still a distant dream.

In this paper, we study the treatment of an HIV positive patient with antiretroviral drugs. In the case of one such drug, the virus will mutate and develop resistance to this drug while in the case of treatment with two or more drugs, there will be virus which has mutated and developed resistance to only one of these drugs, or to two of these drugs, or to more. The virus develops resistance by substitution in one or more nucleotides in its genome sequence, so that it takes longer and longer for the resistance to one, two or three drugs to develop. Our model will show that, under treatment with three drugs (HAART), u_0, u_1, and u_2, the viruses which are resistant to zero drug, to one drug, or to two drugs respectively, will soon disappear and the one with resistance to all three drugs, u_3, will eventually emerge and dominate. The time over which u_3 emerges will be considerably longer than that over which resistance develops in the presence of only one drug. Hence, the success of HAART.

If the treatment is stopped, the model will say that the number of susceptible cells will drop and the wild type virus will come back to dominate as the advantage of resistant virus (in the presence of the drugs) as against the wild type one will gradually vanish.

II. The Model

We take one ml as the unit of volume and one day as the unit of time and write,

$$x_1'(t) = A_1x_1 - A_2x_1x_1 - A_3x_1(u_0+u_1+u_2+u_3) \tag{1.1}$$

$$x_2'(t) = A_4x_1(p_0u_0+p_1u_1+p_2u_2+p_3u_3) - A_5x_2 - A_{15}x_2u_4 \tag{1.2}$$

$$x_3'(t) = A_7x_2 - A_8x_3 \tag{1.3}$$

$$u_0'(t) = A_9A_4((1-Q_1c_1)p_0x_1u_0+Q_2c_1p_1x_1u_1) - c_1u_0 - A_{14}u_0u_4 \tag{1.4}$$

$$u_1'(t) = A_9A_4(Q_1c_1p_0x_1u_0 + (1-Q_1c_1)(1-Q_2c_1)p_1x_1u_1 + Q_2c_1p_2x_1u_2) - c_1u_1 - A_{14}u_1u_4 \tag{1.5}$$

$$u_2'(t) = A_9A_4(Q_1c_1p_1x_1u_1 + (1-Q_1c_1)(1-Q_2c_1)p_2x_1u_2 + Q_2c_1p_3x_1u_3) - c_1u_2 - A_{14}u_2u_4 \tag{1.6}$$

$$u_3'(t) = A_9A_4(Q_1c_1p_2x_1u_2 + (1-Q_2c_1)p_3x_1u_3) - c_1u_3 - A_{14}u_3u_4 \tag{1.7}$$

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$$u_4'(t) = A_{12}x_2 + A_{13}(u_0+u_1+u_2+u_3) - c_4u_4, \quad (1.8)$$

where x_1, x_2, and x_3 are the number of susceptible cells, the productively infected cells, and the latently infected cells respectively per millilitre, u_0 denotes the amount of virus which is resistant to no drug (i.e. the wild type virus) and u_1, u_2, and u_3 denote the amount of virus resistant to one, two and three drugs respectively. The quantity u_4 is the number of antibodies generated by the productively infected cells and the virus, while Q_1 is the probability that u_0 will change to u_1, or that u_1 will change to u_2 in one life cycle of the virus so that $(1-Q_1c_1)$ is the probability that it will not do so in one day, where we have assumed that the virus lives for $1/c_1$ days. Also, Q_2 is the probability that u_2 will change to u_1 or u_3 will change to u_2 in one life cycle. Because of drug pressure, virus has the tendency to change from u_0 to u_1 (or from u_1 to u_2, or from u_2 to u_3) rather than the other way around, so that $Q_1 >> Q_2$. $A_4x_1p_0u_0$ is the number of susceptible cells that become productively infected after being attacked by u_0. Similarly for u_1, u_2 and u_3. A_9 is the number of viruses produced by each infected cell while A_5 denotes the rate at which the infected cells die. The meaning of other parameters is clear from the context.

It should be noted that A_3 is the average infection coefficient of all of different viruses, u_0, u_1, u_2, and u_3. Generally, the infectivity of the wild type virus is higher than that of the resistant virus. However in the presence of HAART, because of the presence of reverse transcriptase inhibitor, the average value of A_3 is expected to be much smaller than its value for the wild type virus. Also, because of the presence of protease inhibitor, the number of productively infected cells which produce infectious virus, is going to be smaller still. We assume that the virus which is resistant to all the three drugs (in a HAART treatment) will, eventually, be able to change the largest number of susceptible cells into virus producing cells. We therefore assume that $1 > p_3 > p_2 > p_1 > p_0$. The equations for u_0, u_1, u_2, and u_3 in our model indicate that our model is based on the premise that every productively infected cell produces viruses. If a cell becomes productively infected, then it will produce A_9 viruses during its lifetime (which is usually quite short). The equations (1.1) and (1.4-7) may also be looked upon as a system of predator-prey equations in which the four types of predators u_0, u_1, u_2, and u_3 prey upon the cells x_1. The cells proliferate in the absence of predators according to the logistic law and die when attacked by the predators. The predators die if left to themselves (no food and killed by antibodies) and proliferate when there is sufficient food. The one which eats the most prey lives to see another day. We shall assume that all the coefficients in our model are non negative unless otherwise noted.

A. Basic Reproduction Ratio

As the virus mutates, slowly the viruses u_0, u_1, and u_2 will disappear and, *eventually*, u_3 will be the dominant virus. So, we look for an equilibrium point (which point is reached as $t\to\infty$) of the above dynamic under the restriction that $u_0 = u_1 = u_2 = 0$ and satisfy the equations (1.1), (1.3), (1.7), and (1.8) to find x_1, x_3, u_3, and u_4. We find that

$$u_3 = (A_1A_4A_9c_4p_3\,(1-Q_2c_1) - A_2(c_1c_4+A_{12}\,A_{14}\,x_2)) / (A_{13}A_{14}A_2 + A_3A_4A_9c_4p_3\,(1-Q_2c_1)).$$

The corresponding point of equilibrium P_3, turns out to be

$$P_3 = \{x_1, x_2, x_3, u_0, u_1, u_2, u_3, u_4\} = \{(A_{13}A_{14}A_1 + A_3c_1c_4 + A_{12}\,A_{14}\,A_3x_2\,)/(A_{13}A_{14}A_2 + A_3A_4A_9c_4p_3(1-Q_2c_1)),\ x_2,\ (A_7x_2)/A_8,\ 0,\ 0,\ 0,\ (A_1A_4A_9c_4p_3(1-Q_2c_1) - A_2(c_1c_4 + A_{12}A_{14}x_2))/(A_{13}A_{14}A_2 + A_3A_4A_9c_4p_3(1-Q_2\,c_1)),\ (-A_{13}(A_2c_1 - A_1A_4A_9p_3(1-Q_2c_1)) + A_{12}A_3A_4A_9p_3(1-Q_2c_1)x_2)/(A_{13}A_{14}A_2+ A_3A_4A_9c_4p_3(1-Q_2c_1))\}$$

Notice that the disease is endemic (u_3 is positive) if and only if the quantity $A_1A_4A_9c_4p_3(1-Q_2c_1)/A_2(c_1c_4 + A_{12}A_{14}x_2)) > 1$. Now the basic reproduction ratio of such a dynamic is the number of infected cells that each infected cell produces. This ratio, if greater than one, will result in the disease becoming endemic.

However, the ratio on the left hand side of the above inequality is not the correct Basic Reproduction Ratio. The Basic Reproduction Ratio is the number of cells that each infected cell produces when the number of susceptible cells is A_1/A_2. The reproduction number (but not the BASIC reproduction number) changes as the number of susceptible cells decreases because it becomes harder and harder for viruses to find susceptible cells to infect. The correct Basic Ratio is found from the consideration that at the point of equilibrium, each newly infected cell must be exactly replacing itself, i.e. producing one new infected cell rather than R, the number it produces when the number of susceptible cells is A_1/A_2 [3]. This is what equilibrium should mean. The susceptible fraction of cells at the point of equilibrium, P_3, therefore, must be 1/R. We therefore must have

$$R = (A_1/A_2) / x_1 = (A_1(A_{13}A_{14}A_2 + A_3A_4A_9c_4p_3(1-Q_2c_1))) / (A_2(A_{13}A_{14}A_1 + A_3c_1c_4 + A_{12}A_{14}A_3x_2)).$$

Under our assumption, all the quantities are now known in terms of x_2, which can be found from $F_2 = 0$ ($x_2' = F_2$), which is a simple second degree equation. This equation was found to have only one root in the positive space in all the cases that we considered. However, the expression for x_2 in terms of all parameters like A_1, A_2 etc. is too long to be reproduced here.

Our assumption that $u_0 = u_1 = u_2 = 0$ eventually, may be seen to be true after a look at equations (1.4), (1.5) and (1.6) for u_0, u_1, and u_2. This is because the equations for u_0, u_1, and u_2 may be written as $M_1u = M_2$ where M_1 is a 3×3 matrix and u is the unknown vector (u_0, u_1, u_2). The matrix M_2 is (0, 0, ϵ) where ϵ is exceedingly small (proportional to $Q_2 << Q_1$). The matrix M_1 is almost diagonal and seen to be non-singular, so that u_0, u_1, and u_2 will be exceedingly small at the equilibrium point and may, therefore, be neglected.

B. Positivity of the Solution

We write $x = (x_1, x_2, x_3, u_0, u_1, u_2, u_3, u_4)$. We shall say

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that x is non-negative if and only if all its components are non- negative. Notice that our equations can be written as x' = F(x) - G(x), where F(x) contains all the positive terms and G(x) contains all the negative terms, i.e. G(x) = ($A_2x_1x_1$ + $A_3x_1(u_0+u_1+u_2+u_3)$, A_5x_2 + $A_{15}x_2u_4$, ...,...,...,...,...,...). Now notice that if at any time t, "x" is in the non-negative space, i.e. $x_i \geq 0$ for all i, then all the terms in $F_i(x)$ are non-negative so that x_i cannot decrease because of any one of these while for any i, if $x_i = 0$, then the corresponding $G_i(x)$ is also zero, so that x cannot go into the non-negative space. Considering that all the components of x' are polynomials, it follows that if at any time t, the particle "x" is in the non-negative space, then it cannot escape. This proves the invariance of the non-negative space.

C. Boundedness of the Solution

In light of positivity of the solution, it is clear from eq.(1.1) that x_1 is bounded by A_1/A_2. At the equilibrium point $x_1 = (A_1-A_2u)/A_2$, where $u = u_0+u_1+u_2+u_3$ is the total virus count which is positive, so that x_1 is less than this value. We also have

$$u' = -(u_0+u_1+u_2+u_3)(c_1+A_{14}u_4) + A_4A_9(p_0u_0+(1+c_1^2Q_1Q_2)(p_1u_1+p_2u_2)+p_3u_3)x_1 < A_4A_9(1+c_1^2Q_1Q_2)ux_1 < A_4A_9(1+c_1^2Q_1Q_2)u(A_1-A_3u)/A_2.$$

This quantity is negative if $u > A_1/A_3$, so that u is bounded. Now x_2+x_3 is seen to be bounded if $A_5 > A_7$ and then u_4 is seen to be bounded from eq. (1.8)

III. Stopping the Treatment

AIDS "treatment" with HAART is a lifetime engagement and while people may change medication to put more hurdles in the path of HIV replication as it develops resistance to current medicines, there is no escape from the infliction itself. The virus almost NEVER goes away. Sometime people stop the treatment either because of side effects or for life style reasons [4]. If we stop the treatment, the virus will revert over time to the dominance of u_0 as against that of u_3 in the presence of HAART. This is because u_0 is more infectious than others (this is why u_0 is the wild type). The roles of u_0, u_1, u_2, and u_3 are now reversed. In the absence of drug pressure, it would be much easier for u_3 to change to u_2 rather than the other way round. We shall, therefore assume the probability of u_3 changing to u_2 (and of u_2 changing to u_1 and of u_1 changing to u_0) to be Q_1 and for the mutation the other way round (u_0 changing to u_1 and so on) to be Q_2. As long as the resistant virus is still there, the governing equations become $x_i'(t) = F_i(x)$, i = 1,...,8 where now

$$x_1'(t) = A_1x_1 - A_2x_1x_1 - A_3x_1(u_0+u_1+u_2+u_3) \quad (2.1)$$

$$x_2'(t) = A_4x_1(p_0u_3 + p_1u_2 + p_2u_1 + p_3u_0) - A_5x_2 - A_{15}x_2u_4 \quad (2.2)$$

$$x_3'(t) = A_7x_2 - A_8x_3 \quad (2.3)$$

$$u_0'(t) = A_9A_4((1-Q_2c_1)p_3x_1u_0+Q_1c_1p_2x_1u_1) - c_1u_0 - A_{14}u_0u_4 \quad (2.4)$$

$$u_1'(t) = A_9A_4(Q_2c_1p_3x_1u_0 + (1-Q_1c_1)(1-Q_2c_1)p_2x_1u_1 + Q_1c_1p_1x_1u_2) - c_1u_1 - A_{14}u_1u_4 \quad (2.5)$$

$$u_2'(t) = A_9A_4(Q_2c_1p_2x_1u_1 + (1-Q_1c_1)(1-Q_2c_1)p_1x_1u_2 + Q_1c_1p_0x_1u_3) - c_1u_2 - A_{14}u_2u_4 \quad (2.6)$$

$$u_3'(t) = A_9A_4(Q_2c_1p_1x_1u_2 + (1-Q_1c_1)p_0x_1u_3) - c_1u_3 - A_{14}u_3u_4 \quad (2.7)$$

$$u_4'(t) = A_{12}x_2 + A_{13}(u_0+u_1+u_2+u_3) - c_4u_4 \quad (2.8)$$

where as before, $p_0 < p_1 < p_2 < p_3 < 1$.

The relevant 'equilibrium' point may again be found by assuming that $u_1 = u_2 = u_3 = 0$. This gives

$$P_3 = \{x_1, x_2, x_3, u_0, u_1, u_2, u_3, u_4\} = \{(A_{13}A_{14}A_1 + A_3c_1c_4 + A_{12}A_{14}A_3x_2) / (A_{13}A_{14}A_2 + A_3A_4A_9c_4p_3(1-Q_2c_1)), x_2, (A_7x_2) / A_8, (A_1A_4A_9c_4p_3(1-Q_2c_1) - A_2(c_1c_4+A_{12}A_{14}x_2)) / (A_{13}A_{14}A_2 + A_3A_4A_9c_4p_3(1-Q_2c_1)), 0, 0, 0, (-A_{13}(A_2c_1 - A_1A_4A_9p_3(1-Q_2c_1)) + A_{12}A_3A_4A_9p_3(1-Q_2c_1)x_2) / (A_{13}A_{14}A_2 + A_3A_4A_9c_4p_3(1-Q_2c_1))\}$$

All these variables are known in terms of x_2 which may again be found from $F_2 = 0$ which is again a second degree equation. It should be noted that A_1 is large compared with A_2 or A_3 and A_9 is large compared with other parameters, so that u_0 is large and positive.

The values of Q_1 and Q_2 need some comment. Q_1 is the probability that virus which is resistant to one drug will mutate into one which is resistant to two of them, or that virus which is resistant to two of them will mutate into one which is resistant to three of them, and so on. Now HIV has about 10K nucleotides. The probability of its mutating at any specific site randomly, therefore, is 1 in 10000. If we assume that it needs to mutate at two of these sites to become resistant to a drug, then this probability turns out to be very close to .00000001, which is the value of Q_1 in our example. It has been suggested that "multiple mutations are required to confer high level zidovudine resistance" [6]. After the virus has developed resistance to one class of drugs by mutating at specific sites, one may change the drug so that the virus has to start all over again. This is where the baseline therapy, the second line therapy, the salvage therapy and so on come in. If u_2 switches back to u_1 for example, it needs to mutate at two specific nucleotides again, the probability of which is Q_2. Other values in our examples are educated guesses and/or taken from the literature [5].

IV. Examples

We shall illustrate the behaviour of our dynamic by taking

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some illustrative examples. The most relevant consideration is the values of the several parameters in our examples. Perhaps, the most important parameter is the infection coefficient A_3. The value of this parameter has been estimated as .000000024 by Rong et. al. for the wild type virus and .00000002 for a virus like u_1 [5]. However, in the presence of HAART (three drugs), this value is expected to be smaller still. We have assumed this value to be .00000001 in our examples.

A. EXAMPLE 1

We take

A_1=.6; A_2=A_1/1000000; A_3=.00000001; A_4=.3A_3; A_5=.5; A_7=.00001; A_8=.001; A_9=1000; A_{12}=.5; A_{13}=.1; A_{14}=0.; A_{15}=0.000025; c_1=2.995; c_4=.5; Q_1=.00000001; Q_2=.00000001Q_1; p_0 =.9; p_1 = .99; p_2 = .999; p_3 = .9999;

For convenience, we write x = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8) = (x_1, x_2, x_3, u_0, u_1, u_2, u_3, u_4), and solve $F_i(x) = 0$ for i = 1,..., 8, numerically on Mathematica8 (without the additional assumption that $u_0 = u_1 = u_2 = 0$), with the values of the parameters given above. We find that apart from the obvious equilibrium points P_1 = (0,0,0,0,0,0,0,0) and P_2 = (A_1/A_2,0,0,0,0,0,0,0), we have only one more point in the non-negative space. This point turns out to be

P_3 = {998433, 288.114, 1.44057, 0, 0, 0, 94009.4, 19090}.

Notice that the values of u_0, u_1, and u_2 are very close to zero (zero to six significant figures). If we presuppose that $u_0 = u_1 = u_2 = 0$ and solve $F_1 = F_2 = F_3 = F_7 = F_8 = 0$, we get the same values for the other variables to six significant figures.

We now solved our equations (1) numerically for x_1, x_2, x_3, u_0, u_1, u_2, u_3, and u_4 for the above values of the parameters in four different cases, We took at t = 0 ,

Case (1): {x_1, x_2, x_3, u_0, u_1, u_2, u_3, u_4} = {1000000, 0, 0, 1, 0, 0, 0, 0},

Case (2): {x_1, x_2, x_3, u_0, u_1, u_2, u_3, u_4} = {1000000, 0, 0, 1000000, 0, 0, 0, 0},

Case (3): {x_1, x_2, x_3, u_0, u_1, u_2, u_3, u_4} = {500000, 0, 0, 1, 0, 0, 0, 0}, and

Case (4): {x_1, x_2, x_3, u_0, u_1, u_2, u_3, u_4} = {500000, 0, 0, 1000000, 0, 0, 0, 0}.

The first case corresponds to a person who has just undergone seroconversion, the second one to a healthy person in whom the disease is well progressed, the third one to a case when the person has suffered a significant loss of T cells but is still quite healthy and the fourth one to a sick person in whom the disease is well advanced. HAART is generally administered to a person in the third or fourth category.

In the first and third cases, u_0 did not advance beyond a count of one. In the second and fourth cases u_0 came down rapidly and almost vanished in about twenty days. This number is consistent with what happens in actual situations. The values of u_0 in the second and fourth cases are given in Fig.1. The figure plots values of u_0 in all the four cases. However, in the first and third cases, the values are too low to show on the graph. Notice that the values of u_0 come down in less than 10 days in the fourth case and in less than twenty days in the second case. The values of u_3 are also shown in all the four cases in Fig. 2. Notice that u_3 becomes significant in about 7000 days (about 19 years) in the second and fourth cases and in about 11000 days (in about 30 years) in the first and third cases. So, if HAART is given to a patient in whom the virus count is low, the disease will be suppressed longer than if given to a patient whose virus count is high. This reinforces the famous advice that "Hit Early and Hit Hard" [7].

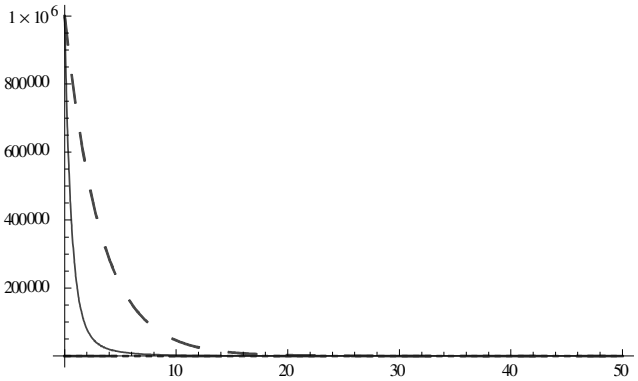

Fig. 1: Values of u_0 come down in a couple of weeks (see text).

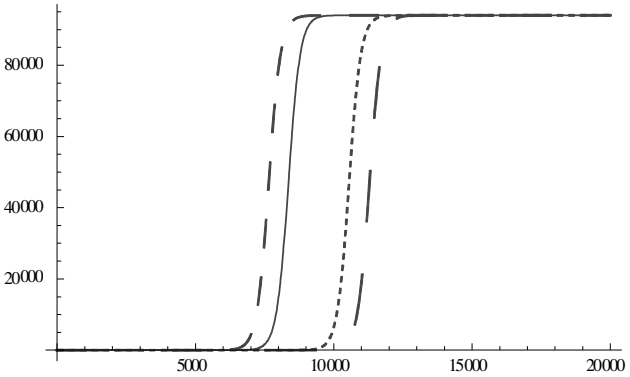

Fig.2: Appearance of resistant virus after the administration of HAART. The four cases are explained in the text. Case one corresponds to small dots, case two corresponds to medium size dots, case three to large dots and case four to solid line. Notice that in the first and third cases, when the initial virus count is low, the resistant virus takes longer to develop (approximately 30 years). This reinforces the very famous advice that "Hit Early and Hit Hard".

B. EXAMPLE 2

In this example, we consider the rebound of virus when HAART is discontinued. If HAART is discontinued, then the survival advantage of all the resistant viruses u_1, u_2, and u_3 is lost and u_0, the wild type, has an advantage over all these. If HAART is stopped after u_3 is dominant, then slowly, u_3 will turn to u_2, to u_1, and then to u_0. We consider the case with the values of the parameters the same as above except that we now take A_3 =.000000012. This is because the infection coefficient of u_0, the dominant virus this time, is expected to be higher than that of u_3 in the previous example.

The governing equations now are given above as equations (2), (notice the progressive advantage to u_0 in

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these equations).

We consider the same four cases as in the previous example. The values of $u_0 + u_1 + u_2 + u_3$ are shown in Fig.3 for the four cases. Notice that the rebound of virus occurs in between 40 and 100 days. Similar numbers for rebound have been reported in the literature [9].

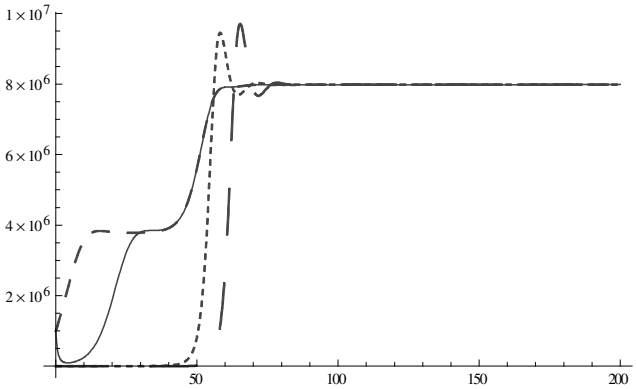

Fig. 3: Rebound of virus after stopping HAART. The four cases are explained in the text. Case one corresponds to small dots, case two corresponds to medium size dots, case three to large dots and case four to solid line. Notice that in the first and third cases, when the initial virus count is low, the virus takes longer to develop (approximately 50 days).

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