On a Mathematical Model of HAART

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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), u0, u1, and u2, 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, u3, will eventually emerge and dominate. The time over which u3 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,

\[ x_1(t) = A_1 x_1 - A_2 x_1 x_1 - A_3 x_1 (u_0 + u_1 + u_2 + u_3) \]  
\[ x_2(t) = A_4 x_1 (p_0 u_0 + p_1 u_1 + p_2 u_2 + p_3 u_3) - A_5 x_2 - A_6 x_2 u_4 \]  
\[ x_3(t) = A_7 x_2 - A_8 x_3 \]  
\[ u_0'(t) = A_9 A_4 ((1 - Q_1 c_1) p_0 x_1 u_0 + Q_2 c_1 p_1 x_1 u_1) - c_1 u_0 - A_{12} u_0 u_4 \]  
\[ u_1'(t) = A_9 A_4 (Q_1 c_1 p_0 x_1 u_0 + (1 - Q_1 c_1)(1 - Q_2 c_1) p_1 x_1 u_1 + Q_2 c_1 p_2 x_1 u_2) - c_1 u_1 - A_{14} u_1 u_4 \]  
\[ u_2'(t) = A_9 A_4 (Q_1 c_1 p_2 x_1 u_2 + (1 - Q_1 c_1)(1 - Q_2 c_1) p_2 x_1 u_2 + Q_2 c_1 p_3 x_1 u_3) - c_1 u_2 - A_{14} u_1 u_4 \]  
\[ u_3'(t) = A_9 A_4 (Q_1 c_1 p_3 x_1 u_3 + (1 - Q_1 c_1)(1 - Q_2 c_1) p_3 x_1 u_3 + Q_2 c_1 p_3 x_1 u_3) - c_1 u_3 - A_{14} u_1 u_4 \]
\( u'_i(t) = A_{12} x_2 + A_{13} (u_0 + u_1 + u_2) - c_i u_i \)

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 \( u_3 \) in one life cycle of the virus so that \((1-Q_1)\) is the probability that it will not do so in one day, where we have assumed that the virus lives for \( 1/c_3 \) days. Also, \( Q_2 \) is the probability that \( u_2 \) will change to \( u_0 \) or \( u_1 \) 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 \( Q_1 \gg Q_2 \). \( A_{x_i} c_i u_0 \) is the number of susceptible cells that become productively infected after being attacked by \( u_0 \). Similarly for \( u_1, u_2, \) and \( u_3 \). \( A_3 \) is the number of viruses produced by each infected cell while \( A_2 \) denotes the rate at which the infected cells die. The meaning of other parameters is clear from the context.

It should be noted that \( A_1 \) 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 \( 1 > p_1 > p_2 > p_3 > p_4 \). 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 \( A_3 \) 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 \( x_1, x_2, x_3, \) and \( x_4 \). We find that

\[
u_3 = \left( A_1 A_2 A_4 c_4 p_4 (1-Q_{c_1}) - A_2 (c_4 u_4 + A_{12} A_{14} x_2) \right) / \left( A_{13} A_{14} A_2 + A_3 A_4 c_4 p_4 (1-Q_{c_1}) \right).
\]

The corresponding point of equilibrium \( P_5 \), turns out to be

\[
P_5 = \{ x_1, x_2, x_3, u_0, u_1, u_2, u_3, u_4 \} = \left\{ \left( A_{13} A_{14} A_1 + A_2 A_3 c_2 + A_{12} A_{14} A_3 x_2 \right) / \left( A_{13} A_{14} A_2 + A_3 A_4 c_4 p_4 (1-Q_{c_1}) \right), \right.
\]

\[
(1-Q_2 x_2) / \left( A_{13} A_{14} A_2 + A_3 A_4 c_4 p_4 (1-Q_{c_1}) \right), \right.
\]

\[
(1-Q_2 x_2) / \left( A_{13} A_{14} A_2 + A_3 A_4 c_4 p_4 (1-Q_{c_1}) \right), \right.
\]

\[
(1-Q_2 x_2) / \left( A_{13} A_{14} A_2 + A_3 A_4 c_4 p_4 (1-Q_{c_1}) \right) \}
\]

Notice that the disease is endemic (\( u_3 \) is positive) if and only if the quantity \( A_1 A_2 A_4 c_4 p_4 (1-Q_{c_1}) / (A_2 (c_4 u_4 + A_{12} A_{14} x_2)) > 1 \). 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 \( A_1 / A_2 \). 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

\[
R = \left( A_1 / A_2 \right) / x_1 = \left( A_1 A_{13} A_{14} A_2 + A_3 A_4 c_4 p_4 (1-Q_{c_1}) \right) / \left( A_{13} A_{14} A_1 + A_2 A_3 c_2 + A_{12} A_{14} A_3 x_2 \right).
\]

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 \( M u = M_1 u \) where \( M_1 \) is a 3x3 matrix and \( u \) is the unknown vector \( (u_0, u_1, u_2) \). The matrix \( M_2 \) is \( (0, 0, \epsilon) \) where \( \epsilon \) 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
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., \( G(x) = (A_2x_1x_2 + A_3x_1(u_0+u_1+u_2+u_3) - A_2x_2 - A_3x_2u_4 \). 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 \( F(x) \) are non-negative so that \( x \) cannot decrease because of any one of these while for any one, if \( x_i = 0 \), then the corresponding \( G(x) \) 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 non-negative if and only if all its components are non-negative.

\[
x_i'(t) = A_ix_i - A_2x_i + A_3x_1(u_0+u_1+u_2+u_3)
\]

\( i = 1, 2, 3 \) (2.1)

\[
x_j'(t) = A_2x_1 - A_2x_2 - A_3x_1(u_0+u_1+u_2+u_3)
\]

\( j = 3 \) (2.2)

C. Boundedness of the Solution

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

\[
u' = - (u_0+u_1+u_2+u_3)(c_1 + A_4u_4) + A_3A_2p_1u_1(1+c_1 Q_1) + p_2u_2 + p_3u_3 + p_4u_4 x_2 < A_3A_2p_1u_1(1+c_1 Q_1) u_4 < A_3A_2(1+c_1 Q_1) u_4 / A_2.
\]

This quantity is negative if \( u > A_2/A_3 \), so that \( u \) is bounded. Now \( x_2 + x_3 \) is seen to be bounded if \( A_3 > A_2 \) 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 \( u_2 \) as against that of \( u_1 \) in the presence of HAART. This is because \( u_2 \) is more infectious than others (this is why \( u_0 \) is the wild type). The roles of \( u_0, u_1, u_2, \) and \( u_4 \) 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 \( u_2 \) changing to \( u_3 \) 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 \( x_i'(t) = F(x), \ i = 1, ..., 8 \) where now

\[x_1'(t) = A_3x_1 - A_2x_1x_2 - A_3x_1(u_0+u_1+u_2+u_3)
\]

\[u_1'(t) = A_9A_4((1-Q_2c_1)p_3x_0u_0 + Q_1c_1p_3x_1u_1) - c_1u_0 - A_4u_4u_4 \]

\[u_2'(t) = A_9A_4((Q_2c_1p_3x_0u_0 + (1-Q_1c_1)(1-Q_2c_1)p_3x_1u_1 + Q_1c_1p_3x_1u_1) - c_1u_0 - A_4u_4u_4 \]

\[u_3'(t) = A_9A_4(Q_2c_1p_3x_1u_1 + (1-Q_1c_1)(1-Q_2c_1)p_3x_1u_2 + Q_1c_1p_3x_1u_1) - c_1u_0 - A_4u_4u_4 \]

\[u_4'(t) = A_9A_4(Q_3c_1p_3x_1u_1 + (1-Q_1c_1)(1-Q_2c_1)p_3x_1u_2 + Q_1c_1p_3x_1u_1) - c_1u_0 - A_4u_4u_4 \]

\[u_5'(t) = A_9A_4(Q_2c_1p_3x_1u_2 + Q_1c_1p_3x_1u_1 - c_1u_0 - A_4u_4u_4 \]

where as before, \( p_0 < p_1 < p_2 < p_3 < 1 \).

The relevant “equilibrium” point may again be found by assuming that \( u_0 = u_2 = u_3 = 0 \). This gives

\[P_5 = \{x_1, x_2, x_3, u_0, u_1, u_2, u_4, u_4 \} = \{(A_1p_1c_1x_1 + A_3c_1c_1x_1 + A_1c_1c_1p_1(1-Q_2c_1)x_1, (A_1p_1c_1), (A_1p_1c_1p_1(1-Q_2c_1)), \}

\[\{(A_1p_1c_1)x_1 + A_1c_1c_1p_1(1-Q_2c_1)) \} = \{(A_1p_1c_1 + A_2c_1c_1p_1(1-Q_2c_1)), \} = \{(A_1p_1c_1 + A_2c_1c_1p_1(1-Q_2c_1)) \} = \{(A_1p_1c_1 + A_2c_1c_1p_1(1-Q_2c_1)) \} = \{(A_1p_1c_1 + A_2c_1c_1p_1(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 \( A_0 \) 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 .0000001, 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 \( u_4 \) 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
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 \( A_5 \). 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

\[
A_1=6; \quad A_2=A_1/1000000; \quad A_3=0.00000001; \quad A_4=3A_1; \quad A_5=5; \quad A_6=0.00000001; \quad A_7=100; \quad A_8=5; \quad A_9=1; \quad A_{10}=0; \quad A_{11}=0.000000025; \quad c_1=2.995; \quad c_2=5; \quad Q_1=0.00000001; \quad Q_2=0.000000001Q_1; \quad p_0=9; \quad p_1=0.99; \quad p_2=0.999; \quad p_3=0.9999; 
\]

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 \( F(x) = 0 \) for \( i = 1, \ldots, 8 \), 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 \( F_1 = F_2 = F_3 = F_4 = F_5 = 0 \), we get the same values for the other variables to six significant figures.

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

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

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): \( \{x_1, x_2, x_3, u_0, u_1, u_2, u_3, u_4\} = \{5000000, 0, 0, 1, 0, 0, 0, 0\} \), and

Case (4): \( \{x_1, x_2, x_3, u_0, u_1, u_2, u_3, u_4\} = \{5000000, 0, 0, 1000000, 0, 0, 0, 0\} \).

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 shown 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 \( u_0 \) are also shown in all the four cases in Fig. 2. Notice that \( u_0 \) 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].

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 \( A_3 = 0.000000012 \). 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
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).](image_url)

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**REFERENCES**


