Dynamic Systems and Applications 16 (2007) 407-424

A MATHEMATICAL MODEL SIMULATING THE EFFECT OF VACCINE INDUCED RESPONSES ON HIV-1 INFECTION

JOHN GUARDIOLA, GIUSEPPE IZZO, AND ANTONIA VECCHIO

Istituto di Genetica e Biofisica "A. Buzzati Traverso" - C.N.R., Italy
(guardiol@iigb.na.cnr.it)
Istituto per le Applicazioni del Calcolo "M. Picone" - Sez. Napoli - C.N.R., Italy
(g.izzo@na.iac.cnr.it)
Istituto per le Applicazioni del Calcolo "M. Picone" - Sez. Napoli - C.N.R., Italy
(vecchio@na.iac.cnr.it)

ABSTRACT. We analyze the mathematical model of the dynamics of HIV-1 infection in an organism reported in [9]. The model consists of a set of second type delay Volterra Integral Equations and takes into account the induction upon vaccination of a humoral and/or cellular immune response; the existence of a distributed delay for intracellular life cycle of the virus and a maximal time period for which an infected cell is allowed to become productive. We perform the analysis of the qualitative behavior of the solution by proving its positivity, boundedness and by providing a threshold parameter whose value permits to predict whether the infection will spread in the organism or not. Some numerical examples are added even if most of numerical analysis of the model is carried out in [9].

1. INTRODUCTION

This paper is can be considered as the mathematical counterpart of [9] where a model for the study of the efficiency of vaccine for HIV-1 infection is proposed. Many mathematical models have been developed to describe the spread of HIV-1 infection in the organism. Most of these models investigate kinetics of viral progression after infection and/or predict viral decline after drug treatment ([5, 6, 13, 16, 17, 18, 20, 21, 23, 24, 25, 26, 27, 28, 29, 30]). In this paper we give the mathematical background of the model reported in [9]. The model accounts for the phenomenological scheme represented in figure 1 and is characterized by the following features: the existence of a distributed delay for the intracellular life cycle of the virus (see Banks et al. [3, 4], Mittler et al. [23]); a maximal time period for which an infected cell is allowed to become productive; and the induction upon vaccination of a humoral and/or cellular

Received September 19, 2005

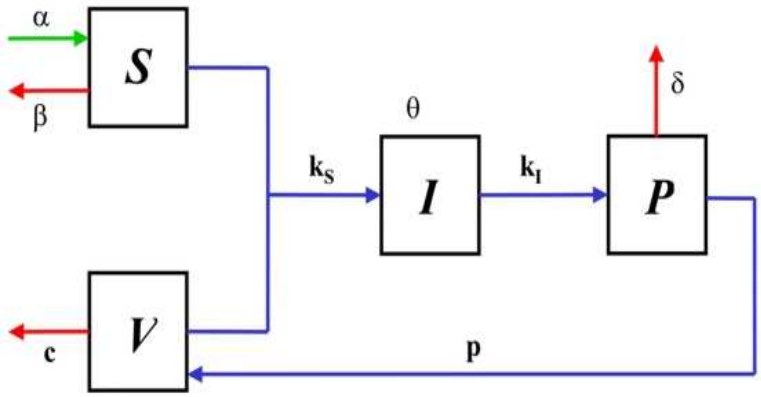

FIGURE 1. Simplified phenomenological model of HIV-1 infection

immune response against HIV-1. In the phenomenological model of Figure 1, the virus (V) infects the target cells (S) at a rate of infection k_s. The resulting infected cells then become virus-producing cells at a transition rate k_i. P cells produce virus at a replication rate p and are removed by clearance at a relative rate δ. The latter includes the death rate of productive cells and other removal mechanisms, such as innate and adaptive immune responses ([5]). We underline that the infected cells are not explicitly represented by a variable in our model because we are interested in the portion of them producing viruses ($P(t)$).

It is known that upon infection with HIV-1 there is an intracellular delay during which the cell is infected but has not yet begun producing viruses. In some models (see [6, 13, 24]) this delay is assumed to be fixed. Here we assume that it is a continuous random variable having a Gamma probability distribution $F(x)$ (see [3, 6, 23, 25]). As the most natural reproduction of a continuous delay is by means of an integral ([3, 6, 23, 25]), the model we are going to study is based on a set of integral equations (integro-differential formulation would be equivalent). Nevertheless, for technical reasons, a large part of the analysis contained in the paper is obtained by transforming it into an equivalent set of delay differential equations involving some internal variables which do not have biological meaning.

We consider a vaccine eliciting a humoral and/or cellular response, i.e., a vaccine which stimulates the production of antibodies (humoral response) and/or killer cells which remove infected cells (cellular response). Mathematically speaking, the vaccine is represented by the functions

$$\phi_1(t) = 1 - \omega v(t) \quad , \quad \phi_2(t) = 1 - \gamma v(t).$$

Here ω is the rate of killing of each killer cell and therefore it represents the ability of each single cell to act as an effector, γ is the rate of neutralization of each antibody

molecule or in other words the ability of each single antibody to act as an effector, $v(t)$ represents the "intensity" of the immune response.

Finally, we attribute to the infected cell a maximal time period for which an infected cell is allowed to become productive, named θ and, because of this, the equations corresponding to the model involve two different expression, with a change from one to the other when the time passed since infection reaches θ. To be more specific the model consists in the following set of second type Volterra Integral Equations (VIEs): (for summary of notation see Table 1)

$$\begin{aligned} P(t) &= (1-\omega v(t)) \int_{d(t)}^{t} F(t-x) e^{-\delta(t-x)} k_I k_S V(x) S(x) dx \\ V(t) &= (1-\gamma v(t)) \left[V_0 e^{-ct} + \int_0^t e^{-c(t-x)} p P(x) dx \right] \qquad t \in [0, t_f] \\ S(t) &= S_0 e^{-\beta t} + \int_0^t e^{-\beta(t-x)} \left[\alpha - k_S V(x) S(x) \right] dx \end{aligned} \tag{1.1}$$

where

$$d(t) = \begin{cases} 0 & t < \theta \\ t-\theta & t \geq \theta \end{cases} \tag{1.2}$$

Observe that for $t \geq \theta$ (1.1) is a system of delay Volterra Integral Equations (DVIE). Moreover, when $d(t) = 0$, the effect of infected cells ($k_I k_S V(x) S(x)$) lasts from the time infection ($x = 0$) to the current time t, whereas in the case $d(t) = t - \theta$ it lasts only a time interval ($[t-\theta, t]$) of length θ.

We suppose that the probability density function of the delay of intracellular life cycle is

$$f_{n,b}(x) = \frac{x^{n-1}}{(n-1)! b^n} e^{-\frac{x}{b}} \qquad n \in \mathbb{N} \quad , \quad b \in \mathbb{R}^+ \tag{1.3}$$

where n and b are the parameters of the Gamma distribution whose product represents the expected value, i.e.

$$E = \int_0^\infty x f(x) dx = nb$$

The probability distribution F is thus given by

$$F(x) = \int_0^x f(s) ds = 1 - e^{-\frac{x}{b}} \sum_{j=0}^{n-1} \frac{x^j}{j! b^j}$$

We refer to [3] for a detailed discussion on the choice of this delay. Observe that in (1.1) there appears $F(x)$, whereas in the formulation of the models reported in [6, 23, 25] we find the function $f(x)$ given in (1.3). This is due to the fact that our model is based an integral formulation, whereas in [6, 23, 25] an integro-differential one is reported. In other words, if we differentiate (1.1) we obtain an integro-differential equation whose kernel contains the function $f(x)$. We have to note that if the vaccine

and the maximal time period for which an infected cell is allowed to become productive are not taken into account ($\omega = \gamma = 0$ and $d(t) \equiv 0$), our model results to be very closed to model (11) in [25]. The main difference between the two models lies in the following fact. In [25] the time $t = 0$ corresponds to starting time of drug therapy and therefore the value assumed by the solution before such a time influences its behavior in any subsequent time $t > 0$ (this explains the presence of the integral from zero to infinity in the formulation of (11) of [25]). In our case the initial time is the time of infection, hence $P(t)$ and $V(t)$ are assumed to be null before such an instant.

The function $v(t)$ has the form:

$$v(t) = \begin{cases} 0 & t < \tau_1 \\ m(t - \tau_1) & \tau_1 \leq t \leq \tau_2 \\ m(\tau_2 - \tau_1) & t \geq \tau_2 \end{cases} \tag{1.4}$$

The parameter m is the number of effector elements induced by the vaccine and therefore reflects the intensity of the immune response that can be attained upon vaccination. The model assumes that if the vaccine is given at time τ_1 its maximal intensity is reached at time τ_2. A vaccine given at time $\tau_1 \leq 0$ (that is before infection) is obviously envisageable as a preventive one, whereas a vaccine inoculated at later times ($\tau_1 > 0$) is therapeutic. It should be noted that, to simplify, we do not make yet a distinction between primary and secondary immune responses. The vaccine "efficiency" parameters appearing in (1.1), ω and γ, of course satisfy $0 \leq \omega \leq 1$, $0 \leq \gamma \leq 1$ and

$$m\omega(\tau_2 - \tau_1) \leq 1 \quad , \quad m\gamma(\tau_2 - \tau_1) \leq 1. \tag{1.5}$$

From (1.1) and (1.4) we observe that if $\tau_1 > 0$ then $V(0) = V_0$, whereas this is not true anymore in the case $\tau_2 < 0$ or $\tau_1 < 0$. Biologically speaking this is a characteristic of a preventive vaccine. In other words we are taking into consideration the fact that a preventive vaccine has an effect also on the number (V_0) of viruses inoculated at the beginning of the infection, before they reach the cells to be infected. Moreover, we are assuming that the vaccine acts on the amount of cells (and viruses) independently of the time at which they are "provided" (x) and depending only on the current time (t) and the time of inoculation of the vaccine (τ_1).

The paper is organized as follows: in section 2 we prove basic properties of the model such as the existence, the positivity and the boundedness of the solution which make the model meaningful from a mathematical and a biological point of view. In section 3 we provide the main result used in [9], that is a threshold parameter whose value allows to predict whether the HIV infection will start in the organism or not. The role of the threshold parameter R_0 and its dependence on the parameters defining the vaccine and the maximal time period for which an infected cell is allowed

to become productive, is analyzed in section 4 thanks to the numerical resolution of the problem. Some concluding remarks are added at the end of the paper.

List of variable and parameters	
Variables	
$S(t)$	susceptible or target cells
$P(t)$	productively infected cells
$V(t)$	viruses
Parameters	
$\theta > 0$	maximal time period for which an infected cell is allowed to become productive
$\alpha > 0$	renewal rate of susceptible cells
$\beta > 0$	rate of clearance of susceptible cells
$k_S > 0$	rate at which viruses infect target cells
$S_0 > 0$	$S(0)$
$c > 0$	rate of clearance of viruses
$p > 0$	rate of virus production
$V_0 > 0$	Number of viruses inoculated at t=0
$\delta > 0$	rate of clearance of productive and infected cells
$k_I > 0$	rate of transition from infected to productively infected cells
$b > 0$	scale parameter of the Gamma function
$n \in \mathbb{N}^+$	shape parameter of the Gamma function
$\tau_1 \in \mathbb{R}$	time of vaccine inoculation
$\tau_2 > \tau_1$	time of maximal immune response
m	Intensity of immune response
$0 \leq \gamma \leq 1$	Rate of neutralization of each antibody molecule
$0 \leq \omega \leq 1$	Rate of killing by each effector cell

Table 1

2. PRELIMINARY RESULTS

In order to make the proposed model "meaningful" from a mathematical point of view we want to prove the existence of the solution of (1.1). By now we shall assume that all parameters in (1.1) satisfy the conditions expressed in Table 1 and (1.5). As we already mentioned, the differential formulation of (1.1) is not completely natural in the modelling of this biological problem because it introduces some internal variables with no biological meaning. For this reason and also because it seems to us more convenient in order to prove positivity and boundedness of the solution we prefer the integral formulation of the model. Nevertheless most of the following results can also be obtained by exploring the function space of the solutions of the differential form

of (1.1) (see section 3) with the help of the the tools of functional analysis (see for example [12, 15]).

Theorem 2.1. *The solution of* (1.1) *exists and it is unique.*

Proof. The proof comes immediately from the theory of nonlinear VIE (see for example [22] (pp.30–33)) and by considering (1.1) subsequently in the interval

$$[0,\theta],[\theta,2\theta],\ldots,[(N-1)\theta,N\theta],[N\theta,t_f]$$

where

$$N=\max\{m\in\mathbb{N}\,:\,m\theta\le t_f\}$$

□

Now in order to make the model meaningful from a biological point of view we want to prove that the solutions $P(t)$, $V(t)$ and $S(t)$ of (1.1) are positive and bounded. In fact, as $P(t)$, $V(t)$, $S(t)$ represent three populations of individuals present in a volume unit of plasma, we expect that they are nonnegative and bounded. Before proceeding to the proof of these results note that, biologically speaking, in the absence of viruses the number of target cells should remain constant, because they are provided and removed at constant rate. This can be mathematically obtained if and only if

$$S_0=\frac{\alpha}{\beta} \tag{2.1}$$

Therefore here and in the sequel we assume that (2.1) holds. In this case (1.1) becomes:

$$\begin{aligned} P(t) &= (1-\omega v(t))\int_{d(t)}^{t} F(t-x)e^{-\delta(t-x)}k_I k_S V(x)S(x)dx \\ V(t) &= (1-\gamma v(t))\left[V_0e^{-ct}+\int_0^t e^{-c(t-x)}pP(x)dx\right] \\ S(t) &= \tfrac{\alpha}{\beta}-\int_0^t e^{-\beta(t-x)}k_S V(x)S(x)dx \end{aligned} \tag{2.2}$$

Theorem 2.2. *The solutions $P(t)$, $V(t)$, $S(t)$ of* (2.2) *are nonnegative for $t>0$.*

Proof. Let us assume $m\omega(\tau_2-\tau_1)\neq 1$ and $m\gamma(\tau_2-\tau_1)\neq 1$. If $S(0)>0$ and $V(0)>0$ it is possible to prove (see [10], thm. 2.1) that the functions $P(t)$,$V(t)$ and $S(t)$ are continuous for $t>0$, and bounded in $[0,\theta]$. Let us prove the positivity of solutions in $[\theta,\infty)$. We know that $P(\theta)>0$,$V(\theta)>0$ and $S(\theta)>0$. Let us prove it by contradiction. To this purpose assume that there exists a point t_0 such that $S(t_0)=0$. Being the function $S(t)$ continuous and piecewise derivable, there exists as point $\overline{t}$ s.t. $S'(t)<0$ with $t\in[\overline{t},t_0)$. So

$$\lim_{t\to t_0^-} S'(t)\le 0. \tag{2.3}$$

On the other hand the following relation holds:

$$S'(t) = \alpha - \beta S(t) - k_S V(t) S(t)$$

and then

$$\lim_{t \to t_0^-} S'(t) = \alpha. \tag{2.4}$$

Taking into account (2.3) and (2.4) we obtain the absurd statement $\alpha \leq 0$. And so we have proved the positivity of the function $S(t)$.

Now, let us suppose that there exists a point $t_0 > \theta$ s.t.:

$$\begin{aligned} &V(t)S(t) > 0 \qquad t \in [\theta, t_0) \\ &V(t_0)S(t_0) = 0. \end{aligned} \tag{2.5}$$

From the first of (2.2) and (2.5) follows

$$P(t) > 0 \qquad t \in [\theta, t_0];$$

and then, taking into account the second of (2.2), it is $V(t_0) > 0$, that together with (2.5.2) implies

$$S(t_0) = 0 \qquad (Absurd).$$

From the positivity of the product $V(t)S(t)$, and from (2.2), the positivity of functions $P(t)$ and $V(t)$ for $t > 0$ follows.

Observe that in the case $m\omega(\tau_2 - \tau_1) = 1$ there results $1 - \omega v(t) = 0$ when $t > \tau_2$ and hence $P(t) = 0$ for $t \geq \tau_2$. The same is true for $V(t)$ if $m\gamma(\tau_2 - \tau_1) = 1$. □

The boundedness of the unknown functions is shown in the following result.

Theorem 2.3. *Assume that i) $\beta \leq \delta$. Then the solutions $P(t)$, $V(t)$, $S(t)$ of (2.2) are bounded for $t > 0$.*

Proof. By the nonnegativity of the product $V(t)S(t)$ and from the third of (2.2) it follows:

$$S(t) \leq \frac{\alpha}{\beta} \qquad t > 0. \tag{2.6}$$

Now, taking into account that $0 \leq F(x) \leq 1$, $0 \leq 1 - \omega v(t) \leq 1$, and $i)$, we obtain:

$$(1 - \omega v(t)) \int_{t-\theta}^{t} F(t-x) e^{-\delta(t-x)} k_I k_S V(x) S(x) dx \leq$$

$$\int_{t-\theta}^{t} e^{-\beta(t-x)} k_I k_S V(x) S(x) dx \leq \int_{0}^{t} e^{-\beta(t-x)} k_I k_S V(x) S(x) dx = k_I \left(\frac{\alpha}{\beta} - S(t) \right).$$

Therefore from the first of (2.2) there results:

$$P(t) \leq k_I \frac{\alpha}{\beta}$$

and from the second of (2.2):

$$V(t) \leq V_0 + \frac{pk_I\alpha}{c\beta}$$

□

Observe that we provide explicit values for the bound of P, V, S. In particular inequality (2.6) means that $S(t)$ cannot outgrow $\frac{\alpha}{\beta}$. This is reasonable, because as said before, the number of the target cells remains constant and equals $\frac{\alpha}{\beta}$ in the absence of virus, while in the presence of virus it can only decrease.

3. ASYMPTOTIC PROPERTIES

In [9] equations (2.2) are solved numerically for different value of the parameter in order to simulate the potential of HIV vaccines having different strengths and efficacies. The numerical resolution was performed because we needed to know the quantitative behavior of P, V and S immediately after the infection and/or after the inoculation of the vaccine, whereas the asymptotic behavior of the model is completely determined by the results contained in this section.

In order to study the asymptotic behavior of $P(t)$, $V(t)$, $S(t)$ we assume

$$t > t_i = \max\{\theta, \tau_2\}$$

and observe that, thanks to the form of the kernel of the integral equations (2.2), our model can be transformed into a set of delay differential equations by using the classical transformation which is known as *method of stages* (MOS) ([19]). By making this transformation we increase the dimension of the mathematical problem which passes from a system of 3 VIEs to a system of $n+3$ ODEs. Nevertheless, such a transformation is more convenient for the following analysis. Put

$$E_j(t) = \int_{t-\theta}^{t} f_j(t-x)e^{-\delta(t-x)}k_Ik_SV(x)S(x)dx \tag{3.1}$$

where $f_j(t) \equiv f_{j,b}(t)$, $j = 1, \ldots, n$. From here and from the boundedness of V and S we have that E_j, $j = 1, \ldots, n$ are derivable and bounded functions for all $t > t_i$. Let us derive (3.1) and (2.2). We obtain

(3.2)

$$E_1'(t) = \tfrac{1}{b}k_Sk_IV(t)S(t) - \tfrac{1}{b}e^{-\left(\frac{1}{b}+\delta\right)\theta}k_Sk_IV(t-\theta)S(t-\theta) - \left(\tfrac{1}{b}+\delta\right)E_1(t)$$

$$E_j'(t) = -f_j(\theta)e^{-\delta\theta}k_Sk_IV(t-\theta)S(t-\theta) + \tfrac{1}{b}E_{j-1}(t) - \left(\tfrac{1}{b}+\delta\right)E_j(t), \quad 2 \leq j \leq n$$

$$P'(t) = -\delta P(t) + (1-\omega v(t))\left[-F(\theta)e^{-\delta\theta}k_Sk_IV(t-\theta)S(t-\theta) + E_n(t)\right], \quad t \in [t_i, t_f]$$

$$V'(t) = -cV(t) + (1-\gamma v(t))pP(t)$$

$$S'(t) = \alpha - k_SV(t)S(t) - \beta S(t).$$

The initial values can be obtained computing (2.2) and (3.1) in t_i and they are:

$$P(t_i) = (1 - \omega v(t_i)) \int_{t_i-\theta}^{t_i} F(t_i - x) e^{-\delta(t_i-x)} k_I k_S V(x) S(x) dx$$

$$V(t_i) = (1 - \gamma v(t_i)) \left[V_0 e^{-ct_i} + \int_0^{t_i} e^{-c(t_i-x)} p P(x) dx \right]$$

$$S(t_i) = \frac{\alpha}{\beta} - \int_0^{t_i} e^{-\beta(t_i-x)} k_S V(x) S(x) dx$$

$$E_j(t_i) = \int_{t_i-\theta}^{t_i} f_j(t_i - x) e^{-\delta(t_i-x)} k_I k_S V(x) S(x) dx \qquad j = 1, \ldots, n$$

Note that the function E_j given in (3.1) are auxiliary functions related to the probability density and they do not represent any specific biological component.

Before proving the convergence at infinity of the functions P, V and S, we recall some known results which can be found in [14].

Lemma 3.1. *Let $\tau : \mathbb{R}^+ \to \mathbb{R}$ be any function such that i) $\tau'(t)$ exists and is bounded for $t \in \mathbb{R}^+$; ii) $\int_0^\infty \tau(t) dt < \infty$. Then*

$$\lim_{t\to\infty} \tau(t) = 0.$$

Lemma 3.2. *If $\tau : \mathbb{R}^+ \to \mathbb{R}$ is a differentiable function and $\liminf \tau(t) < \limsup \tau(t)$, then there exist two divergent sequences $\{t'_j\}_{j\geq 0}$ and $\{t''_j\}_{j\geq 0}$ such that*

$$\lim_{j\to\infty} \tau(t'_j) = \liminf \tau(t), \qquad \tau'(t'_j) = 0, j \geq 0$$

$$\lim_{j\to\infty} \tau(t''_j) = \limsup \tau(t), \qquad \tau'(t''_j) = 0, j \geq 0$$

Theorem 3.3. *Assume that i) $\beta \leq \delta$. If one of the functions $V, P, S, E_1, \ldots, E_n$ has a finite limit at at infinity then also the remaining functions have a finite limit at infinity.*

Proof. With no loss of generality, assume $\lim_{t\to\infty} V(t) = l_V \geq 0$. Observe that $V(t)$ is bounded on $[0, \infty]$ and its derivative is a continuous and bounded function on $[0, \infty]$, therefore it is a Lipschitz continuous function and hence a uniformly continuous one. So $\lim_{t\to\infty} V'(t) = 0$. Now, from (3.2), easily follows that $\lim_{t\to\infty} P(t) = l_P \geq 0$, and $\lim_{t\to\infty} E_j(t) = l_{E_j} \geq 0$, $j = 1, \ldots, n$.

Assume that $S(t)$ does not converge at infinity, i.e.

$$\liminf_{t\to\infty} S(t) < \limsup_{t\to\infty} S(t) \tag{3.3}$$

and apply lemma 3.2. The evaluation of (3.2.5) in the points of both the sequences $\{t'_j\}$ and $\{t''_j\}$ leads to

$$\liminf S(t) = \limsup S(t) = l_S = \frac{\alpha}{(\beta + k_S l_V)}$$

which contradicts (3.3). □

Denote by $B(t)$ the following continuous functions which plays a fundamental role in the proof of the next theorem:

$$B(t) = V(t) + \frac{\overline{\omega}\,\overline{\gamma} p k_I k_S}{\delta} \int_{t-\theta}^{t} [\varphi(t-x) - \varphi(\theta)]\, V(x) S(x) dx \qquad t \in [t_i, t_f] \tag{3.4}$$

where

$$\varphi(y) = \frac{1}{(1+b\delta)^n} \left[F(y) e^{-\delta y} (1+b\delta)^n - F\left((1+b\delta)y\right) + 1 \right]$$

and

$$\overline{\omega} = 1 - \omega m(\tau_2 - \tau_1), \quad \overline{\gamma} = 1 - \gamma m(\tau_2 - \tau_1).$$

It can be easily proved that

$$\varphi'(t) = -\delta F(t) e^{-\delta t} \leq 0, \tag{3.5}$$

thus $\varphi(t)$ is a decreasing function and this implies that $B(t)$ is a positive one.

The derivative of (3.4) is given by:

$$B'(t) = cV(t) \left(\frac{1}{\lambda} S(t) - 1 \right) \tag{3.6}$$

where

$$\lambda = \frac{\delta c (1+b\delta)^n}{\overline{\omega}\,\overline{\gamma}\, k_I k_S p \left[F\left((1+b\delta)\theta\right) - F(\theta) e^{-\delta\theta} (1+b\delta)^n \right]}. \tag{3.7}$$

Now we are ready to prove the main result of this section which provides a necessary and sufficient condition for the vanishing of the function $V(t)$.

Theorem 3.4. *Assume that i) $\beta \leq \delta$. Then*

$$\lambda \geq \frac{\alpha}{\beta} \Leftrightarrow \lim_{t\to\infty} V(t) = 0$$

Proof. "$\Rightarrow$" From (3.6) and (2.6) we have:

$$B'(t) \leq \eta V(t) \leq 0 \tag{3.8}$$

where $\eta = c\left(\frac{\alpha}{\beta\lambda} - 1\right) \leq 0$. Thus the function $B(t)$ converges at infinity and because of its uniform continuity, it holds:

$$\lim_{t\to\infty} B'(t) = 0 \tag{3.9}$$

If $\lambda > \frac{\alpha}{\beta}$, integrating both sides of (3.8) from t_i to t, we obtain:

$$\int_{t_i}^{t} B'(x) dx \leq \eta \int_{t_i}^{t} V(x) dx$$

hence:

$$-\eta \int_{t_i}^{t} V(x) dx + B(t) \leq B(t_i).$$

So $V(t)$ satisfies the hypotheses of lemma (3.1) and therefore $\lim_{t\to\infty} V(t) = 0$.

Now let us consider the case $\lambda = \frac{\alpha}{\beta}$ and suppose that $S(t)$ does not converge at infinity, then there exists a divergent sequence $\{t_j\}$ s.t. $S'(t_j) = 0$, $0 < S(t_j) < \frac{\alpha}{\beta}$ $\forall\, j \in \mathbb{N}$:

$$\lim_{j\to\infty} S(t_j) = \liminf_{t\to\infty} S(t) = l'_S < \frac{\alpha}{\beta}.$$

From (3.2.5) and $\alpha > 0$ we have $l'_S > 0$. Evaluation of (3.2.5) in t_j furnishes:

$$V(t_j) = \frac{\alpha - \beta S(t_j)}{k_S S(t_j)}$$

and passing to the limit as j goes to infinity, we get:

$$\lim_{n\to\infty} V(t_j) = \frac{\alpha - \beta l'_S}{k_S l'_S} > 0 \tag{3.10}$$

On the other hand, computing (3.6) in t_j:

$$\frac{B'(t_j)}{c\left(\frac{1}{\lambda}S(t_j) - 1\right)} = V(t_j);$$

passing to the limit as j goes to infinity, and taking into account (3.9), we have:

$$\lim_{n\to\infty} V(t_j) = 0$$

which contradicts (3.10). This, together with theorem 3.3, implies that the functions $S(t)$ and $V(t)$ convergence at infinity. Taking into account (3.6) and (3.9) we obtain:

$$\lim_{t\to\infty} V(t) = 0$$

or

$$\lim_{t\to\infty} S(t) = \frac{\alpha}{\beta}.$$

In the second case the thesis follows from (3.2.5) by passing to the limit as t goes to infinity.

"$\Leftarrow$".

$$\lim_{t\to\infty} V(t) = 0 \;\Rightarrow\; \lim_{t\to\infty} P(t) = 0, \quad \lim_{t\to\infty} E_j(t) = 0, \quad j = 1, \ldots, n, \quad \lim_{t\to\infty} S(t) = \frac{\alpha}{\beta}$$

and then:

$$\lim_{t\to\infty} B(t) = 0.$$

$B(t)$ is a positive function vanishing at infinity, therefore there exists a divergent sequence $\{t_j\}$ s.t $B'(t_j) \le 0$ for $j \ge 0$.

Computing (3.6) in t_j we obtain $S(t_j) \le \lambda$, and the thesis follows as j goes to infinity. □

Now put

$$R_0 = \frac{\alpha}{\beta\lambda}$$

From theorem 3.3 we immediately derive

Theorem 3.5. *Assume that i) $\beta \leq \delta$; then*

$$R_0 \leq 1 \Leftrightarrow \lim S(t) = \frac{\alpha}{\beta} \quad , \quad \lim V(t) = 0$$

$$R_0 > 1 \Leftrightarrow V(t) \text{ does not vanish as } t \text{ goes to } \infty$$

Such a result provides a necessary and sufficient condition for the outbreak of HIV-1 infection. Moreover we note that the condition $\lim_{t\to\infty} V(t) = 0$ and $\lim_{t\to\infty} S(t) = \frac{\alpha}{\beta}$ derived in the case $R_0 \leq 1$ seems to imply the healing of the patient. When no vaccine is inoculated this of course is absurd because we are dealing with HIV-1 infection. Corollary (3.6) clarify that in this case we not only have $\lim_{t\to\infty} V(t) = 0$ but it is also $V(t) \leq V(0)$, which biologically speaking means that no infection occurs.

Corollary 3.6. *Assume that i) $\beta \leq \delta$; ii) $\omega = \gamma = 0$. Then $R_0 \leq 1$ is equivalent to say that no infection occurs.*

Proof. "⇒". Let us define the function $\hat{B}(t)$ as:

$$\hat{B}(t) = V(t) + \frac{pk_I k_S}{\delta} \int_{d(t)}^{t} [\varphi(t-x) - \varphi(\theta)]\, V(x)S(x)dx \qquad t \in [0, t_f] \tag{3.11}$$

where $d(t)$ is given by (1.2). It can be easily proved that:

$$\hat{B}'(t) = cV(t)\left(\frac{1}{\lambda}S(t) - 1\right)$$

Following the lines of the proof of theorem 3.4 and taking into account ii) it can be easily seen that $\hat{B}'(t) \leq 0$ and thus

$$V(t) \leq \hat{B}(t) \leq \hat{B}(0) = V(0).$$

"⇐". If the infection does not occurs we can assume $\lim V(t) = 0$. This in view of theorem (3.5) leads to $R_0 \leq 1$. □

Thus we can claim that the infection by HIV-1 can get started if an only if $R_0 > 1$. Therefore R_0 is a very important threshold parameter, the value of which allows to decide whether the HIV-1 infection can take over in an organism. In this sense we can also state that R_0 plays the role of the basic reproduction number (see [7, 8]) of our model. From the expression (3.7) we can see that λ increases when the overall efficiency of the vaccine increases ($\omega m(\tau_2 - \tau_1) \to 1$ and $\gamma m(\tau_2 - \tau_1) \to 1$) and hence in both the cases we get $R_0 \leq 1$. The same is true when $\theta \to 0$, as we could expect. On the other hand we note that when θ increases, R_0 increases and the DVIE (2.2) tends to a classical VIE. Finally observe that in the case $\omega = 0$ (or $\gamma = 0$) and $\theta = \infty$, the expression of λ coincides with the corresponding threshold parameter given in [10] where a general model of virus dynamics which does not take

into account the vaccine and the maximal time period for which an infected cell is allowed to become productive is studied.

In order to completely describe the behavior of $P(t)$, $V(t)$ and $S(t)$ at infinity we prove the following theorem which explicitly gives the limiting value in the case $R_0 > 1$.

Theorem 3.7. *Assume that i) $\beta \leq \delta$; ii) $R_0 > 1$; iii) one of the functions V, P, S, $E_1,\ldots,E_n$ converges at ∞. Then*

$$\lim_{t\to\infty} S(t) = \lambda$$

and

$$\lim_{t\to\infty} V(t) = \frac{\alpha - \beta\lambda}{k_S\lambda} \qquad \lim_{t\to\infty} P(t) = \frac{c\,(\alpha - \beta\lambda)}{\overline{\gamma}pk_S\lambda}$$

Proof. From theorem 3.3 we have that each of the functions V, P, E_i, $i = 1,\ldots,n$ converges at infinity and hence

$$\lim_{t\to\infty} B\prime(t) = 0.$$

In view of theorem 3.4 we have $\lim_{t\to\infty} V(t) > 0$ and therefore from (3.6) we obtain

$$\lim_{t\to\infty} S(t) = \lambda.$$

The rest of the thesis comes immediately from (3.2). □

All the results given in this section can be compared in with those reported in [9], where the problem is solved numerically by using the kinetics parameters obtained from experimental and clinical observations. Here we only want to underline that, since the most popular mathematical software (see for example Matlab, Mathematica, Maple, Nag, Netlib) present an absolute lack of numerical code for solving DVIEs, we prefer to transform equation (2.2) into the system (3.2) of delay differential equations (DDEs) and to solve it by using one of the few codes available. In particular, we used the routine dde23 of the software Matlab® (The mathWorks Inc., Natick, MA, USA). Of course the transformation mentioned above is possible only thanks to the particular form of Equation (2.2) (in other words the transformation from DVIEs to DDEs is not always possible) and it is not very convenient from a computational point of view. In fact the dimension of the DDEs system is considerably larger than that of the original one. The software package developed for the simulation of viral kinetics, namely VKS-B1.2, is freely available into the software section at www.na.iac.cnr.it (web site).

It is also worth to point out that, even if the code may be not readily downloadable, there are in literature several numerical schemes proposed to numerically solve a large variety of Delay Functional Differential Equations (see for example [1, 2]).

4. THE ROLE OF R_0

In this section we want to illustrate the role of R_0 in our model. To this purpose we compare some numerical results, obtained as described above, to the analytic ones of the previous section. Figure 1 shows how the vaccine influences R_0. In fact in fig. 1a, where no vaccine is inoculated ($\omega = 0$), a virus production occurs. This corresponds to $R_0 > 1$. In figure 1b the vaccine reaches it maximal efficiency ($\omega m(\tau_2 - \tau_1) = 1$), no virus production occurs and $R_0 < 1$. In Figure 1c we see how R_0 varies depending on θ. Observe that as θ decreases R_0 does the same (Fig. 1c), but as it is once again $R_0 > 1$ we still have an infection, the amount of virus at equilibrium is less than that in the case 1a and the peak has a different shape. Finally in Fig. 2 we have $\theta = 1$, $R_0 < 1$ and no infection occurs. We recall that a large variety of resolution of (2.2) has been reported in [9] to the purpose of illustrating the applicability of the proposed model.

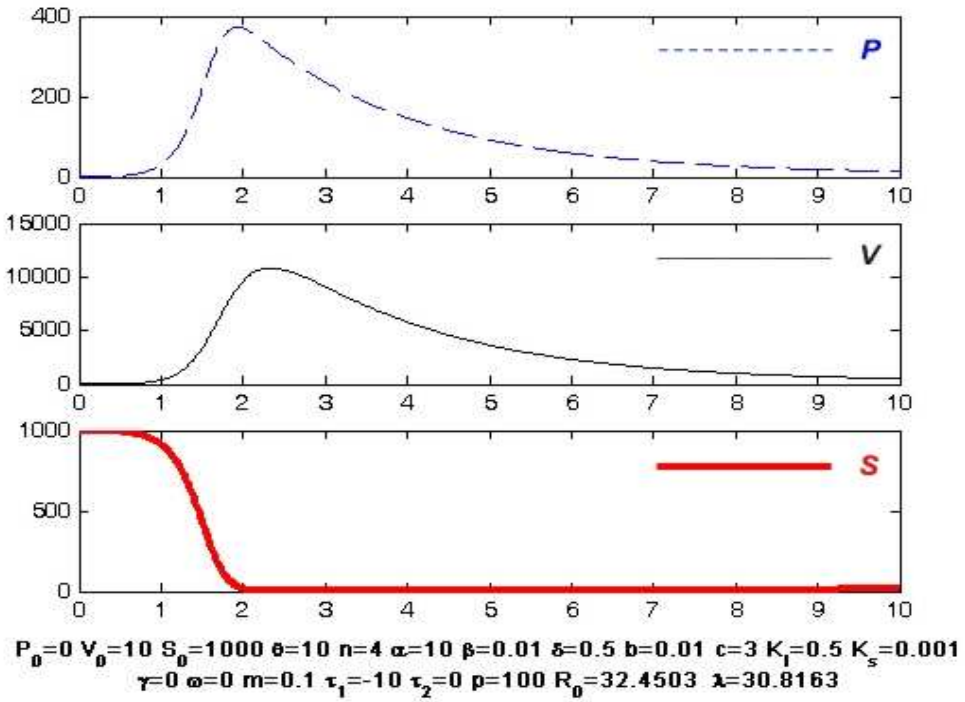

Fig. 1a

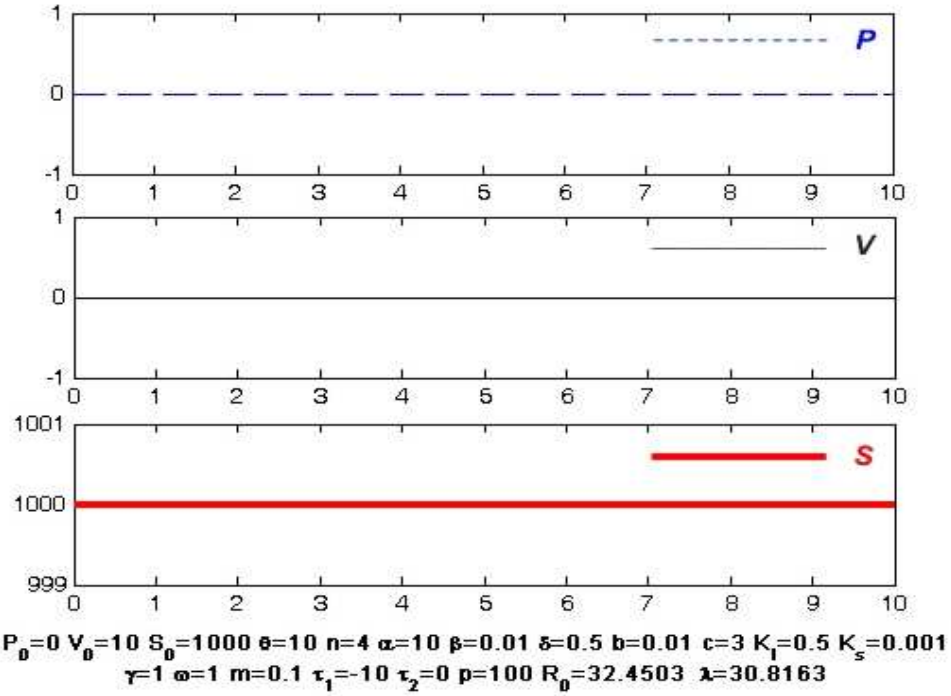
P
V
S
P_0=0 V_0=10 S_0=1000 θ=10 n=4 α=10 β=0.01 δ=0.5 b=0.01 c=3 K_I=0.5 K_s=0.001
γ=1 ω=1 m=0.1 τ_1=-10 τ_2=0 p=100 R_0=32.4503 λ=30.8163

Fig. 1b

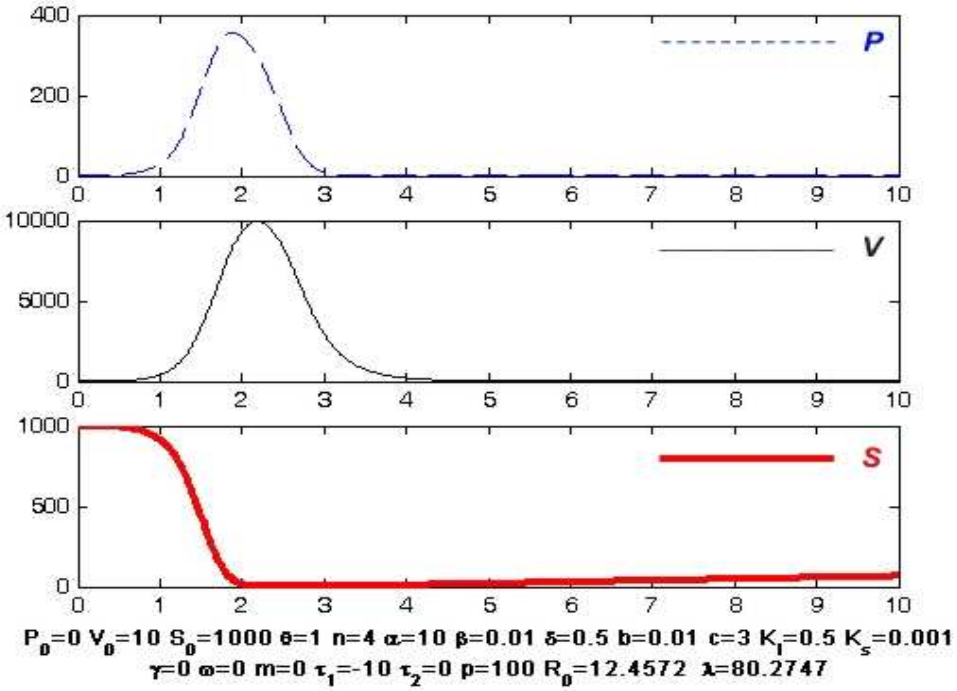
P
V
S
P_0=0 V_0=10 S_0=1000 θ=1 n=4 α=10 β=0.01 δ=0.5 b=0.01 c=3 K_I=0.5 K_s=0.001
γ=0 ω=0 m=0 τ_1=-10 τ_2=0 p=100 R_0=12.4572 λ=80.2747

Fig. 1c

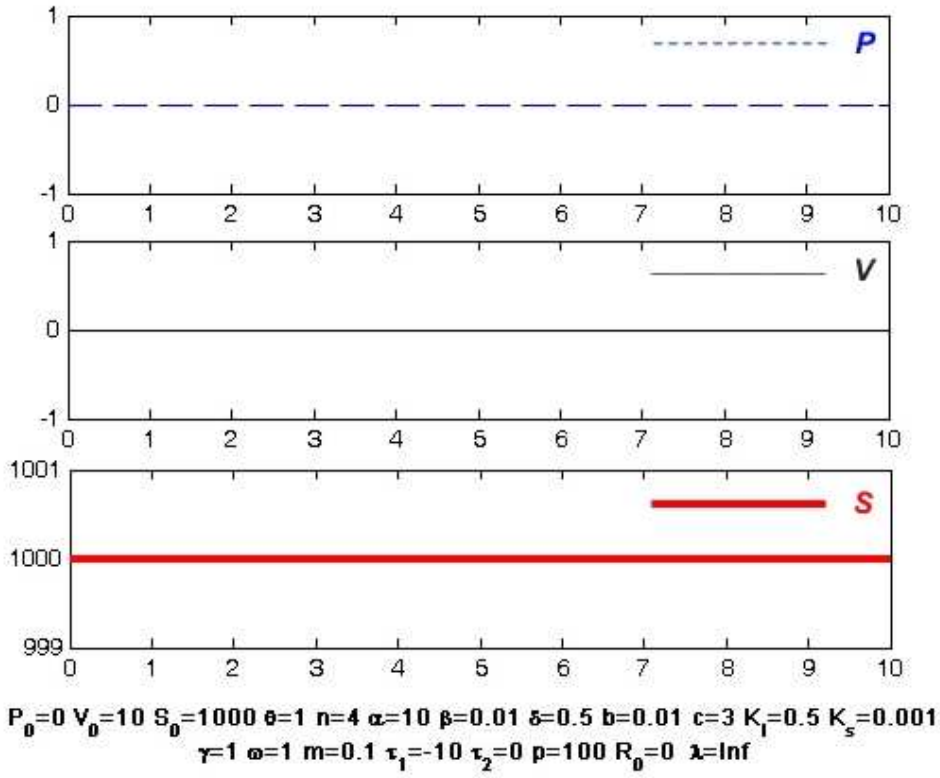

Fig. 2

5. CONCLUDING REMARKS

We have performed the qualitative analysis of a model whose applicability was discussed in [9]. We provide the threshold parameter R_0 and we prove that starting from any value V_0, the amount of virus vanishes if and only if $R_0 \leq 1$. This, from another point of view means that the point $(P(0) = 0,\ V(0) = \phi_2(0)V_0,\ S(0) = \frac{\alpha}{\beta})$ is a globally stable stationary point. Moreover we have proved that the condition $R_0 \leq 1$ not only assures that $\lim V(t) = 0$, but also that we do not have infection at all because $V(t)$ does not overcome its initial value $V(0)$. The value of R_0 also allows to predict whether a vaccine is sufficiently efficient to avoid the infection.

REFERENCES

[1] Banks H.T., Burns J.A., *Hereditary Control Problems: Numerical Methods based on Averaging Approximations*, SIAM J. Control and Optimization 16, No. 2, 169–208 (1978).

[2] Banks H.T., Kappel F., *Spline approximations for Functional Differential Equations*, J. Differential Equations 34, 496–522 (1979).

[3] Banks H.T., Bortz D.M., Holte S.E., *Incorporation of variability into the modeling of viral delays in HIV infection dynamics*, Math. Biosci. 183, 63–91 (2003).

[4] Banks H.T., Bortz D.M., *A parameter sensitivity methodology in the context of HIV delay equation models*, J. Math. Biol. 50, 607–625 (2005).

[5] Callaway D.S., Perelson A.S., *HIV-1 infection and low steady state viral loads*, Bull. Math. Biol. 64:29, (2002).

[6] Culshaw R.V., Ruan S., Webb G., *A mathematical model of cell-to-cell spread olf HIV-1 that includes a time delay*, J. Math. Biol. 46, 425–444 (2003).

[7] Diekmann O., Heesterbeek J.A.P., *Mathematical epidemology of infections disease; Model building, analysis and interpretation*, Wiley, New York (2000).

[8] Diekmann O., Heesterbeek J.A.P., Metz J.A.J., *On the definition and computation of the basic reproduction ratio R_0 in models for infections diseases in heterogeneous populations*, J.Math.Biol., 28, 365–382 (1998).

[9] Guardiola J., Izzo G., Vecchio A., *Simulating the effect of vaccine-induced immune responses on HIV infection*, Human Immunol., 64, 840–851 (2003).

[10] Guardiola J., Vecchio A., *A distributed delay model of viral dynamics*, WSEAS transaction on biology and biomedicine, Issue 1, V. 2, 36–42 (2005).

[11] Guardiola J., Vecchio A., *Modelling vaccine effects on HIV-1 viral dynamics*, 2002 WSEAS Int. Conf. Proc. 452–202 (2003).

[12] Hale J.K., Verduyn Lunel S. M. , *Introduction to Functional Differential Equations*, Springer-Verlag, New York (1993).

[13] Herz A.V.M., Bonhoeffer S., Anderson R.M., May R.M., Nowak M.A.: *Viral dynamics in vivo: Limitations on estimates of intracellular delay and virus decay*, Proc. Natl. Acad. Sci. USA 93,7247–7251 (1996)

[14] Hirsch W.M., Hanish H., Gabriel J.P., *Differential equation models of some parasitic infections: methods for the study of asymptotic behavior*, Comm. Pure Appl. Math., 38, pp.733–753 (1985).

[15] Ito K., Kappel F. *Evolution equations and approximations.*, River Edge, N.J.: World Scientific (2002).

[16] Kirschner D.E., Webb G., *A model for treatment strategy in the chemotherapy of AIDS*, Bull. Math. Biol. 58, 167–190 (1996).

[17] Kirschner D.E., Webb G.F., *Understanding drug resistance for monotherapy treatment of HIV infection*, Bull. Math. Biol. 59, 763–785 (1997).

[18] Kirschner D.E., Webb G.F., *A mathematical model of combined drug therapy of HIV infection*, J. Theor. Med. 1, 25–34 (1997).

[19] MacDonald N., *Biological Delay Systems: Linear Stability Theory*, Cambridge University Press, Cambridge, UK, (1989).

[20] McLean A.R., Emery V.C., Webster A., Griffith P.D. *Population dynamics of HIV within an individual after treatment with zidovudine*, AIDS 5:485 (1991).

[21] McLean A.R., Kirkwood T.B.L., *A model of human immunodeficiency virus infection in T helper cell colnes*, J. Theor. Biol 147, 177–203 (1990).

[22] Miller R.K., *Nonlinear Volterra integral equations*, Benjamin, Menlo Park (Cal), (1971).

[23] Mittler J.E., Sulzer B., Neumann A.U., Perelson A.S., *Influence of delayed viral production on viral dynamics in HIV-1 infected patients*, Math. Biosci. 152:143 (1998).

[24] Nelson P.W., Murray J.D., Perelson A.S., *A model of HIV-1 pathogenesis that includes an intracellular delay*, Math. Biosci. 163, 201–215 (2000).

[25] Nelson P.W., Perelson A.S., *Mathematical analysis of delay differential equation models of HIV-1 infection*, Math. Biosci. 179, 73–94 (2002).

[26] Nowak M.A., May R.M., *Mathematical Biology of HIV infections: Antigenic variation and diversity threshold*,Math. Biosci. 106, 1–21 (1991).

[27] Nowak M.A., May R.M., *AIDS Pathogenesis: mathematical models of HIV and SIV infections*, AIDS 7, S3–S18 (1993).

[28] Perelson A.S., *Modelling the interaction of the immune system with HIV. In: Mathematical and Statistical Approaches to AIDS Epidemiology*, C.Castillo-Chavez (ed.) Springer-Verlag, New York, 1989, pp. 350–370.

[29] Perelson A.S., Nelson P.W., *Mathematical analysis of HIV-1 dynamics in vivo*, SIAM Rev 41:3, (1999).

[30] Phillips A.N., *Reduction of HIV concentration during acute infection: independence from a specific immune response*, Science 271:497 (1996).