Mathematical models of HIV pathogenesis and treatment

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Summary

We review mathematical models of HIV dynamics, disease progression, and therapy. We start by introducing a basic model of virus infection and demonstrate how it was used to study HIV dynamics and to measure crucial parameters that lead to a new understanding of the disease process. We discuss the diversity threshold model as an example of the general principle that virus evolution can drive disease progression and the destruction of the immune system. Finally, we show how mathematical models can be used to understand correlates of long-term immunological control of HIV, and to design therapy regimes that convert a progressing patient into a state of long-term non-progression. ***BioEssays*** **24:1178–1187, 2002.**

Introduction

The dynamics between virus infections and the immune system involve many different components and are multifactorial. In such a scenario, the principles governing the dynamics and the outcome of infection cannot be understood by verbal or graphical reasoning. Mathematical models provide an essential tool to capture a set of assumptions and to follow them to their precise logical conclusions. They allow us to generate new hypotheses, suggest experiments, and measure crucial parameters.

A particular example is HIV infection. The interactions between HIV and the immune system are more complex compared to most other infections. While immune responses have the potential to fight the virus, HIV infects CD4 T helper cells, which are a central component orchestrating the generation of specific immune responses. Depending on co-receptor usage, HIV can infect other immune cells, such as macrophages and dendritic cells, that are also involved in the generation of antiviral immunity. Thus, suboptimal immune responses develop early during the acute phase of the infection and can contribute to viral persistence and to the ability of the virus to mutate and evolve. The infection remains asymptomatic for years before the virus load sufficiently increases and the population of CD4 T cells falls to low levels leading to the development of AIDS. Disease progression is associated with the evolution of specific viral variants that are more virulent and pathogenic (e.g. evolution of strong T cell tropism, escape from immune responses, faster viral replication, and higher degrees of cytopathicity). Anti-retroviral drug therapy has successfully been used to significantly suppress viral replication and to delay disease progression in many patients. Currently, these drugs act by two mechanisms: reverse transcriptase inhibitors interfere with the process of reverse transcription and prevent the virus from infecting a cell; protease inhibitors prevent the assembly of new infectious virus by an infected cell. Because HIV integrates into the host genome, however, the infected cells remain unaffected and provide a viral reservoir. While most productively infected cells have a relatively short lifespan, many cells are latently infected and are very long lived. Thus, virus eradication by drug therapy is not possible during the life time of the host. Because continued administration of drugs is associated with many problems such as side effects and the generation of drug resistance, more recent research efforts have been directed at finding therapy regimes that boost HIV-specific immune responses.

In this review, we show how mathematical models can be used to understand the dynamics of HIV infection and therapy. We start by describing a basic model of virus infection and continue to show how it was used to get some crucial insights into the dynamics during the asymptomatic phase of the disease. We explore how HIV evolution can drive disease progression, and how mathematical models can be used to design specific treatment regimes that can boost anti-viral immunity and induce long-term virus control.

The basic model of virus dynamics

The basic model of virus dynamics (Fig. 1) has three variables: the population sizes of uninfected cells, x, infected cells, y, and free virus particles, v. These quantities can either denote the total abundance in a host, or the abundance in a given volume blood or tissue.

Free virus particles infect uninfected cells at a rate proportional to the product of their abundances, βxv. The rate constant, β, describes the efficacy of this process, including the rate at which virus particles find uninfected cells, the rate of

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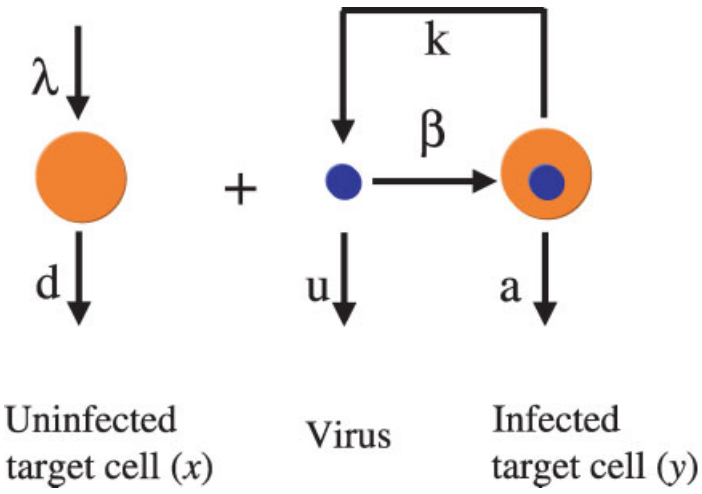

Figure 1. Schematic illustration of the basic model of virus dynamics. Uninfected cells "react" with free virus to give rise to infected cells; the rate constant is β. Infected cells produce free virions at a rate *k*. Uninfected cells, free virus and infected cells die at the rates *d*, *u* and *a*, respectively. Uninfected cells are replenished at a constant rate λ.

virus entry, and the rate and probability of successful infection. Infected cells produce free virus at a rate proportional to their abundance, *ky*. Infected cells die at a rate *ay*, and free virus particles are removed from the system at rate *uv*. Therefore, the average life-time of an infected cell is $1/a$, whereas the average life-time of a free virus particle is $1/u$. The total amount of virus particles produced from one infected cell, the "burst size", is k/a.

Uninfected cells are produced at a constant rate, λ, and die at a rate *dx*. The average life-time of an uninfected cell is $1/d$. In the absence of infection, the population dynamics of host cells is given by $\dot{x} = \lambda - dx$. This is a simple linear differential equation. Without virus, the abundance of uninfected cells converges to the equilibrium value λ/d.

Combining the dynamics of virus infection and host cells, we obtain the basic model of virus dynamics[1]:

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta xv \\ \dot{y} &= \beta xv - ay \\ \dot{v} &= ky - uv. \end{aligned} \qquad (1)$$

This is a system of nonlinear differential equations. An analytic solution of the time development of the variables is not possible, but we can derive various approximations and thereby obtain a complete understanding of the system.

Before infection, we have $y = 0$, $v = 0$, and uninfected cells are at equilibrium $x = \lambda/d$. Denote by $t = 0$ the time when infection occurs. Suppose infection occurs with a certain amount of virus particles, v_0. Thus the initial conditions are $x_0 = \lambda/d$, $y_0 = 0$, and v_0. Whether or not the virus can grow and establish an infection depends on a condition very similar to the spread of an infectious disease in a population of host individuals. The crucial quantity is the basic reproductive ratio, R_0, which is defined as the number of newly infected cells that arise from any one infected cell when almost all cells are uninfected. The rate at which one infected cell gives rise to new infected cells is given by $\beta kx/u$. If all cells are uninfected then $x = \lambda/d$. Since the life-time of an uninfected cell is $1/a$, we obtain $R_0 = \beta\lambda k/(adu)$.

If $R_0 < 1$ then the virus will not spread, since every infected cell will on average produce less than one other infected cell. The chain reaction is subcritical. On average, we expect $1/(1 - R_0)$ rounds of infection before the virus population dies out.

If, on the other hand, $R_0 > 1$, then every infected cell will on average produce more than one newly infected cell. The chain reaction will generate an explosive multiplication of virus. Virus growth will not continue indefinitely, because the supply of uninfected cells is limited. There will be a peak in virus load and subsequently damped oscillations to an equilibrium. The equilibrium abundance of uninfected cells, infected cells and free virus is given by $x^* = x_0/R_0$, $y^* = (R_0 - 1)du/(\beta k)$, $v^* = (R_0 - 1)d/\beta$.

At equilibrium, any one infected cell will on average give rise to one newly infected cell. The fraction of free virus particles that manage to infect new cells is thus given by the reciprocal of the burst size, a/k. The probability that a cell (born uninfected) remains uninfected during its life-time is $1/R_0$. The equilibrium ratio of uninfected cells before and after infection is $x_0/x^* = R_0$.

If the virus has a basic reproductive ratio much larger than one, then x^* will be greatly reduced compared to x_0, which means that, during infection, the equilibrium abundance of uninfected cells is much smaller than before infection. In other words, the above simple model cannot explain a situation where during a persistent virus infection almost all infectable cells remain uninfected ($x^* \approx x_0$), except in the case when R_0 is only slightly bigger than unity (which is a priori unlikely in general).

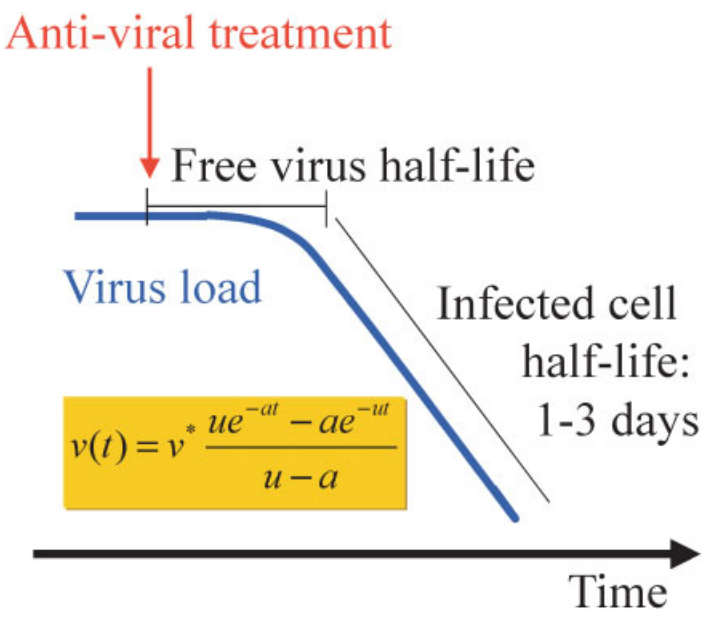

Figure 2. Initial dynamics of HIV decay following the onset of anti-viral therapy. Infected cells fall purely as an exponential function of time, whereas free virus falls exponentially after an initial shoulder phase.

Furthermore, if $R_0 \gg 1$, then the equilibrium abundance of infected cells and free virus is approximately given by $y^* \approx \lambda/a$ and $v^* \approx (\lambda k)/(au)$. Interestingly, both quantities do not depend on the infection parameter β[2]. The reason is that a highly infectious virus (large β) will rapidly infect uninfected cells but, at equilibrium, there will only be few uninfected cells in the system. A less infectious virus (smaller β) will take longer to infect uninfected cells, but the equilibrium abundance of uninfected cells is higher. For both viruses, the product βx will be the same at equilibrium, resulting in a constant rate of production of new infected cells, and therefore in similar equilibrium abundances of infected cells and free virus.

For a highly cytopathic virus (a much larger than d), the equilibrium abundance of infected cells will be small compared to the abundance of cells prior to infection. In fact, the larger a, the smaller the abundance both of infected cells and of free virus.

For a non-cytopathic virus ($a \sim d$), the equilibrium abundance of infected cells will be roughly equivalent to the total abundance of susceptible cells prior to infection.

Virus dynamics and anti-viral therapy

In HIV infection, reverse transcriptase inhibitors prevent infection of new cells. Suppose first, for simplicity, that the drug is 100% effective and that the system is in equilibrium before the onset of treatment. Then we put $\beta = 0$ in eq. (1), and the subsequent dynamics of infected cells and free virus are given by $\dot{y} = -ay$ and $\dot{v} = ky - uv$. This leads to $y(t) = y^* e^{-at}$ and $v(t) = v^*(ue^{-at} - ae^{-ut})/(u-a)$ assuming $u \neq a$. Infected cells fall purely as an exponential function of time, whereas free virus falls exponentially after an initial "shoulder phase" (Fig. 2). Since the half-life of free virus particles is significantly shorter than the half-life of virus producing cells, $u \gg a$, plasma virus abundance does not begin to fall noticeably until the end of a shoulder phase of duration $\Delta t \approx 1/u$. Thereafter virus decline moves into its asymptotic phase, falling as e^{-at}. Hence, the observed exponential decay of plasma virus reflects the half-life of virus-producing cells, while the half-life of free virus particles determines the length of the shoulder phase. Note that the equation for $v(t)$ is symmetric in a and u, and therefore if $a \gg u$ the converse is true.

In the more general case when reverse transcriptase inhibition is not 100% effective, we may replace β in eq (1) with $\bar{\beta} = s\beta$, with $s < 1$ (100% inhibition corresponds to $s = 0$). If the time-scale for changes in the uninfected cell abundance, $1/d$, is longer than other time-scales ($d \ll a;u$), then we may approximate $x(t)$ by x^*. It follows that the asymptotic rate of decay is $\exp[-at(1-s)]$ for $u \gg a$ while the duration of the shoulder phase remains $\Delta t \approx 1/u$. Thus the observed half-life of virus producing cells, $T_{1/2} = (\ln 2)/[a(1-s)]$, depends on the efficacy of the drug.

Protease inhibitors prevent infected cells from producing infectious virus particles. Free virus particles, which have been produced before therapy starts, will for a short while continue to infect new cells, but infected cells will produce non-infectious virus particles, w. The equations $\dot{y} = \beta xv - ay$, $\dot{v} = -uv$, $\dot{w} = ky - uw$. The situation is more complex, because the dynamics of infected cells and free virus are not decoupled from the uninfected cell population. However, we can obtain analytic insights if we again assume that the uninfected cell population remains roughly constant for the time-scale under consideration. This gives the total virus

abundance as $v(t) + w(t) = v^*[e^{-ut} + \{(e^{-at} - e^{-ut})u/(a-u) + ate^{-ut}\}u/(a-u)]$. For $u \gg a$ this function describes a decay curve of plasma virus with an initial shoulder (of duration $\Delta t = -(2/a)\ \ln(1 - a/u) \sim 2/u$) followed by an exponential decay as e^{-at}. The situation is very similar to reverse transcriptase inhibitor treatment. The main difference is that the virus decay function is no longer symmetric in u and a, and therefore a formal distinction between these two rate constants is possible.

Sequential measurements of virus load in HIV-1-infected patients treated with reverse transcriptase or protease inhibitors usually permit a good assessment of the slope of the exponential decline, which reflects the half-life of infected cells, (ln2)/a (Fig. 3). This half-life is usually found to be between 1 and 3 days.[3–7] The half-life of free virus particles is of the order of a few hours, possibly even less. The process that leads to the clearance of virus particles from the peripheral blood is not understood. The half-life of virus producing cells is determined by a combination of anti-viral CTL responses and viral cytopathicity.[8]

Only a small fraction of HIV-1-infected cells, however, have a half-life of 2 days. These short-lived cells are thought to be productively infected CD4 T cells. They account for the production of about 99% of the plasma virus present in a patient. But most infected peripheral blood mononuclear cells (PBMC) live much longer. During highly active anti-retroviral therapy (HAART), the relatively fast decline of plasma virus load only lasts for about one or two weeks. Subsequently the decline in virus load enters a second and slower phase.[6] This second phase has a half-life of the order of 10 days (Fig. 3). The rate of decline is thought to slow down even further with time, characterized by a half-life of up to 100 days.[9] The population of long-lived infected cells is heterogeneous. It may comprise productively infected antigen-presenting cells, such as macrophages. But more importantly, cells can become latently infected with HIV, and this population of infected cells is characterized by the longest life-span.[9]

These observations have two important implications for understanding HIV infection and therapy. (i) The high turn-over rate of most productively infected cells allows the virus to mutate and evolve fast. This could contribute to progression of the disease. (ii) While successful therapy can suppress virus load below detection limit, complete virus eradication from the patient is not possible under normal circumstances because of long-lived latently infected cells. Since life-long therapy is not feasible (problems with compliance, resistance and side-effects), it is important to seek therapeutic strategies that result in a boost of immunity and long-term virus control in the absence of continuous therapy. Both of these points will be addressed in the following sections.

Virus evolution and disease progression in individual patients

An important insight from the above studies was that HIV is not latent during the asymptomatic phase of the infection, but that it is continuously replicating with a high turn-over rate. This enables the virus to evolve at a fast rate.

HIV disease progression shows a complex pattern. Patients take on average 10 years to progress from infection to AIDS. Some HIV-infected patients have died within 2 years of infection, while others remained free of AIDS for more than 15 years. A theory for this pattern of disease progression has to provide a mechanism that shifts the steady-state between virus and immune cell dynamics (on a time scale of days) in favor of the virus (on a time scale of years). Virus evolution in individual patients could provide a mechanism for such a shift.

During the very early stages of infection, the virus population has been observed to be relatively homogeneous.[10] During the course of progression, the virus population greatly diversifies with respect to many different aspects. This reflects the variety of selection pressures exerted by the host

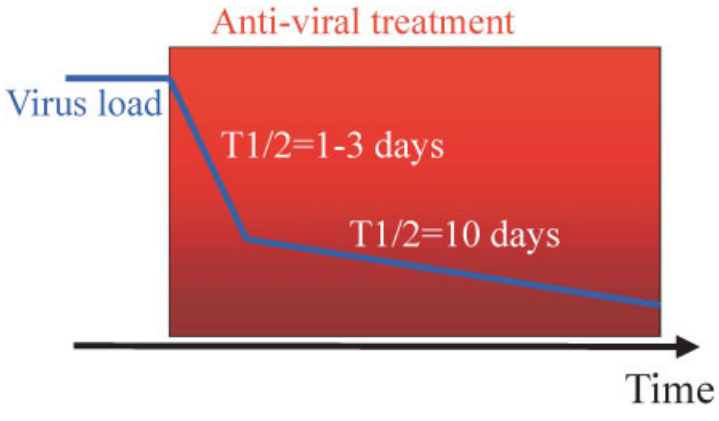

Figure 3. Long-term dynamics of virus decay following onset of anti-viral therapy. The first and rapid decay of virus (infected cell half-life of 1–3 days) is followed by a second decay phase which is significantly slower (infected cell half-life of 10 days and longer).

on the virus. Virus adaptation and evolution can result in the emergence of strains that are more virulent and more damaging to the immune system, resulting in the development of AIDS.

An important factor that influences the ability of HIV to grow and cause disease is the range of target cells that it can infect. Mainly two cell types, macrophages and CD4 T cells, are thought to be significant in the context of disease progression.[10] Related to this topic is the co-receptor usage of HIV. Two particular co-receptors have attracted attention.[11] These are CCR5 (present on macrophages and CD4 T cells) and CXCR4 (present mostly on CD4 T cells). Some HIV variants may specialize on CCR5 (R5 tropic strains) or CXCR4 (X4 tropic strains). Other HIV variants are dual tropic. CCR5 tropism is characteristic of the early stages of HIV infection, while CXCR4 tropism is thought to arise later and might contribute to the loss of CD4 T cells. In 50% of patients, development of AIDS is associated with the emergence of X4 virus. Mathematical models have been used to study the evolution of target cell range and co-receptor usage of HIV in relation to disease progression.[12–14] In particular, these studies addressed the conditions under which CXCR4 tropic strains could emerge. According to mathematical models, the evolution of X4 tropic strains is promoted by the evolution of fast viral replication as well as escape from immune responses.

The evolution of antigenic escape has been studied in detail as a mechanism of HIV disease progression.[15–17] The simplest mathematical model that captures antigenic escape dynamics is the following

$$\begin{aligned} dv_i/dt &= v_i(r - px_i - sz); \quad i = 1, \ldots, n \\ dx_i/dt &= kv_i - bx_i - uvx_i; \quad i = 1, \ldots, n \\ dz/dt &= k'v - bz - uvz. \end{aligned} \tag{2}$$

The model has three types of variables, v_i, x_i and z. Here v_i denotes the population size of virus mutant labeled i; x_i denotes the immune response (e.g. density of antibodies, B cells or T cells) specifically directed against virus strain i; and z denotes the group-specific immune response directed against all different virus mutants. The total number of different virus strains is given by n; mutational events occur throughout the infection and therefore increase this number, n, as time goes by. We use the notation $v = \Sigma v_i$ where v denotes the total population of virus.

The model has seven parameters, r, p, s, k, k', b and u. The parameter r denotes the average rate of replication of all different virus strains; p specifies the efficacy of the strain-specific immune responses and k specifies the rate at which they are evoked; similarly s specifies the efficacy of group-specific immune responses and k' the rate at which they are evoked. In the absence of further stimulation, the immune response decays at a (slow) rate given by the constant b. Lentiviruses can impair immune responses, either by directly killing infected CD4-positive cells or by indirect mechanisms. These effects are summarized in the loss terms, $-uvx_i$ and $-uvz$. Thus the parameter u characterizes the ability of the virus to impair immune responses. By impairing CD4 cell function, the virus impairs indirectly B cell and cytotoxic T cell mediated immune responses.

This mathematical model represents a deliberately simplified concept of virus-immune system interactions. The individual virus strains are defined as being different with respect to strain-specific immune responses. In reality, viruses have several different epitopes that can be recognized by immune responses. Some virus mutants may differ in one epitope, but coincide in others. This means that a given immune response may be able to recognize a number of different virus strains, but fail to recognize others. There is a variety of more or less group-specific and strain-specific immune responses. The model only considers the two extreme possibilities of completely group-specific and completely strain-specific immune responses. The whole spectrum of more or less cross-reactive responses is covered by assigning parameter values to balance the relative importance of the two extreme possibilities.

We also assume in eq. (2) that the parameters r, u, p, s, k and k' are the same for all different virus strains. This means essentially that all virus strains have the same average replication rate and cytopathic effects, and are controlled by immune responses of equal strength. This simplification is not necessary, but it makes the mathematical analysis more transparent. More general models with different rate constants have been discussed.

From eq (2) we obtain an equation for the rate at which the total virus population changes:

$$dv/dt = v\left(r - \frac{pkv}{b+uv}D - \frac{sk'v}{b+uv}\right). \tag{3}$$

For this we have assumed that the x_i converge to their steady-state levels $x_i^* = kv_i/(b+uv)$, and that z converges to $z^* = k'v/(b+uv)$, on time scales short compared with those on which the total virus population changes. D denotes the Simpson index, $D = \Sigma(v_i/v)^2$,which is an inverse measure for viral diversity: if there is only one virus strain present then $D = 1$; if there are n strains present, all of them exactly at the same abundance, then $D = 1/n$. D is always between 0 and 1; it is actually the probability that two viruses chosen at random belong to the same strain. The concept of a virus strain, v_i, is well defined in the mathematical model. It is simply a subpopulation of viruses that are all recognized by the same strain-specific immune response, x_i.

From eq. (3) we see that v converges towards the steady state

$$v^* = rb/(sk' + pkD - ru). \tag{4}$$

The product sk' specifies the efficacy of the group-specific immune responses, such as antibodies or CTLs directed at epitopes that are conserved between different virus strains. The product pkD denotes strain-specific immune responses, such as antibodies or CTLs directed at variable regions. The efficacy of these strain-specific responses depends on the antigenic diversity of the virus population. Equation 4 shows that increasing diversity (decreasing D) increases the total population size of the virus and hence drives disease progression. The model has three distinct parameter regions, which correspond to three qualitatively different courses of infection.

If $ru > sk' + pk$, there is no asymptomatic phase and the virus population immediately replicates to high levels. In this case virus replication cannot be controlled by the combination of group-specific and strain-specific responses. There may be no antigenic variation, but simply selection for the fastest growing virus strain. The immune system does not have time to select for diversification.

If $sk' > ru$ there is chronic infection, but no disease. In this case, the group-specific responses alone can control the virus.This parameter region applies to non-pathogenic SIV infection.[18–21]

The third, and most interesting, situation arises when the combined effects of group-specific and strain-specific immune responses are able to control the virus replication (of the individual strains), but the group-specific responses alone are unable to do so. Mathematically this means that $sk' + pk > ru > sk'$. If the virus diversity is low (D large) then the total population size is regulated to some equilibrium value (given by eq. 4). If viral diversity is high (D low) then the denominator in eq. 4 becomes very small, and hence the virus population size very large. The critical transition occurs when

$$D \frac{ru - sk'}{pk}. \qquad (5)$$

Beyond this point, the total virus population grows unboundedly. Equation (5) gives the diversity threshold. Once this threshold of viral diversity is exceeded, then the virus population escapes from control by the immune response and tends to arbitrarily high densities (Fig. 4). This process may be interpreted as the development of immunodeficiency disease, which is characterized by high virus counts and depletion of CD4+ cells. During the asymptomatic phase, on the other hand, the diversity is increasing, but the immune system is able to control viral densities and to maintain CD4 cell levels (Fig. 4).

The model describing the effect of antigenic escape on disease progression has been illustrated in more detail as an example of the more general principle that viral evolution in vivo can shift the dynamics between HIV and the immune system over time, resulting in progression of the disease.

The evolutionary model of HIV disease progression was controversial when introduced about 12 years ago[15] and has remained so, but without warrant in our opinion. A large number of experimental studies (reviewed in Ref. 17) have demonstrated the enormous potential of the virus to escape from any kind of selective pressure exerted by CTL responses, antibody responses or drug treatment. As outlined by our theory, the necessary consequence is that the viral population in any one patient will evolve away from control by the immune system (or drug treatment) toward faster

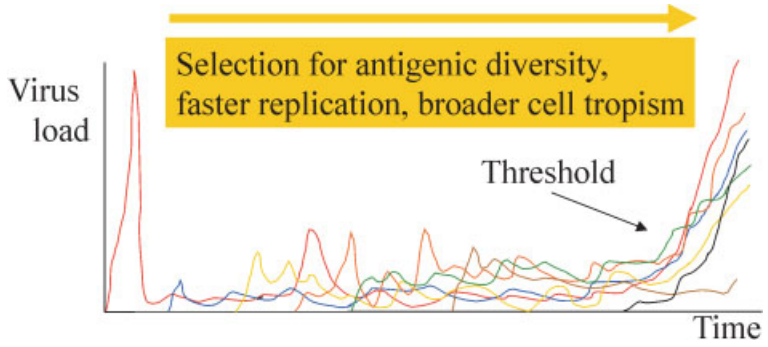

Figure 4. Evolution of antigenic diversity and HIV disease progression. During the initial acute phase of the infection, the virus population is relatively homogeneous. The immune system downregulates this initial viremia. During the asymptomatic phase of the infection, the virus evolves towards increased antigenic diversity. Once the diversity threshold has been crossed, the HIV-specific immunity collapses and the virus grows to high levels. More generally, there is not only evolution of increasing antigenic diversity but also faster virus replication and broader cell tropism. The evolutionary theory of HIV pathogenesis suggests that various selection pressures act on the virus and evolve a virus population that eventually can no longer be controlled by the immune responses.

reproduction and broader cell tropism. Hence, the rapid Darwinian evolution of HIV in vivo is the most obvious candidate mechanism for disease progression.

CTL-mediated control of HIV and anti-viral therapy

As described earlier in this review, the anti-viral therapy currently available cannot eradicate HIV from the host during the life-time of the patient. Since life-long treatment is not feasible, research has focused on identifying therapy regimes that could result in long-term immune-mediated control of HIV in the absence of drugs. Among immune responses, cytotoxic T lymphocyte (CTL) responses have been shown to be particularly effective at fighting HIV replication.[22,23] The development of protective CTL responses depends on the presence of CD4 T cell help. HIV infects and kills CD4 T cells and this can result in significant impairment of immunity against HIV. Indeed, HIV-specific helper cell impairment has been documented even in patients during the primary phase of infection.[24]

How does this helper cell impairment influence the dynamics between HIV and specific CTL responses? In order to understand the nature of immune impairment, we have to know the immunological factors that are required for efficient control of viral replication, or virus clearance. Mathematical models have identified two parameters. First, the rate of CTL activation/proliferation in response to antigen is important for limiting virus load,[1] and this has been shown in persistent infections such as HIV and HTLV.[25,26] However, in addition, virus clearance, or efficient long-term CTL-mediated control also requires antigen independent long-term persistence of memory CTLp.[27,28] This ensures that immune pressure is maintained on the declining virus population, and this drives the virus extinct. If CTLp are short-lived in the absence of antigen, they will decline after virus load has been reduced to low levels following CD8-mediated activity. This enables the virus to regrow, resulting in an equilibrium describing persistent virus infection in the presence of an ongoing CTL response, maintained by the persisting antigen. Hence, antigen-independent persistence of memory CTLp is required for clearance of infection. This is a new role for the antigen-independent persistence of memory CTL in viral infections.

Experiments in LCMV-infected mice have shown that the development of a long-lived memory CTL response requires CD4 T cell help.[29–32] In HIV infection, the high virus load attained during the acute phase has been shown to result in the absence of significant CD4 T cell proliferative responses.[24] This absence of CD4 T cell help could result in the failure to generate memory CTL that are long-lived in the absence of antigen. According to theory, the early impairment could be the reason for persistent HIV replication and eventual loss of virus control. This hypothesis is supported by data showing that many of the CTL seen in chronic HIV infection are short-lived when virus load is reduced by drug treatment.[33] This indicates that they cannot be maintained in the absence of antigenic stimulation. These CTL might be suboptimal, developing in the absence of CD4 T cell help.

These immune impairment dynamics have been captured by the following mathematical model.[34]

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta xv \\ \dot{y} &= \beta xv - ay \\ \dot{v} &= ky - uv \\ \dot{w} &= czyw - cqyw - bw \\ \dot{z} &= cqyw - hz. \end{aligned} \tag{6}$$

The model is based on the simple virus dynamics equations described at the beginning of this review (system 1). The target cells, x, are now assumed to be immune cells that are susceptible to HIV and that are involved in the delivery of "help" (e.g. CD4 T cells or antigen presenting cells). In addition, we introduce a CTL response. The population of CTL is subdivided into precursors or CTLp, w, and effectors or CTLe, z. CTLp are assumed to proliferate in response to antigenic stimulation, and then to differentiate into effectors. CTLp proliferate at a rate $cxyw$ and die at a rate bw. This means that proliferation not only requires antigen, y, but also the presence of uninfected helper cells, x. The higher the virus load, the more the uninfected helper cells become depleted, and the stronger the degree of immune impairment. Differentiation into effectors occurs at a rate $cqyw$ and is thus not assumed to require help. Finally, CTLe die at a rate hz. Thus, the mechanism of impairment underlying the model is that low levels of help result in more CTL differentiation than proliferation, which eventually leads to extinction of the helper-dependent CTL response. The results do not, however, rely on this particular mechanism. The conclusions reached from this model remain qualitatively similar as long as it is assumed that high levels of virus load increase the amount of immune impairment (e.g. by alternative mechanisms such as anergy).

The behavior of the model depends on the rate of viral replication relative to the strength of the CTL response. Three parameter regions can be distinguished (Fig. 5). (i) If the viral replication rate is slow and lies below a threshold, the degree of immune impairment is weak and CTL memory is established. The outcome of infection is long-term control. This outcome could correspond to the long-term non-progressors. They are characterized by sustained high levels of CTL despite very low viral loads even 15 to 20 years after infection. (ii) If the replication rate of the virus is high and lies above a threshold, virus growth and immune impairment are overwhelming. CTL memory cannot be established and long-term virus control cannot be achieved. (iii) If the replication rate of the virus is

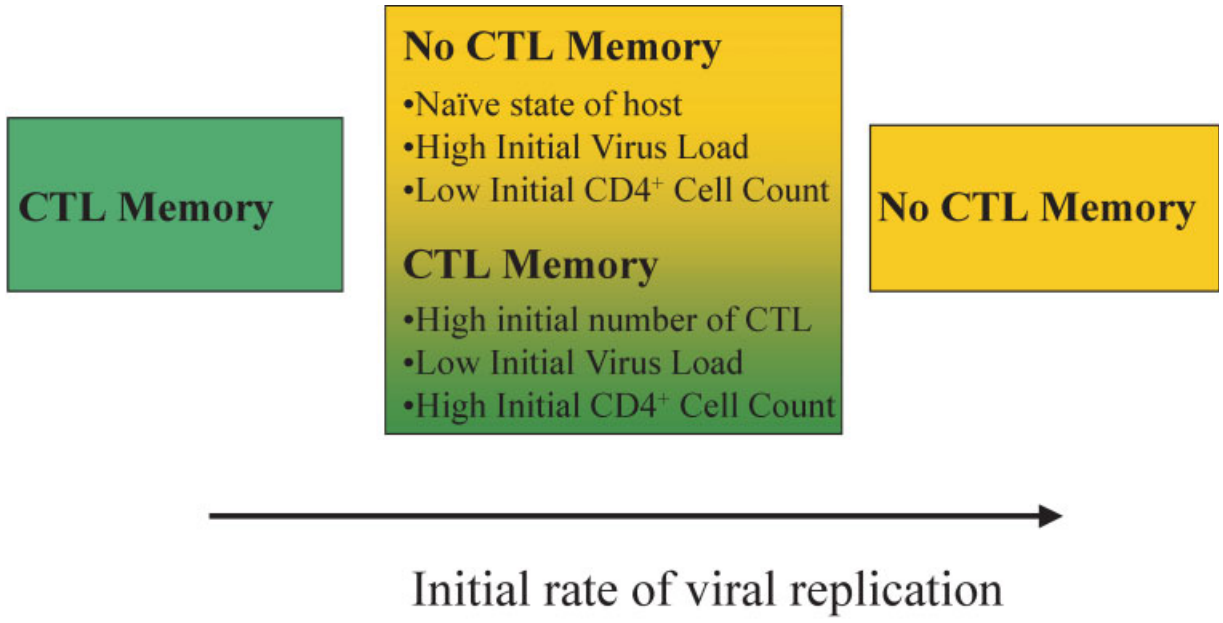

Figure 5. Three different outcomes of the model describing CTL memory and the control of HIV. The outcome of infection depends on the replication rate of the virus. If it replicates slowly, the degree of immune impairment is low and CTL memory is generated. This corresponds to long-term non-progression. If the replication rate of the virus is high, immune impairment is strong and CTL memory can never be established, resulting in progression of disease. If the replication rate of the virus is intermediate, both outcomes are possible, depending on the initial conditions, as indicated in the diagram.

intermediate, both outcomes of infection are possible: establishment of CTL memory leading to long-term control of HIV, and failure to establish CTL memory leading to disease progression. Which of the two outcomes is attained depends on the initial conditions, most importantly on the initial number of CTL. On the one hand, if a host is naive and the initial number of specific CTL is low, the system is likely to converge to the outcome describing failure of CTL memory and disease progression. This outcome is also promoted by high initial virus loads. On the other hand, if the initial number of specific CTL is high, maintenance of sustained CTL memory and long-term control is achieved. This outcome is also promoted by low initial virus loads.

We assume that HIV lies in the parameter region where the outcome of infection depends on the initial conditions. In this scenario, naive hosts fail to establish CTL memory and become progressors. However, since the CTL memory and control equilibrium is still stable, the model suggests that HAART can be used establish CTL memory and to switch a progressor into a state of long-term non-progression. According to the model this can be done by a phase of early therapy (Fig. 6). The immune system is provided with an antigenic stimulus, but treatment prevents the virus growing to high levels and significantly impairing immunity. Sufficient levels of specific CD4 T cell help are preserved, and a CTL memory response can develop. Once the memory CTL have been generated, cessation of treatment will result in maintenance of virus control. This is because the starting conditions have been altered by therapy: the initial level of memory CTL upon cessation of treatment is high.

These therapy regimes have also been studied experimentally.[35,36] Macaques were infected with SIV, and treatment was started 24 hours and 72 hours postinfection (p.i.). Animals that received treatment 24 hours p.i. showed boosted CD4 cell proliferative responses and long-term virus control if therapy was stopped after 4 weeks. Animals that received treatment 72 p.i. required 8 weeks of therapy to achieve improved immunological control. Animals that were characterized by undetectable virus load following cessation of treatment received a homologous rechallenge (with the same SIV isolate). Rechallenge was followed by a self-contained small blip of viremia. which was subsequently reduced below the limit of detection. Similar results were observed when the same animals were rechallenged with a more virulent SIV strain about a year after infection. When CD8 T cells were subsequently depleted with antibodies, virus load increased dramatically. These experimental results suggest that early therapy can substantially alter the dynamics between HIV and the immune system, and that sustained virus control can be achieved. They further demonstrate that protection is based

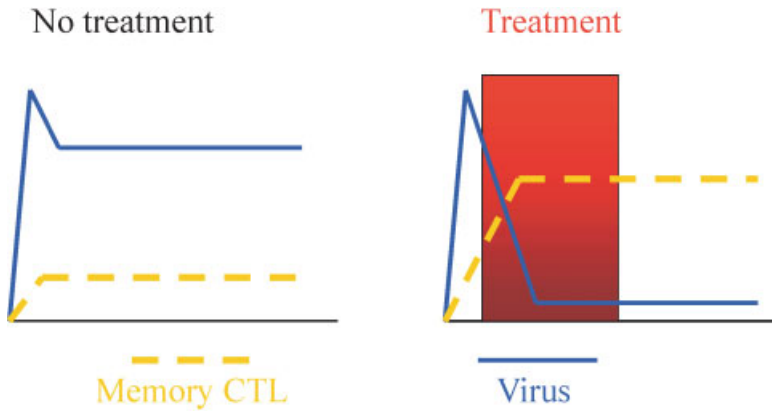

Figure 6. Early therapy can lead to long-term control of HIV. During natural infection, HIV replicates to high levels during the asymptomatic phase of the infection. This results in high levels of immune impairment, failure to generate CTL memory, and high virus load. Early therapy prevents HIV from overwhelming the immune system while providing an antigenic stimulus. This allows the development of a CTL memory response. Once memory has been generated, it will be maintained upon cessation of treatment. Hence, early therapy can convert a progressor into a state of long-term non-progression. Experimental verification of this idea comes from SIV infection in macaques[35,36] and HIV infection in humans.[24]

on CTL responses, and that memory has been successfully generated (protection against re-challenge), as suggested by our model.

This treatment schedule can be modified to achieve long-term immunological control in patients that are chronically infected with HIV and are in the asymptomatic phase of the infection. In traditional treatment regimes, virus load falls to very low levels, but when drugs are withdrawn, virus load re-emerges to pre-treatment levels. In dynamical terms, withdrawal of drugs in a chronically infected patient is similar to events occurring during acute infection: the HIV population grows from low levels and the immune response tries to expand. According to mathematical models, a temporary drug window, followed by a second phase of drug treatment can result in the development of an efficient memory CTL response that is long-lived in the absence of antigen. This is because the interruption allows the antigen to stimulate the immune response without overwhelming it. Once boosted during the secondary phase of treatment, virus control will be maintained if therapy is stopped. If the immune system is already relatively weak, repeated phases of intermittent therapy are required to progressively achieve virus control. According to mathematical models, this can be achieved even more efficiently by combining drug therapy with vaccination, although this approach has practical limitations at the moment. There are some clinical data that suggest that structured therapy interruptions can boost immunity against HIV, especially when performed relatively early after infection.[24,37–39] An interesting study is concerned with a cohort of patients who were diagnosed during the acute phase of the infection and treated immediately.[24] Treatment during the acute phase was followed by a number of therapy interruptions that correlated with a boost of HIV-specific CD4 T cell and CD8 T cell responses, as well as lower virus loads in the absence of the drugs. A more controlled study of treatment interruptions in SIV-infected macaques during the early chronic phase of the infection also showed very promising results.[40] In patients with chronic infection, treatment interruptions have been shown to boost HIV-specific immunity in some cases. A later start of interruption therapy, however, tends to be less efficient.[41] In addition to the possible 13 benefits of treatment interruptions, it is important to consider virus evolution and the rise of drug resistance during these therapy regimes. This has also been subject of mathematical modeling.[42]

Conclusion

This review has shown the importance of mathematical models for understanding infection dynamics, and in particular HIV dynamics. We demonstrated how a simple model of virus infection can be applied to data in order to measure crucial parameters that can lead to important new insights. We described how mathematical models can be used to generate new hypotheses regarding the mechanism of disease progression and the principles underlying immunological control. These insights were applied to guide therapy regimes aimed at long-term control of HIV. While some of the theoretical results have been backed up by experimental studies of SIV-infected macaques and by clinical data from HIV-infected patients, more experimental work has to be coupled with mathematical models in order to test theories in more detail and to measure more parameters.

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