HIV INFECTION

10

THE EMERGENCE of the human immunodeficiency virus (HIV) in the early 1980s demonstrated that infectious diseases represent a major problem for human health all over the world and that newly arising infectious agents can be especially devastating. As the human species becomes more abundant on the globe, having crossed the six billion threshold in 1999, the opportunity increases dramatically for infectious agents of other species to invade the human host. Despite tremendous progress in molecular biology and medicine, our methods to combat infectious diseases are limited. There are successful vaccines against a number of agents, but all attempts have so far failed to construct an HIV vaccine. The reasons for this failure are not clear, but include the virus's ability to infect cells of the immune system and to mutate away from any opposing selective forces.

HIV belongs to the class of retroviruses, which reversely transcribe their RNA genome into DNA (Figure 10.1). Howard Temin and David Baltimore won a Nobel Prize in Medicine for the discovery of the reverse transcriptase enzyme. The viral DNA can be integrated into the genome of the host cell and can remain there for an effectively unlimited time. Anywhere between 2% and 8% of the human genome consists of "burnt-out" retroviruses that

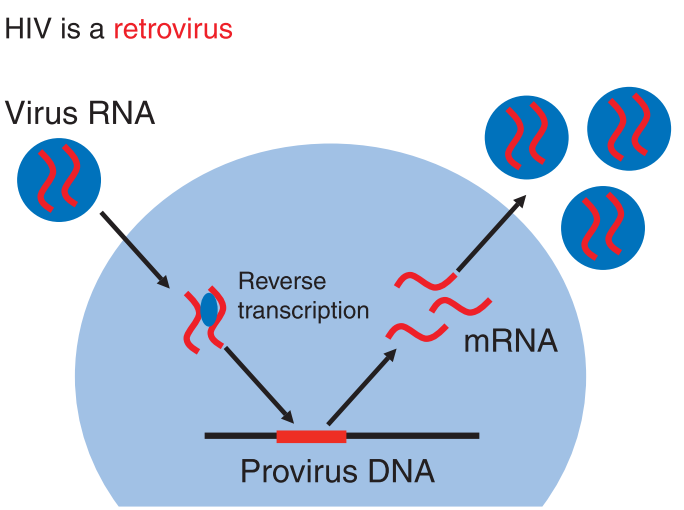


Figure 10.1 The life cycle of the human immunodeficiency virus (HIV). The virion contains two copies of the viral genome in form of single-stranded RNA. After entry into the host cell, the reverse transcriptase that comes with the virion uses both copies of the RNA genome to produce an RNA-DNA hetero-duplex and subsequently double-stranded viral DNA. This viral DNA (the provirus) is integrated into the genome of the host cell. The provirus can remain silent for a long time or can immediately induce the host cell to produce messenger RNA (mRNA). The viral mRNA has a dual purpose: (i) it is used for biosynthesis of viral proteins and (ii) it serves as viral genome for the virions that will eventually leave the host cell.

have integrated at some point in our genomic history and have subsequently received inactivating mutations.

The closest relatives of HIV are the simian immunodeficiency viruses (SIV) that infect many primate species. There are two types of human viruses: HIV-1 is very closely related to SIV from chimpanzees; HIV-2 is very closely related to SIV from sooty mangabeys. Remarkably, the SIV viruses appear not to cause disease in their natural hosts. When transmitted to another host species, however, they can induce a disease very similar to the acquired immunodeficiency syndrome (AIDS) in humans. For example, SIV from African green monkeys can induce AIDS in Asian macaques.

In humans, HIV leads to a primary infection with flu-like symptoms. During the primary infection, there is high virus load, but immune responses

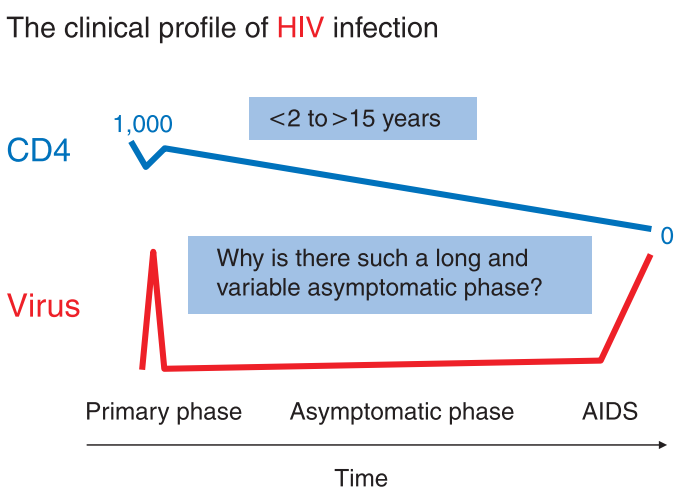


Figure 10.2 The pattern of disease progression of HIV infection requires a mechanistic explanation. There is a short primary phase, with high virus load, followed by a long and variable asymptomatic phase, usually with lower virus load. Eventually patients develop the fatal immunodeficiency disease AIDS. The asymptomatic phase can last less than two years or longer than fifteen years. The average length (without therapy) is about ten years. During disease progression the CD4 cell count drops (as a nearly linear function of time) from 1,000 to essentially 0. AIDS is defined as a CD4 cell count of less than 200. The question is: given that the characteristic time scale of the infection (the generation time of the virus) is on the order of days, why does it take years to develop disease?

against HIV may not yet be detectable. The patient can be negative when tested for HIV antibodies, but is usually positive when tested for the presence of HIV RNA. Subsequently, patients enter an asymptomatic phase that can last for many years (Figure 10.2). Over time there is a linear decline in the number of CD4 cells, the primary target cell of HIV in the human host. When the CD4 cell count drops from about 1,000 initially to below 200, patients enter the final stage of disease called AIDS (acquired immune deficiency syndrome). The failing immune system can no longer control the HIV virus, which replicates to high levels. In addition, the patient is overwhelmed and killed by other opportunistic infections.

CD4 cells represent an important component of the human immune system. CD4 cells are stimulated by the presence of foreign antigens. Once stimulated, they divide and send activation signals to CD8 cells and B cells. CD8 cells recognize and kill virus-infected cells. B cells release antibodies that attack viruses and other infectious agents. By infecting and depleting the CD4 cell population, HIV attacks the immune system that is meant to control it.

There are about twenty anti-HIV drugs. Some of the drugs were originally developed as anticancer drugs and were by coincidence inhibitors of the virus-encoded replication enzyme, reverse transcriptase. Other drugs were specifically designed to inhibit a virus-encoded protease enzyme. All these drugs interfere with virus reproduction. HIV can rapidly evolve resistance to any one of them, but is usually controlled when combinations of three or more drugs are used simultaneously. Successful drug treatment leads to a dramatic reduction in the abundance of virus, the so-called virus load. The drugs, however, do not cure patients, because they cannot eradicate the virus. Drug treatment can nevertheless greatly enhance the life expectancy of patients and can delay the onset of symptoms. Although the anti-HIV drugs constitute an amazing success of biomedicine, it is unclear whether they will have any impact on the global pandemic. The majority of all infected people worldwide are in the poorest countries and have little or no access to expensive drugs. The most effective epidemiological use of anti-HIV drugs may be to prevent mother-to-infant transmission of the virus. In any case, a highly effective vaccine is urgently needed.

Here we will address the following questions: What is the mechanism of HIV disease progression? Given that the virus infects and kills CD4 cells on a time scale of days, why is there such a long and variable asymptomatic period? Without treatment, it takes on average ten years to progress from infection to AIDS. Some people have died within one or two years of infection, while others are still asymptomatic after fifteen or more years. Furthermore, why does HIV cause a fatal disease in humans, while the very closely related SIV virus apparently does not cause disease in its natural hosts?

I will present a model of HIV (and SIV) disease progression. The main idea is that the key mechanism of disease progression is virus evolution in individual patients. During primary infection, there is selection for the fastest-growing virus mutant. Once immune responses emerge, there is selection for

virus mutants that escape from these responses. This process is called antigenic variation. The number of different antigenic variants of the virus, the "antigenic diversity," increases over time. The virus evolves more and more successfully to evade any opposing immunological pressure and is finally driven to a point at which the immune system can no longer control it. In this theory, virus evolution in individual patients is responsible for disease progression. The theory can also explain the difference between pathogenic and apathogenic SIV infections.

A central assumption of this theory, which was first proposed in 1990, is that the virus is rapidly replicating in the presence of immune responses. This rapid turnover was confirmed in 1995. Furthermore, the theory assumes that the virus can readily produce escape mutants that evade current immunological attack. Evidence for this fact has been mounting since 1991, but a clearer quantitative picture of viral escape from immune responses has been emerging only in recent years. Finally, the theory requires the virus to impair immune responses. There has been some discussion about the detailed mechanism of how HIV eliminates CD4 cells (some investigators claim that HIV is not directly cytopathic), but there can be no doubt that the CD4 cell population is being destroyed during HIV infection.

We will begin by studying the simplest possible model for the evolutionary dynamics of antigenic variation and subsequently add the HIV-specific property of impairing immune responses.

10.1 ANTIGENIC VARIATION

The simplest model of antigenic variation describes a replicating viral (or other) pathogen that is opposed by strain-specific immune responses. Let v_i denote the population size of virus strain (or mutant) i and x_i the magnitude of the specific immune response against strain i. Consider the following system of ordinary differential equations:

$$\begin{aligned} \dot{v}_i &= r v_i - p x_i v_i \\ \dot{x}_i &= c v_i - b x_i \end{aligned} \qquad i = 1, \ldots, n \tag{10.1}$$

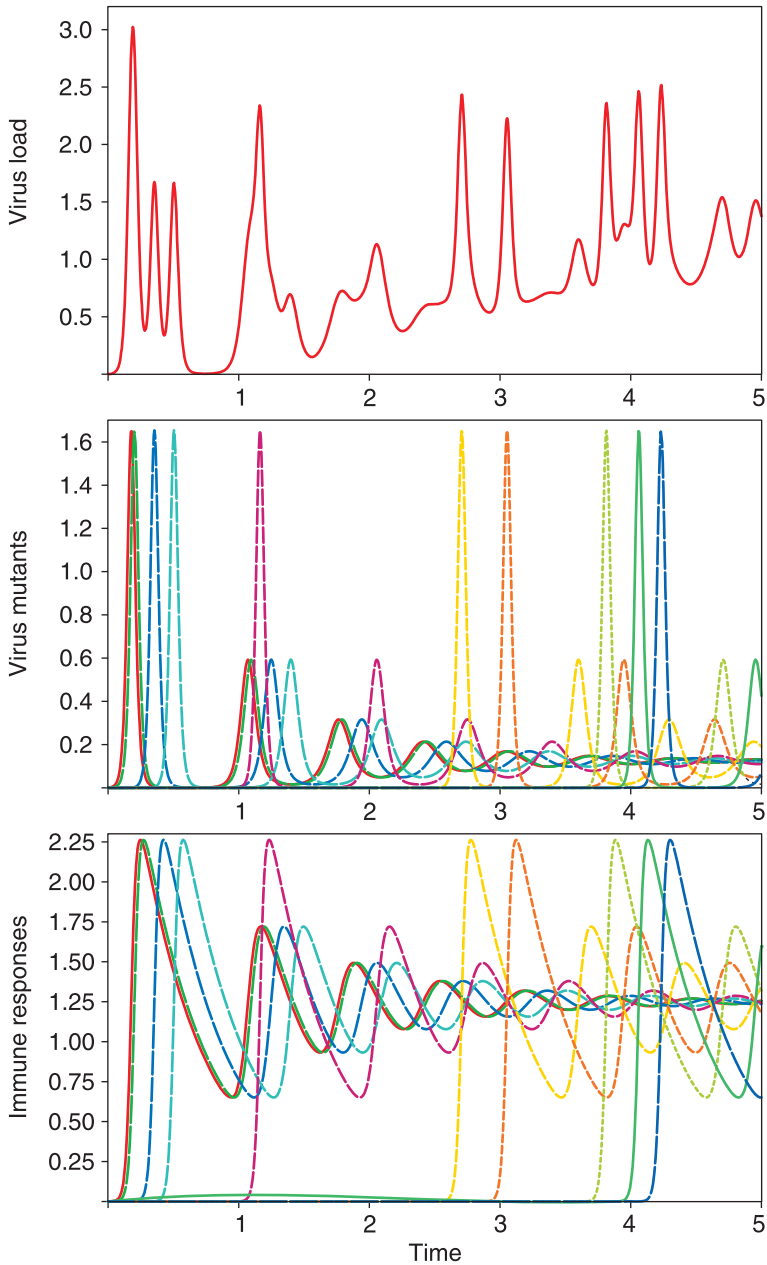
In the absence of immune responses, viral growth is exponential at rate r. Immune responses are stimulated at the rate cv_i, which is proportional to the abundance of virus. Immune responses eliminate virus at the rate px_iv_i. Finally, immune responses decay in the absence of further stimulation at rate bx_i. In this model, there are n virus strains, which are opposed by n specific immune responses. Each immune response, x_i, can only recognize virus strain v_i.

Figure 10.3 shows a computer simulation of the above model. We start with a single virus strain, v_1. Initially virus growth is exponential at rate r, but the virus stimulates the specific immune response, x_1, which reduces virus growth and eventually brings an end to viral expansion. Virus load reaches a maximum value and subsequently starts to decline. Similarly the immune response, x_1, reaches a maximum value and then declines. The system settles in damped oscillations to the equilibrium

$$v_1^* = \frac{br}{cp} \qquad x_1^* = \frac{r}{p}. \tag{10.2}$$

We assume that mutation continuously generates new viral strains, which can escape from the specific immune responses. In the computer simulation of Figure 10.3, the generation of new mutants is a stochastic process. The probability that a new mutant emerges in the time interval $[t, t + dt]$ is given

Figure 10.3 Dynamics of the basic model of antigenic variation as defined by equation (10.1). Each viral strain is only opposed by a strain-specific immune response. There is no cross-reactive immunity. Therefore the dynamics of each strain are independent of all other strains. Each strain rises to high abundance and is subsequently down-regulated in damped oscillations by a specific immune response. Virus load increases in an oscillatory fashion as new strains are being generated. The equilibrium virus load is an increasing function of antigenic diversity. The figure shows the total virus load, v, the abundance of individual strains, v_i, and the strength of specific immune responses, x_i. Parameter values are $r = 2.5$, $p = 2$, $c = 0.1$, and $b = 0.1$. The infection starts with a single strain. The probability that a new mutant arises in the time interval $[t, t + dt]$ is given by Pdt with $P = 0.1$. Reprinted from Nowak and May (2000) by permission of Oxford University Press.



by Pdt, where P is the mutation rate. The simplest assumption is that P is a constant. Alternatively, we can assume that P is proportional to virus load, $v = \sum_{i=1}^{n} v_i$, because the number of mutation events is proportional to the number of replication events.

In Figure 10.3 the new variant, v_2, escapes from the immune response x_1 and grows unchecked initially, but it induces an immune response, x_2, which brings it down after some time. Meanwhile another escape mutant, v_3, has emerged, and so on. The result is a sequence of antigenically different variants that all grow for some time before being controlled by immune responses. If there are n viral variants present in the system and if all are at the equilibrium value given by (10.2), then the total virus abundance is given by

$$v = \frac{brn}{cp}. \tag{10.3}$$

We observe that virus load, v, is an increasing function of antigenic diversity, n.

Equation (10.1) defines the simplest model of antigenic variation. Each virus strain, v_i, is only controlled by one specific immune response, x_i. This means that the dynamics of any one strain are independent of all other strains; the two differential equations describing the dynamics of one strain and its specific immune response are decoupled from the equations for other viral strains.

10.1.1 Strain-Specific and Cross-Reactive Immunity

The most obvious extension of the basic model is to include a cross-reactive immune response that can recognize several (or all) virus mutants. Thus new antigenic variants escape from all existing strain-specific responses but are still recognized by the cross-reactive response.

Denote by z the strength of a cross-reactive immune response that is active against all virus mutants. This leads to the system of equations

$$\begin{aligned} \dot{v}_i &= v_i(r - px_i - qz) \qquad i = 1, \ldots, n \\ \dot{x}_i &= cv_i - bx_i \qquad\quad i = 1, \ldots, n \\ \dot{z} &= kv - bz \end{aligned} \tag{10.4}$$

The cross-reactive immune response, z, is stimulated by all virus mutants at rate kv_j and decays at the rate bz. The main consequence of this model extension is that new antigenic variants do not completely escape from all existing immune responses, and therefore do not grow to the same abundance as the original virus mutant. The dynamics of individual strains are no longer independent of one another. A computer simulation is shown in Figure 10.4.

For n virus mutants, the equilibrium virus load is now given by

$$v = \frac{brn}{cp + kqn}. \tag{10.5}$$

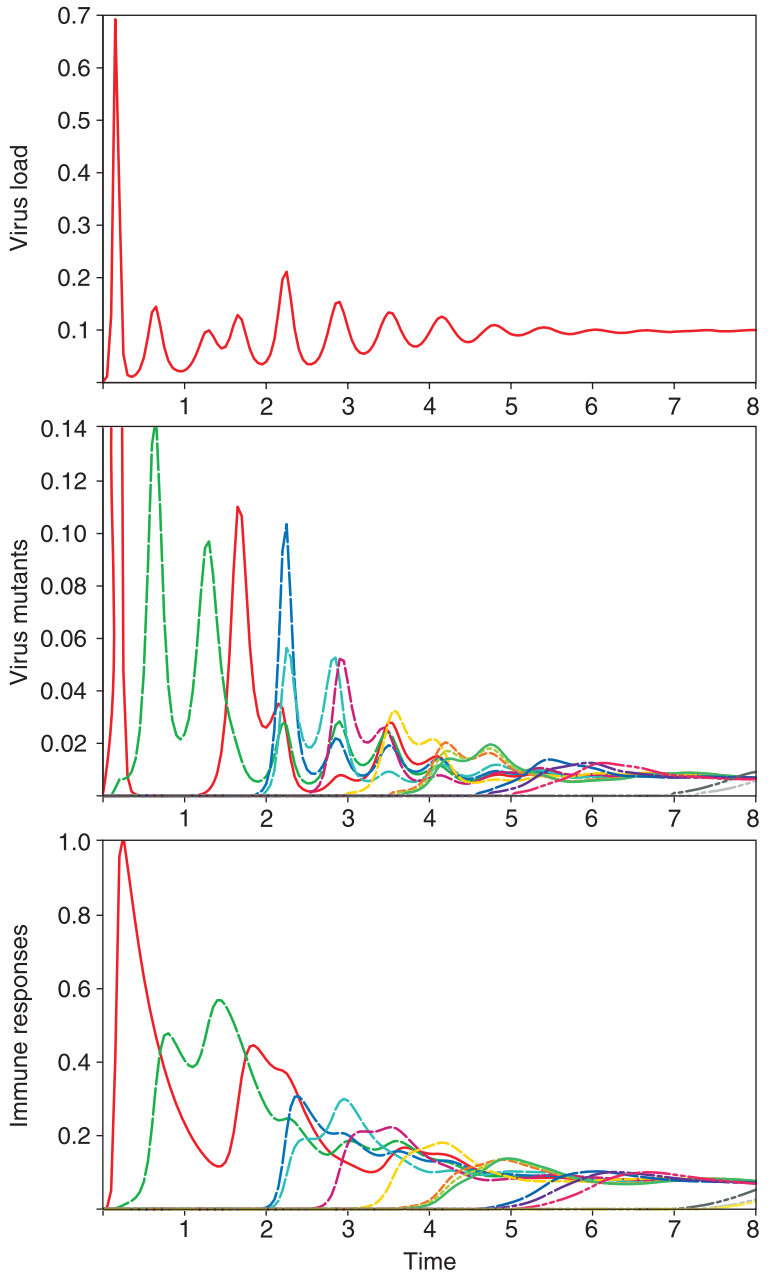
Once again viral load is an increasing function of antigenic diversity, n, but saturates for high values of n. The maximum possible equilibrium virus load is $v_{max} = (br)/(kq)$, which represents the equilibrium virus load in the presence of the cross-reactive immune response alone. Thus increasing antigenic diversity eliminates the effect of strain-specific immunity.

10.2 DIVERSITY THRESHOLD

In the previous section we analyzed general models of antigenic variation. They can in principle describe any virus or other infectious agent that establishes a persistent infection in its host and can mutate to escape from immune responses. Let us now add another feature, which makes the model more specific for HIV. We will assume that the virus can impair immune responses:

$$\begin{aligned} \dot{v}_i &= v_i(r - px_i - qz) \qquad i = 1, \ldots, n \\ \dot{x}_i &= cv_i - bx_i - uvx_i \qquad i = 1, \ldots, n \\ \dot{z} &= kv - bz - uvz \end{aligned} \tag{10.6}$$

As before, v_i denotes the population size of virus mutant i, while x_i denotes the immune response specifically directed against virus strain i. The cross-reactive immune response directed against all different virus strains is given by z. Mutational events occur throughout the infection and increase the number of virus strains, n, as time goes by. The total virus load is given by $v = \sum_i v_i$.



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 c specifies the rate at which they are evoked; similarly q denotes the efficacy of cross-reactive immune responses and k the rate at which they are induced. In the absence of further activation, immune responses decay at rate b. HIV and other lentiviruses can impair immune responses by killing CD4-positive cells, which help B cells and cytotoxic T cells to mount immune responses against the virus. We summarize this effect of HIV in the loss terms $-uvx_i$ and $-uvz$. Thus the parameter u characterizes the ability of the virus to impair immune responses; by depleting CD4 cells the virus indirectly impairs immune responses mediated by B cells and cytotoxic T cells. The immune responses converge to

$$x_i^* = \frac{cv_i}{b + uv} \qquad i = 1, \ldots, n \tag{10.7}$$

and

$$z^* = \frac{kv}{b + uv}. \tag{10.8}$$

Once the immune responses have reached these levels, the total virus population changes as

$$\dot{v} = \frac{v}{b + uv}[rb - v(cpD + kq - ru)]. \tag{10.9}$$

Figure 10.4 Antigenic variation in the presence of strain-specific and cross-reactive immune responses. The simulation begins with a single viral strain, which induces both strain-specific and cross-reactive immune responses. Subsequent strains escape from the strain-specific response, but not from the cross-reactive response. The equilibrium virus load is an increasing function of antigenic diversity, but saturates for high levels of antigenic diversity. The simulation is based on equation (10.4), with the parameter values $r = 2.5$, $p = 2$, $q = 2.4$, $c = k = 1$, and $b = 0.1$. The probability that a new mutant arises in the time interval $[t, t + dt]$ is given by Pdt with $P = 0.1$. Reprinted from Nowak and May (2000) by permission of Oxford University Press.

The variable D denotes the Simpson index,

$$D = \sum_{i=1}^{n} (v_i/v)^2. \tag{10.10}$$

This quantity is a number between 0 and 1 and represents an inverse measure of diversity. The Simpson index denotes the probability that two virus particles chosen at random belong to the same strain. If only one virus strain is present, then $D = 1$. If n virus strains present, all with the same frequency, then $D = 1/n$.

The product kq specifies the efficacy of the cross-reactive immune responses. The product cpD denotes strain-specific immune responses. The efficacy of these strain-specific responses depends on the antigenic diversity of the virus population. Equation (10.9) shows that increasing diversity (decreasing D) increases the total population size of the virus.

The model has three distinct parameter regions, which correspond to three qualitatively different courses of infection (Figure 10.5).

i. Immediate Disease

If $ru > kq + cp$, then a single virus strain can outrun the combined effect of strain-specific and cross-reactive immunity. In this case, there is no asymptomatic phase; the virus population immediately replicates to high levels and causes disease and death. Viral replication, r, and/or cytopathic effects, u, are large compared with the combined effects of cross-reactive and strain-specific immune responses, $kq + cp$. The immune response is unable to control the virus, which replicates to high levels within a short time. No antigenic variation is necessary.

An example for this type of behavior is the rapid progression to disease and death of pig-tailed macaques infected with the acutely lethal variant SIVsmm-pbj14, which was isolated from sooty mangabeys. The virus kills within two weeks of infection. The primary manifestation of disease, and the cause of death, is diarrhea and its sequelae (rather than immunodeficiency). Our model only predicts that the immune responses are unable to control the virus, which in turn replicates to very high levels and thereby causes disease. To validate our model in this particular example, one would have to check if

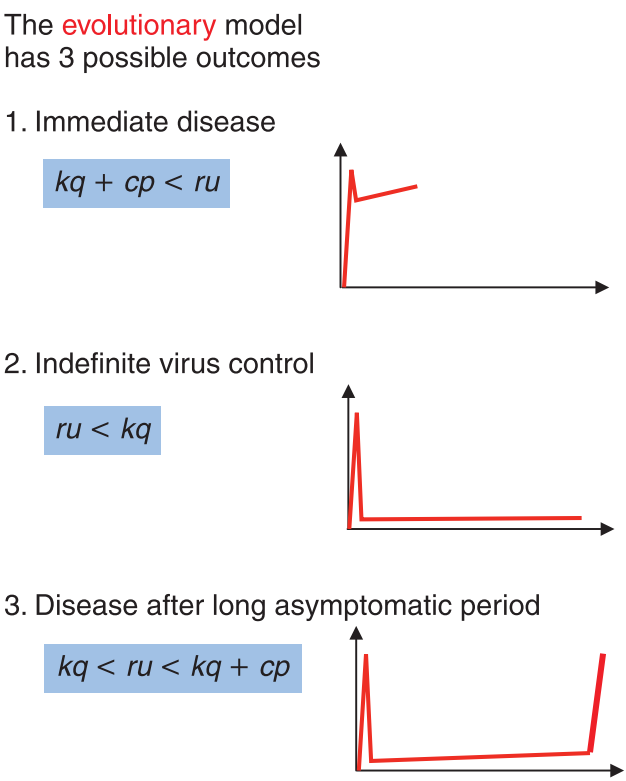


Figure 10.5 The mathematical model of HIV infection (given by equation 10.6) has three possible outcomes, which correspond to observed patterns of lentivirus infection. (i) If the virus cannot be contained despite the combined effort of strain-specific and cross-reactive immune responses, then there is immediate development of disease without need for viral diversification and evolution. This pattern is observed in some cases of very fast disease progression in HIV infection and experimental SIV infection. (ii) If the virus can be contained by cross-reactive immune responses alone, then there is asymptomatic infection without development of disease. This pattern is observed in most natural SIV infections. (iii) If viral replication and cytopathicity can be contained by the combined effort of strain-specific and cross-reactive immune responses, but not by cross-reactive responses alone, then there is evolution toward disease over a long and variable period of infection. This pattern corresponds to human HIV infection or many experimental SIV infections.

virus concentrations are very high in the sick animals. Another test would be to construct an SIVsmm-pbj variant with a reduced replication rate. This may cause not immediate disease and death but a chronic infection (maybe with slow development of immunodeficiency disease).

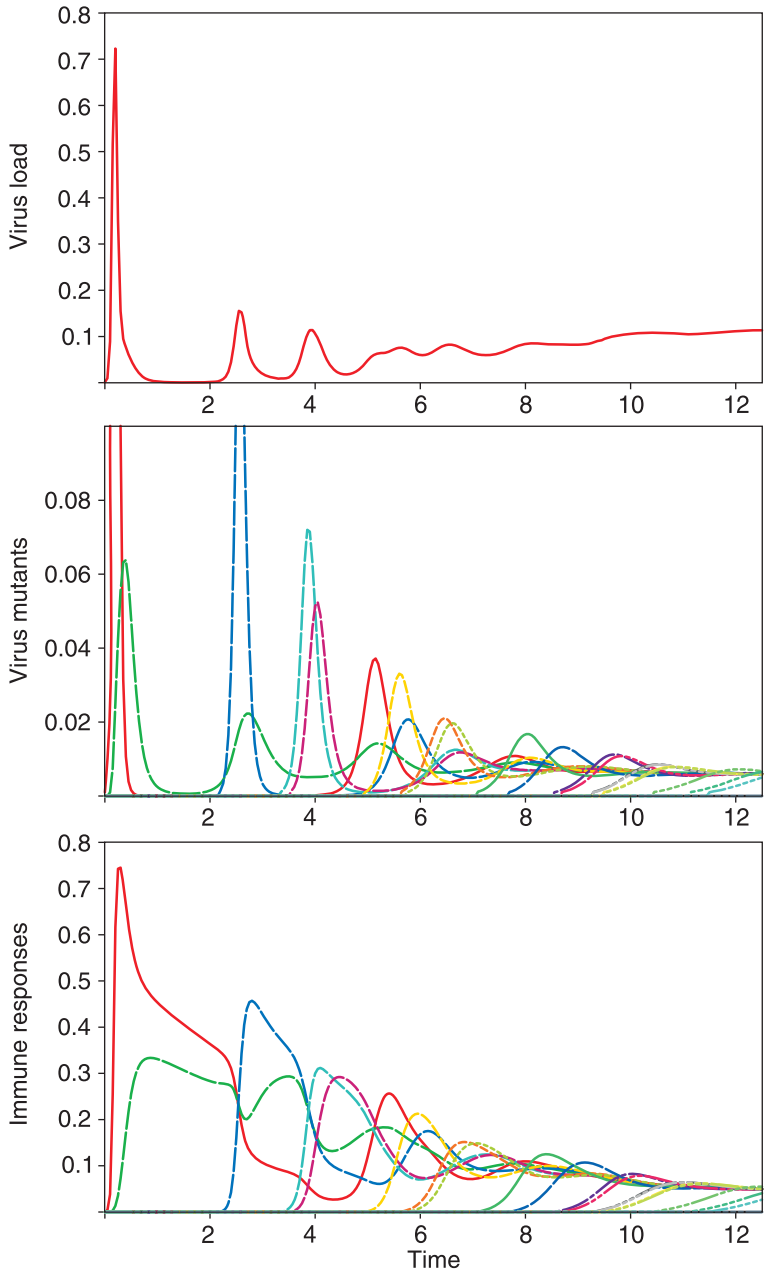
ii. Chronic Infection without Disease

If $kq > ru$, then the effect of cross-reactive immunity alone is sufficient to control the virus. Antigenic variation will occur and will increase virus load over time, but the immune system is able to control the virus indefinitely (Figure 10.6).

This parameter regime corresponds to infections that SIV viruses cause in their natural hosts. For example, a large proportion of African green monkeys (AGMs) are infected with SIVagm, but do not succumb to immunodeficiency disease. The functional immune response of AGMs to SIVagm seems to be similar to the response of humans to HIV. There is also a productive infection of CD4 cells, and SIVagm has a viral load equivalent to that in asymptomatic HIV-1–infected humans. There is a similar degree of genetic variation. All these observations are consistent with our model. The parameter regions (ii) and (iii) can give rise to similar viral loads and similar antigenic diversities.

The critical difference is that in parameter region (ii) the virus population is effectively controlled by the cross-reactive immune responses alone, and so there is no diversity threshold. The difference between SIV in AGMs and HIV in humans could be caused by a slightly smaller replication rate of SIVagm in AGMs or, more likely, by a more effective cross-reactive immune response.

Figure 10.6 A strong cross-reactive immune response (directed at the conserved epitopes of the virus) can lead to a chronic infection without development of disease. This situation occurs if the cross-reactive response alone is sufficiently strong to control the virus population, that is, if $kq > ru$. The computer simulation is based on equation (10.6), with the parameter values $r = 2.3$, $p = 2$, $q = 2.4$, $c = k = u = 1$, and $b = 0.01$. The infection starts with a single strain. The probability that a new mutant arises in the time interval $[t, t + dt]$ is given by Pdt with $P = 0.1$. Reprinted from Nowak and May (2000) by permission of Oxford University Press.



This is plausible: the long-established interaction between SIVagm and its natural host should have selected for efficient cross-reactive immune response, which is directed at parts of the virus that cannot mutate (or only mutate with substantial fitness reduction).

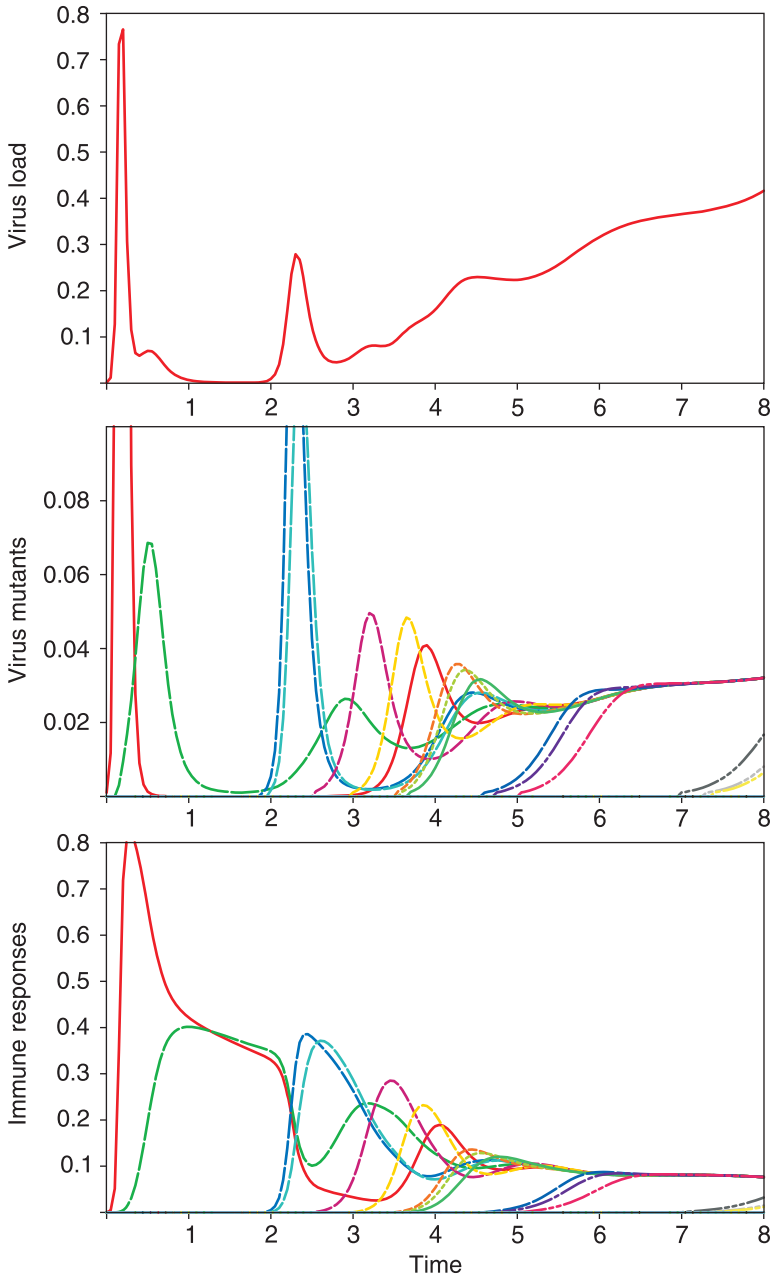
iii. Chronic Infection and Disease after a Long Incubation Period

If $kq + cp > ru > kq$, then the combined effect of cross-reactive and strain-specific immune responses can control any one strain, but cross-reactive immunity alone is not sufficient to control the virus (Figure 10.7). Over time, antigenic variation reduces the effect of strain-specific immunity. In the beginning antigenic diversity is low, and the total virus population size is regulated to some equilibrium value. Antigenic diversity increases over time. Eventually antigenic diversity is so high that equation (10.9) no longer has a steady state for virus load. Now virus load increases without control. Remember that D is an inverse measure for antigenic diversity. In the beginning D is large. D decreases during infection as antigenic diversity increases. The immune system loses control when D drops below a critical value given by

$$D < \frac{ru - kq}{cp}. \tag{10.11}$$

This inequality defines the "antigenic diversity threshold." Once the threshold is exceeded, the virus population escapes from control by the immune response and tends to arbitrarily high values. This process may be interpreted

Figure 10.7 A diversity threshold occurs if the cross-reactive immune response by itself is unable to control the virus population, but a combination between cross-reactive and strain-specific responses can control any one strain. In mathematical terms, this means $kq + cp > ru > kq$. Increasing antigenic diversity enables the virus population to escape from the immune response after a long incubation period. The computer simulation is based on equation (10.6) with the parameter values $r = 2.5$, $p = 2$, $q = 2.4$, $c = k = u = 1$, and $b = 0.01$. The infection starts with a single strain. The probability that a new mutant arises in the time interval $[t, t + dt]$ is given by Pdt with $P = 0.1$. Reprinted from Nowak and May (2000) by permission of Oxford University Press.



as the development of immunodeficiency disease, which is characterized by high virus load and almost total depletion of CD4-positive cells.

Parameter region (iii) corresponds to the typical HIV-1 or HIV-2 infection in humans and also to experimental SIV infection, where an animal is infected with a virus from another species.

The "antigenic diversity threshold" is an intuitive concept. In a natural setting, the original infection occurs with a heterogeneous virus population. But the immune system in the newly infected patient has not yet been activated. There is exponential expansion of the invading virus, selecting for the fastest-growing strain without consideration for immunological escape. This initial phase will lead to a virus population with very low genetic and antigenic diversity. Subsequently the immune system becomes activated and selects for antigenic variation in those epitopes that are recognized by relevant immune responses. The increasing antigenic diversity makes it more and more difficult for the immune system to down-regulate all the various mutants simultaneously. The reason for this loss of control is the asymmetric interaction between immunological and viral diversity. Each virus strain can impair all immune responses by cutting off their CD4 help, but individual strain-specific immune responses can only attack specific virus strains. In more heterogeneous virus populations, the ratio between immune response–induced killing of virus and virus-induced killing of immune cells is shifted in favor of the virus. This shift eventually leads to a complete breakdown of the immune system and uncontrolled virus replication.

I call this phenomenon the "diversity threshold," because in the simplest mathematical model there is a critical number of antigenically distinct variants that can be controlled simultaneously by the immune system. In more realistic and more complicated versions of the model, this "diversity threshold" condition takes a more general form, and indicates the point at which the immune system fails to control the virus population. These complications arise, for example, when one acknowledges that different virus strains have different replication rates or immunological properties, or that the basic parameters of the model are not constant but change during the course of infection (such as increasing virus replication rates, resulting from increasing CD4 cell activation). Many different versions of the model have been studied, including

responses to multiple epitopes, deletion of epitopes, cost of escape, and target cell limitation.

It is important to note that the model does not predict that patients with higher genetic or antigenic diversity must necessarily progress faster than patients with lower diversity. First of all, observe that the fastest progression occurs in parameter region (i) without any antigenic variation. Second, patients will differ in the strength of their immune response to HIV. Patients with a weak strain-specific response will tend to allow higher virus load without selecting for large antigenic diversity. In contrast, patients with strong strain-specific responses will reduce virus load to low levels, but also select for high antigenic diversity. Hence there need not be a simple relation between viral diversity and rate of disease progression in a comparison between different patients.

Finally, we note that the model does explain the difference between pathogenic and apathogenic SIV and HIV infections. Apathogenic infections correspond to parameter region (ii), where the cross-reactive immune responses suffice to control the virus. Pathogenic infections correspond to parameter region (iii), where cross-reactive and strain-specific responses are needed to control the virus; in this case, virus evolution will allow escape from strain-specific responses and lead to disease progression over time. Therefore understanding the reason why natural SIV infections seem to be apathogenic, while HIV causes a fatal disease in humans, requires a quantitative measurement of the virological and immunological parameters of the infection that make the difference between parameter regions (ii) and (iii).

We have seen that HIV evolution in individual infections provides a plausible mechanism for disease progression. The virus is initially controlled by immune responses, but continuously evolves to escape from these responses. Virus evolution can lead to increasing antigenic diversity, more efficient avoidance of immune responses, faster replication rates, and broader cell tropism (meaning that the virus can infect a larger number of different cell types). After some time, virus evolution reaches a threshold above which the immune system can no longer control the virus (Figure 10.8).

The evolutionary mechanism of disease progression has three parameter regions that correspond to three different outcomes of lentivirus infections: (i) there is immediate disease and death if the combination of cross-reactive

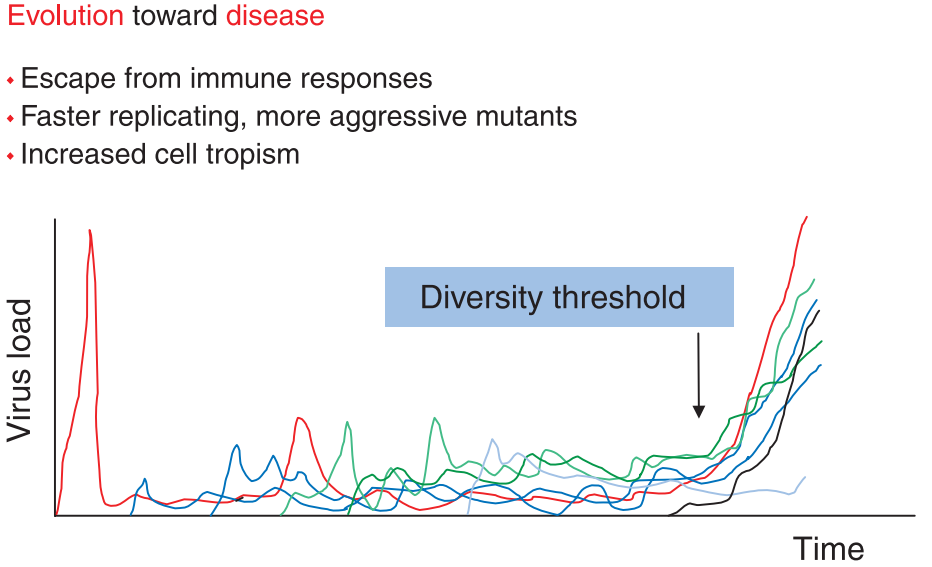


Figure 10.8 HIV disease progression is a consequence of viral evolution that occurs in individual patients. The virus continuously evolves to escape from antiviral immune responses (and drug treatment). In addition, the virus can generate mutants that replicate faster in a particular patient and can infect a wider variety of cells (increased cell tropism). Eventually the virus evolution reaches a point, called the "diversity threshold," at which the immune system loses control.

and strain-specific immune responses fails to control the invading virus strain; (ii) there is asymptomatic infection without disease if the cross-reactive immune responses alone can control the virus; (iii) there is progression to disease after a long and variable asymptomatic period if the combined effect of cross-reactive and strain-specific immunity can control any one strain, but cross-reactive immunity alone is not enough; in this case, virus evolution will eventually lead to AIDS.

Although the theory was received with skepticism originally and misunderstood at times, in the meantime every confirmed fact of HIV biology is in agreement with an evolutionary model of disease progression. It is therefore likely that this model provides the correct mechanism of HIV disease progression.

SUMMARY

- HIV infects CD4 cells, which represent a crucial component of the human immune system. CD4 cells help other cells, such as CD8 cells and B cells, to mount immune responses.
- CD4 cell numbers decline during HIV infection.
- The generation time of HIV in an infected patient is about one to two days. Yet it takes on average ten years for HIV to destroy the entire CD4 cell population. The crucial question arises: what is the mechanism for the slow disease progression in HIV infection?
- HIV evolves during individual infections.
- Antigenic variation allows HIV to escape from immune responses that are meant to control it.
- Antigenic variation leads to increasing viral diversity, increasing viral load (= abundance) and declining immunological control.
- Eventually this evolutionary process reaches a point (a "diversity threshold") above which the immune system can no longer control the virus.
- The diversity threshold is a consequence of the asymmetric interaction between HIV and the immune system: different virus mutants can kill CD4 cells irrespective of the mutants' specificity, but specific immune responses are only active against specific virus mutants.
- The model has three different parameter regions, which correspond to the observed patterns of HIV and SIV infection: (i) rapid progression to disease and death, (ii) asymptomatic infection without disease, and (iii) development of disease after a long and variable asymptomatic period.
- According to the proposed model, HIV disease progression is caused by the evolutionary dynamics in individual infections.