Evolutionary dynamics of HIV-induced subversion of the immune response

Symptoms of human immunodeficiency virus (HIV) disease progression is characterized by a slow but steadily decline in the number of CD4+ T cells. This decline in the development of AIDS when the immune response is overwhelmed and the virus goes uncontrolled. Pathogenicity of HIV may be due in part to the loss of effective immune responses as well as virus-induced immune impairment. Here we discuss how the dynamic interactions between the virus population and the immune response may lead to the development of AIDS. In particular, we argue that the evolution of HIV may be the driving force successfully weakening the immune system. This may lead to increased levels of viremia as well as in the evolution of more virulent phenotypes which indicate progression in AIDS. These insights are important for understanding the disease process and for designing effective treatment regimes.

In the dynamics of HIV

Recent quantitative virological data from HIV-1 infected patients receiving antiretroviral therapy, in conjunction with mathematical models, have for the first time provided precise information on the kinetics of virus turnover in vivo (1–8). It was shown that the half-life of productively infected cells is around 2 days (3, 4). Free virus particles in the plasma have an even shorter half-life. The current estimate is about 6 h, but it is likely that the actual figure is lower than this, which suggests that close to 100% of the free virus population is in the plasma, of a patient turns over every day (6). These studies provide conclusive evidence that the asymptomatic phase of HIV-1 infection is not a period of latency but a dynamic process involving continuous rounds of viral replication and infection, and that HIV is not a "slow virus" in terms of its daily replication potential. These findings are crucial for understanding the driving forces underlying disease progression in HIV-1 infected patients: the rapid viral turnover during the asymptomatic phase indicates a great potential for the virus to evolve in response to selection pressures exerted either by the immune system or by drug treatment (3, 4, 9, 10). The potential for rapid viral evolution is demonstrated by finding that wild-type virus can be re-
placed by drug-resistant strains within 14–28 days of drug therapy (4, 11).

Such infection dynamics involve non-linear interactions of many different components, and this makes the use of mathematical models necessary to provide a correct interpretation of empirical results, to generate new insights and hypotheses and to guide further experimental work. In this review we will demonstrate how mathematical models have been used to identify evolutionary mechanisms that may drive disease progression in HIV-infected patients and to achieve a better understanding of the principles underlying antiretroviral therapy.

HIV pathogenesis and subversion of cellular immunity

In the primary phase of the disease, after an individual has been infected with HIV, the virus replicates to relatively high levels for a short but variable period of time. The subsequent rise of the immune response suppresses this primary viremia and the patient enters the asymptomatic phase. During this phase, the virus waxes and wanes at low levels and one observes a slow decline in the CD+ cell count of the patient. The duration of the asymptomatic phase varies widely between individuals. Fast progressors develop AIDS within a few years, whereas slow or non-progressors remain without symptoms for 10–15 years. The final development of AIDS is often characterized by an upsurge in viral load accompanied by a fall in the number of CD+ cells found in the blood. It is now common to define AIDS-finite if the number of CD+ cells reduces to below 200 per mm3 (1); a healthy, infected person has about 1,000 CD+ cells per mm3.

At the beginning of the infection, there is little sequence variation in the HIV population isolated from a patient (12–15). In the course of infection, HIV mutates in the cyto
toxic T lymphocytes (CTLs) and antibody epitopes, resulting in an increase in antigenic diversity until the patient develops AIDS (16–29).

Virus variants isolated in the asymptomatic phase tend to use the CCR5 co-receptor (R5 virus type) (25–26). Therefore, they do not infect primary T cells, but also have the ability to infect macrophages. These isolates tend to show a slow rate of replication (27) and a low degree of cytopathogenicity and are usually associated with the non-syncytium-inducing (NSI) phenotype (14, 28–34). During the asymptomatic phase of the infection, HIV evolves to show stronger tropism for T cells (32). These virus strains tend to replicate at a faster rate (27), and are characterized by higher degrees of cytopathogenicity (33–36). Such isolates may either use both the CCR5 and the CXCR4 co-receptors (termed R5X4 strains) (25, 26) or, in about 50% of the patients, become specialized to use the CXCR4 receptor only (termed X4 viruses) (25, 26). X4 strains have lost the ability to infect macrophages, are associated with the syncytium-inducing phenotype and are markers of disease progression (10, 12, 35, 36).

Central to the understanding of HIV pathogenesis is the concept of immune impairment. During the course of the infection, HIV evolves towards phenotypes that are characterized by increased virulence, especially T-helper cells. Loss of T-helper cell function reduces the efficacy of the CTL response. This allows the virus to replicate more efficiently and to reach to more pathogenic phenotypes, which in turn increases viral load. Therefore, the observed negative correlation between virus load and CTL in HIV-infected patient (37) indicates that the subversion of the CTL response by the virus is an important factor governing progression of the disease (D. Wolber, S. Hall, G. Ogg, A. J. McMichael, M. A. Nowak, C. R. M. Bangham, submitted; D.Wolber, S. Hall, C. R. M. Bangham, M. A. Nowak, submitted).

In the following we will show how mathematical models may explain this subversion of the CTL response, and how impairment of the immune system facilitates the evolution of viral phenotypes that indicate progression to AIDS.

Dynamics of immune impairment to HIV

Mathematical models suggest that the impairment of the immune response may result from the dynamical interaction of the virus population with both T-helper cells and CTL. In the evolution of HIV may shift the balance between HIV replication and the immune response successively in favour of the virus, eventually resulting in the collapse of the immune system and uncontrolled viral replication. We have identified two evolutionary forces which may result in similar patterns of CTL impairment: evolution towards increased antigenic diversity and evolution towards increased rates of replication. These will be discussed in turn.

Antigenic diversity and immune impairment

Since there is no proof-reading mechanism during reverse transcription, HIV is characterized by a relatively high mutation rate of about one base per genome per replication cycle (38, 39). This high mutation rate, together with the selection pressure exerted by the antiviral immune response, provides ideal conditions for the evolution of antigenic escape mutants (13, 22, 23). In fact, the error rate of the reverse transcriptase of HIV seems to maximise the chance of producing antigenic escape mutations (40). These escape mutants may in turn be controlled.
by rising immune responses specific for the newly evolved virus strains. However, there is an inherent asymmetry in the interaction between the evolving virus population and the anti-viral immune response. While a given immune response may arise to be specific for a given virus strain in order to kill it, each virus strain can infect and kill any T-helper cell regardless of its specificity. These basic assumptions can be captured in simple mathematical models (9, 41-44). Such models take into account the evolving virus population, strain specific immune responses as well as cross-reactive immune responses. The evolutionary dynamics also involve a stochastic process where the probability that a new mutant emerges is either constant or more realistically proportional to the viral load, since the number of infections is proportional to the number of replication events.

Such models are characterized by three parameter regimes, depending on the relationship between viral replication and/or immune impairment and the strength of the strain-specific and cross-reactive immune responses. i) Viral replication together with immune impairment can result in uncontrolled viral replication and the development of AIDS without the presence of a prolonged asymptomatic period. No antigenic variation will be observed and the fastest replicating strain will emerge to dominate the virus population. Such dynamics are observed in rapid progressors (45). ii) If the cross-reactive immune response alone is sufficiently large compared to virus replication and the amount of immune impairment, then the immune system may effectively control the virus population with the development of disease. In this case, the level of viral load controlled by the immune response depends on the rate of viral replication, the amount of immune impairment to the virus, the efficacy of the immune response and the number of antigenic variants present. However, uncontrolled viral replication is not possible in this parameter regime. Although some HIV-infected patients are long-term non-progressors and may fall in this parameter regime, it is not clear whether they will develop symptoms at a later stage. Chronic infectious without development of disease is, however, the rule for simian immunodeficiency virus infections in their natural hosts (46). The lack of disease progression in this case may be due to strong cross-reactive immune responses as well as slower replication rates of the virus. iii) The most interesting case predicting the course of HIV infection in humans when the combination of cross-reactive and strain-specific immune responses may control the virus, but the strain-specific response alone is unable to do so. In this case, the dynamics depend on the amount of antigenic diversity. If antigenic diversity is low, the virus can be controlled, corresponding to the asymptomatic phase of the infection. Increasing antigenic diversity results in an increase in viral load. The immune system keeps the virus population in check as long as the antigenic diversity law below a threshold. Crossing the diversity threshold leads to uncontrolled viral growth accompanied by a collapse of the immune system. A typical course of disease progression predicted by the model is illustrated in Fig. 1. The length of the asymptomatic period is determined by the magnitude of the diversity threshold, which in turn depends on the efficacy of the immune response as well as on the amount of viral replication and immune impairment. Variation in these parameters among patients may therefore account for the variability observed in the
disease process. In addition, the stochastic nature of the emergence of escape mutants may also contribute to the variability of the disease process. Whether the first few escape mutants arise soon or later may vary, and this may contribute to marked differences in the pattern of disease progression (43). A summary, viral evolution towards increased antigenic diversity may be the cause rather than the consequence of disease progression and may contribute to the transition from the asymptomatic period of the disease to AIDS.

Wallis et al. (43) interpreted their finding that rapid progressors can have low genetic variation as being at variance with the 'fittest' threshold theory. This conclusion is incorrect. As explained in the first papers on the diversity threshold idea, rapid progression is expected to occur with low antigenic diversity if the patient has high anti-HIV immune responses.

In most viral infections, including HIV, there are immune responses against several epitopes that complement viral dynamics and the effect of antigenic variation. Therefore, a theoretical framework was developed to explore the dynamics of an antigenically variable virus population and an array of CTL responses directed against multiple epitopes (47-49). This multiple epitope theory has also been applied to other infectious diseases (50, 51). Consider the understanding of the effect of CTL responses against multiple epitopes that these CTL clones are in competition with one another. The different CTL clones can be viewed as species of predators that proliferate, with different efficiencies, in response to a common food source (the virus population). Consider first the simple assumption of an antigenically homogeneous virus population. In such a scenario, the model predicts that the CTL response with the strongest immunogenicity will outcompete all other CTL responses. This is analogous to the competitive exclusion principle in ecology; the strongest competitor will reduce viral load to levels that are not sufficiently high to stimulate the comparatively inferior CTL responses. This may explain the concept of immunodominance in that a virus that is immunodominant against one or only a few epitopes (52-56).

For a heterogeneous virus population, the situation is more complicated than this. One has to distinguish between two cases. Either all antigenic variants have the same replication rate, or their replication kinetics differ. Consider the simplest case of equal replication rates first. The model predicts that the occurrence of immunodominance, but not the competitive ability of a CTL response against a given epitope not only depends on its immunogenicity but also on viral diversity in the epitope. Viral diversity essentially reduces immunogenicity. Assume that CTL proliferate equally well in response to all variants of a given epitope. Denoting the immune responsiveness against epitope A as \( a \) and the immune responsiveness against epitope B as \( b \), the number of mutant variants in the respective epitopes as \( n_a \) and \( n_b \), the immune response against epitope A will dominate if \( a/n_a > b/n_b \).

On the other hand, if the antigenic variants replace at different rates, the model predicts the coexistence of CTL responses directed against different epitopes. Under these conditions, a heterogeneous virus population characterized by concomitant differences in the viral replication kinetics induces the lack of immunodominance.

Antigenic variation in multiple epitopes can lead to coexistent 'antigenic oscillations' (Fig. 7), in that distinct peaks in viral abundance, often dominated by a single genome, that arise when the CTL response against a given variant is too low to decrease viral loads due to temporary lack of stimulation. This can lead to oscillations in viral abundance and the emergence of new variants (antigenic drift). Antigenic oscillations are the result of the non-linear dynamics between the existing heterogeneous virus population and CTL responses against multiple epitopes and do not require the emergence of new mutants.

Next, consider the emergence of a new mutant in a given epitope. Suppose the existence of a heterogeneous virus population and an immunodominant CTL response against one of two epitopes (epitope A). The emergence of an escape mutant in epitope A may lead to one of four possible outcomes depending on the replication rates and the immunogenicities of the mutant relative to the wild type (Fig. 8). The replication rate of wild type and mutant variants is \( r_0 \) and \( r_0 \), respectively. The immunogenicity of epitope B is described by \( k \). The four outcomes are as follows:

1. A new specific response against epitope A is induced by the mutant without affecting epitope B. This results in the expansion of epitope A, and will be observed if \( r_0 > k < 1 \).
2. No new response against epitope A is induced by the mutant, but the response against epitope B is enhanced. This is a partial shift in immunodominance and will occur if \( 1/k > r_0 > k \) and \( r_0 > r_0 \).
3. The mutant may induce a new response against epitope B which outcompetes the response against the wild type, consequently causing a partial shift in immunodominance. The condition for this outcome is given by \( r_0 > 1/k > 1/k \) and \( r_0 > r_0 \). Finally, if \( r_0 > 1/k \) and \( r_0 < r_0 \), the mutant virus outcompetes the wild type, resulting in a complete shift in immunodominance. Therefore, the selective advantage of the escape mutant becomes negligible, and it may not
In terms of HIV infection, this analysis extends and reinforces the idea that viral evolution towards increased antigenic diversity may drive progression of the disease. A stable response against an invariant epitope will lead to efficient control of the virus and slow progression. Viral diversity may lead to unstable dynamics, and the evolution of new antigenic variants may result in a shift in immunodominance to weaker epitopes, leading to less efficient control of HIV and an increase in virus load. These notions have been confirmed experimentally by borrow et al. (21), Goulder et al. (23), and Price et al. (24).

Replication rate and immune impairment

The notion that changes in the replication rate of HIV may be important for disease progression has often been pointed out (24, 36, 57-59). Cossart & Mo (27) analyzed sequential HIV-1 isolates from a patient who progressed to AIDS within 5 years. Viral strains isolated at the beginning of the infection were characterized by relatively slow replication kinetics. During the symptomatic phase they observed a strong and steady increase in the replication rate of the virus until the onset of AIDS. The increasing abundance of faster replicating variants during disease progression has been described mathematically by Nowak & May (41, 42), de Boer & Boelrijk (61) and Scherf (62).

More specifically, Vodarz et al. (43) showed how viral evolution towards increased replication kinetics in the asymptomatic phase may contribute to the transition to full-blown AIDS. They considered a mathematical model where the target cells are antigen-presenting cells or T-helper cells (which are both infected by HIV). They distinguished between precursor and effector CTL and assumed that the proliferation of precursor CTL requires the help of uninfected CD4+ T-cells e.g. via cytokine production. These assumptions lead to the result that the
A heterogeneous virus population with an immunodominant epitope A gives rise to four possible outcomes: (A) Emergence of an escape mutant in epitope A leads to one of four possibilities.

(I) Diversification in epitope A

(ii) No new response against epitope A; partial shift in immunodominance

(iii) New response against epitope A; partial shift in immunodominance

(iv) Complete shift in immunodominance to epitope B

Fig 2. Antigenic variation may shift immunodominance. The emergence of an escape variant in an immunodominant epitope A leads to one of four possible outcomes. For details see text.

Virus may induce the exhaustion of the virus-specific CTL response. In terms of HIV, two parameters are important in determining the fate of the CTL response. These are replication rate threshold beyond which the HIV-specific CTL response will be exhausted. The higher the immunodominance of the host, the higher the replication rate of the virus required to induce CTL exhaustion. CTL exhaustion has been postulated as a possible mechanism for the eventual breakdown of the immune system upon progression to AIDS (e.g. 64-66).

Fig 3 demonstrates how evolution towards increased replication rates of HIV may lead to a pattern of disease progression similar to that observed in HIV-infected patients. As long as the replication rate of the virus is sufficiently low for the CTL response to persist, evolution towards faster replication results in a relatively slow decline of the uninfected T-helper cell and a slow rise in virus load. When the virus evolves beyond the replication rate threshold, it induces the exhaustion of the specific CTL response, allowing virus load to shoot up to really high levels, causing a sharp drop in the number of T-helper cells found in the patient. As was the case with the discrete threshold model, variation in the immune responsiveness of the host may account for variability in the duration of the asymptomatic phase of the infection, with a stronger response remaining asymptomatic for a longer period of time. As can be
seen in Fig. 4, the model also predicts that the CTL precursor population starts to decline earlier and declines at a faster rate than the CTL effector population. Thus, when the CTL precursors have largely vanished, one might still expect to see considerable CTL effector activity. Such observations have been made by Nunheko et al. (64, 67). They found that there was a correlation between CTL effector activity and time, and that towards the end stage of the disease, a significant CTL effector response was still present, possibly owing to residual memory.

Evolution towards higher replication rates is related to evolution of antigenic diversity in that mutation in the CTL epitopes may allow effectively faster viral replication. This may occur either through simple escape mutations or through the evolution of altered peptide ligands, which may act as TCR antagonists (48–71) or promote responses with inappropriate specificity (22, 72–76). Moreover, evolution of resistance to immune responses inhibiting the overall replication kinetics of the virus, such as interferon or antibodies, may also contribute to the exhaustive process.

Immune impairments and phenotypic switching

The differential treatment of HIV for macrophages and T cells may be a key element of HIV pathogenesis (11, 13, 72–85). Since using the CCR5 co-receptor (R5 viruses) infect primary T cells and macrophages, they are slowly replicating and relatively non-virulent (N2 phenotype). As disease progresses, HIV becomes increasingly T-cell specific, using the CXCR4 co-receptor. Viral strains may use both the CCR5 and the CXCR4 co-receptors (tremendous R5A virus) (75, 76), as they evolve to specialize in the CXCR4 co-receptor (X4 virus) (75, 76); as happens in about 50% of the patients. Such isolates have lost their ability to infect macrophages, replicate as a faster rate and tend to show the syncytium-inducing phenotype. The evolution of viral X4 strains is associated with progression to AIDS and mathematical models can help us identify factors that lead to the emergence of virulent CCR4 virus mutants.

Mathematical models have so far focused on two basic concepts concerning cell tropism in HIV infection. First, there is a difference in the biology of macrophages and T cells, while HIV can only replicate in activated T cells, activation and cell division does not seem to be required for macrophage infection (86, 87). The reason for this difference rests in the mechanisms underlying the transport of the HIV genome into the nucleus of the two cell types (86–91). While the HIV preintegration complex that reaches the macrophage nucleus by active transport, this mechanism does not work in T cells, where breakdown of the nuclear envelope is required for infection. Second, there

![Graphs showing the dynamics of HIV infection](image)

Fig. 4: Implications of CTL exhaustion for HIV disease progression. The graphs show the effect of viral evolution towards higher replication kinetics on the number of (A) CTL precursor cells, (B) CTL effector cells, (C) virus load, (D) the number of infected target cells. At each time interval the viral replication rate (b) is increased by a maximum amount and the equilibrium states of the respective variables calculated. Set text for details.
is a difference in the viral phenotypes of the strains, the CCR5 and the CXCR4 receptors. While R5 viruses are supposed to be core-synaptic and slowly replicating, X4 viruses are thought to be strongly cytopathic and faster replicating.

Macrophage versus T-cell infection

Macrophage infection by HIV can be modelled by the basic equations describing virus dynamics set out at the beginning of this review. However, in order to study T-cell infection in a more realistic way, Wodare et al. (93) modified the basic virus infection model to take into account resting target cells that cannot be infected, and susceptible target cells that are generated from the resting cell population through activation in response to antigen. These assumptions complicate the dynamics of HIV infection, if the rate of background activation of T-cells due to other pathogens being present at the time of HIV infection is relatively low, the outcome may depend on a complex interplay between host and viral parameters as well as the initial conditions. An important host factor is the immune responsiveness, if the immune responsiveness lies above a certain threshold, the infection is cleared. The reason for this is that a relatively strong CTL response will deplete the virus load to very low levels, so that the virus load is not enough to maintain a significant number of activated T-helpers cells. Since these are the target cells of the virus, the infection will vanish.

Among the viral parameters, the replication rate of the virus is required to be above a certain threshold for infection to be possible in the paratenic region, where the virus may establish a persistent infection. The outcomes of the dynamics depend on the initial abundance of virus and virus-specific CTL (Fig. 5). The initial virus load must lie below a certain threshold level in order to activate a sufficient number of target cells for infection to be possible. Given that the initial virus load is sufficiently high to allow invasion, the CTL response may either clear the infection or control a persistently replicating virus. If the initial virus load lies below a threshold, the CTL response can grow fast enough to reduce the virus population quickly by a significant amount. This in turns leads to a decline in the number of activated target cells, making it impossible to support persistent replication. Consequently, the virus population cannot recover and becomes extinct. On the other hand, intermediate initial values of virus load allow virus replication to outstrip the CTL response, which can only grow as a slower rate. Thus, persistent replication can be established. The highest the initial abundance of CTL, the lower the threshold level of virus load required to achieve clearance of the infection. Above a certain initial CTL abundance, the establishment of persistent infection becomes impossible.

This model has been extended to take into account both types of virus strains: R5 viruses capable of infecting macrophages and X4 viruses capable of infecting T-cells only. We assumed that T-helper cells are activated by both types of virus. The presence of strains capable of infecting macrophages significantly enhances the invasion of CXCR4-tropic strains, eliminating the complex dependence on initial conditions. The model identifies three parameter regions (93), if the immune responsiveness to macrophage-tropic HIV is above a certain threshold, CXCR4-tropic strains cannot invade the host. On the other hand, if the immune responsiveness to macrophage-tropic virus is sufficiently low, so the invasion of CXCR4-tropic mutants is possible, one has to distinguish between two situations (Fig. 6). If the immune responsiveness to both virus strains is too low enough, CXCR4-tropic strains may initially grow to a peak, but this is only temporary, while the CTL response is still strong enough to suppress these mutations to very low levels, indicating extinction. If CXCR4-tropic strains
are produced continuously, this may result in the appearance of "flips" of CCR4 tropic HIV which immediately goes extinct (Fig. 6). Finally, if the immune responsiveness to each strain is reduced below a threshold, the immune system is not strong enough to suppress these HIV variants, leading to the permanent rise of CCR4 tropic HIV (Fig. 6).

To summarize, these studies indicate that infection of macrophages may be essential for maintaining a persistent infection and for facilitating the eventual rise of CCR4 tropic mutations once the immune system has been sufficiently weakened by the virus. Yet, due to a genetic variation, these results are in line with the observation that individuals with a deletion in the CCR5 co-receptor, making macrophage infection impossible, are unlikely to become infected by HIV (94–101).

RS versus V4 viruses

While CCR5 tropic HIV persists throughout the infectious process, the virus specializes on the use of the CCR4 co-receptor in about 50% of the patients. This is associated with the syncytium-inducing phenotype and ranks progression to the end stage of the disease. Mathematical models suggest a possible reason for the rise of such specialist HIV is only about half of the parents. Webster & Nowak (manuscript in preparation) devised an evolutionary model describing the dynamics of cell switch. They considered a virus strain that could infect two alternative target cell types with different efficiencies. The rate of target cell entry of the successive mutants was assigned in such a way that it increased nonmonotonically in one cell type while it decreased monotonically in the alternative cell type (Fig. 7). As can be seen in Fig. 7, the change in the rate of target cell entry in the successive mutants can either be greater than linear or less than linear. In biological terms, a greater than linear change in the viral replication kinetics may occur, for example, the accumulation of mutations leads to an increasing effect on viral replication. Similarly, a less than linear change may occur if the viral mutations have a relatively large effect on viral replica-
Fig. 7. Evolution of generalisation versus specialism assuming the existence of two target cell types. We also assume that the viral replication kinetics increase monotonically from strain 1 to strain 10 in one cell type, while they decrease monotonically in the alternative cell type. The resulting fitness landscape of the virus mutants can be divided into two categories.

The change in the replication rate of the susceptible mutants may be (A) less than linear or (B) greater than linear. If the change is less than linear, the virus population evolves under both cell types with similar efficiency (generalisation), while a greater-than-linear change leads to the evolution of specialism.

The correlation between co-receptor usage and tropism for macrophages and T cells is complex. While macrophage infection is dependent on the CCR5 receptor, both the CCR5 and the CXCR4 receptors may promote T-cell infection. However, it has been reported that, in T cells, expression of the CCR5 and the CXCR4 receptors is subset dependent and needs to be mutually exclusive (103–106). Therefore, we can distinguish between two 'target cell types': those that are susceptible mainly to 50 strains and those that are susceptible mainly to X4 virus. Consequently, our model for the evolution of cell tropism may be applied, and it predicts that whether HIV evolves to specialise on the CXCR4 co-receptor in a given patient depends on the exact fitness landscape of the virus. Full X4 strains will evolve only if the fitness landscape of the virus is greater than linear, otherwise B/X4 strains will evolve, using both co-receptors with similar efficiencies. The fitness landscape may differ between patients. This may simply be due to chance in the mutations occurring in the course of evolution of the virus. Moreover, a greater-than-linear change in the replication kinetics of the susceptible mutants may also be promoted by escape from mechanisms limiting viral replication.

Assuming that the fitness landscape of the viral mutants allows the evolution of specialism, Wodarz & Nowak (1997) adopted this model specifically for HIV and investigated the evolution of X4 strains in the absence and presence of various immune responses. The fitness landscape of HIV mutants assumed in these studies is shown in Fig. 8. In accordance with empirical findings (e.g. (33, 34, 108)), we assume that CXCR4 tropic HIV may evolve to higher replication kinetics and at a faster rate than CCR5 tropic strains, and that the half-life of cells infected with X4 virus is shorter than that of cells infected with R5 strains. This fitness landscape leads to the dominance of CCR5 tropic HIV with CXCR4 tropic strains being suppressed.

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to relatively low levels (Fig. 9A). We explored the effect of four types of immune responses on the course of evolution. These included an antibody response, CR-mediated lysis, CR-mediated inhibition of viral entry into target cells, and CR-mediated inhibition of virus production. The evolutionary outcomes of these models is shown in Fig. 9B–9E. Clearly, different types of immune responses have different effects on the rate of CRX4 or CRX6, regardless of the virus. Before it has integrated into the host genome (antibodies and CR-mediated inhibition of infection) select against the rate of CRX4 or CRX4, suppressing these variants to relatively low levels, while immune responses acting on infected cells (CR-mediated lysis and inhibition of virus production) favor the rate of CRX4 or CRX4, leading to the coexistence of CRX and X4 virus with similar abundances.

These results are the consequence of the finding that, without an immune response or under the pressure of immune responses acting on the virus before integration into the host genome, non-cytopathic viruses attain significantly higher levels of virus load than cytopathic ones while this is not the case under immune responses acting on infected cells (109). Moreover, these studies have also shown that the viral replication kinetics do not significantly influence the equilibrium number of infected cells. Thus, while in certain circumstances non-cytopathic R5 variants may have a selective advantage over cytopathic X4 strains, this advantage is not cancelled out by the relatively slow replication kinetics of CRX4 or CRX6.

Directly after infection, HIV can replicate freely before the rise of any immune responses. Since the models have demonstrated that such conditions select against the rise of virulent CRX4 or CRX6, these dynamics may also help us to understand why only non-virulent, slowly replicating R5 viruses are found at the beginning of HIV infection and why individuals carrying a deletion in the CR5 receptor are unlikely to become successfully infected by HIV (94–102). The nature of the virus infection also supports the idea that different immune responses may exert different selective pressures on virulent CRX4 or CRX6.

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Fig. 6. Effect of different immune responses on the rate of viral infection. 
C. CTL-mediated inhibition of virus entry. D. CTL-mediated inhibition of viral replication. 1. CTL-mediated lysis. The graphs show the time before integration into the host genome (A & C) suppress virulent CXCR4 R5-tropic variants in low levels. On the other hand, γδ T-cell responses acting on infected cells (D & E) allow viral mutants with similar levels compared to CXCR4 R5-tropic ones.

Conclusion

This review has shown how mathematical models may help us understand the role in which viral evolution is not only constrained to the progression from the asymptomatic period of the infection to the development of AIDS. In particular, evolutionary toward increased viral diversity and replication may influence the development of the immune system, paving the way for the evolution of most pathogenic phenotypes that increase progression to AIDS.

These findings also have implications for vaccination strategies to delay or prevent the onset of AIDS. Norval & McKeage (118) showed that the average number of escape mutants produced by a virus strain must be suppressed to below unity for the vaccine to be successful. This goal will only be achieved if the immune response against a sufficiently large number of variants is boosted, no matter how immunogenic the vaccine is. Therefore, the chance of successful vaccination will be maximal when a cross-reactive immune response is boosted (9, 118).

In addition, because of the competition occurring between CTL against different epitopes, it would be advisable to boost the immune response against a single conserved epitope, even if this is not the immunodominant one, since this would lead to more stable and effective control of the viral population (47, 48, 49).
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91. Ogurtsov V, Daidone MC. Search for an AIDS vaccine. 
92. Ogurtsov V, Daidone MC. Search for an AIDS vaccine. 
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100. Ogurtsov V, Daidone MC. Search for an AIDS vaccine. 
102. Ogurtsov V, Daidone MC. Search for an AIDS vaccine. 
103. Ogurtsov V, Daidone MC. Search for an AIDS vaccine. 