Specific therapy regimes could lead to long-term immunological control of HIV

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We use mathematical models to study the relationship between HIV and the immune system during the natural course of infection and in the context of different antiviral treatment regimes. The models suggest that an efficient cytotoxic T lymphocyte (CTL) memory response is required to control the virus. We define CTL memory as long-term persistence of CTL precursors in the absence of antigen. Infection and depletion of CD4+ T helper cells interfere with CTL memory generation, resulting in persistent viral replication and disease progression. We find that antiviral drug therapy during primary infection can enable the development of CTL memory. In chronically infected patients, specific treatment schedules, either including deliberate drug holidays or antigenic boosts of the immune system, can lead to a re-establishment of CTL memory. Whether such treatment regimes would lead to long-term immunologic control deserves investigation under carefully controlled conditions.

Antiviral therapy for HIV-infected patients has greatly improved the recent years. Administration of drug cocktails consisting of three or more different drugs can reduce and maintain virus load below detection limit in many patients. Nevertheless considerable problems remain such as viral resistance, side effects, and lack of compliance during prolonged therapy (1–4). Furthermore it is unlikely that combination therapy alone can eradicate HIV from infected patients because of long-lived infected cells and sites within the body where drugs may not achieve effective levels (5–8). Hence there is considerable interest in searching for therapy regimes that may reduce virus load and restimulate immune responses, thereby turning the balance between HIV and the immune system in favor of the immune system.

There is convincing evidence that antiviral immune responses play an important role in determining virus load and the rate of disease progression in infected patients (9–12). Long-term non-progressors often have good CD4- and CD8-mediated immune responses against HIV and low virus load, whereas rapid progressors tend to have weak anti-HIV and high virus load (13–21). Experimental depletion of CD8 cells in simian immunodeficiency virus-infected macaques leads to a dramatic increase in virus load (22).

Here we design a mathematical model to study the interaction between HIV and the immune system and to analyze how specific antiviral treatment regimes can lead to the establishment of effective immune responses and long-term control of HIV.

Results and Discussion

We analyze a model containing four variables: uninfected CD4+ T cells (x), infected CD4+ T cells (y), cytotoxic T lymphocyte (CTL) precursors (CTLp) (w), and CTL effectors (z). The model is given as follows.

\[
\begin{align*}
\dot{x} &= \lambda - dx - \beta xy, \\
\dot{y} &= \beta xy - ay - pyz, \\
w &= cxyw - cqw - bw, \\
\dot{z} &= cqw - hz.
\end{align*}
\]

Uninfected CD4+ T cells are produced at a rate \(\lambda\), die at a rate \(d\), and become infected by free virus at a rate \(\beta y\). Infected cells decay at a rate \(a\) and are killed by CTL effectors at a rate \(py\). In accordance with experimental findings (23–26) we assume that establishment of a lasting CTL response depends on CD4+ T cell help, and that HIV impairs T helper cell function. Thus, proliferation of the CTLp population is given by \(cxyw\) and is proportional to both virus load \(y\) and the number of uninfected T helper cells \(x\). CTLp die at a rate \(bw\) and differentiate into effectors at a rate \(cqzw\). CTL effectors die at a rate \(h\).

The model has the interesting property that after viral infection the system may go to one of two equilibria: (i) either an effective, sustained CTL response becomes established and virus load is contained at low levels or (ii) an effective, sustained CTL response is not established and viral load is at high levels. In the model, the development of a lasting CTL response depends on host and viral parameters as well as initial conditions. More specifically, the dynamics between virus and CTL depend on the balance between the rate of viral replication (\(\beta\)) and the quality of the CTL response (CTL activation rate, \(c\) and CTL death rate, \(b\)), reflected in the virus load attained during primary infection. If the rate of viral replication is below a threshold and is low compared with the immune responsiveness of the host, an effective CTL response is always established. On the other hand, if the rate of viral replication is above a threshold and is fast relative to the immune responsiveness of the host, the virus may replicate to high levels and an effective, sustained CTL response fails to become established because of high degrees of immune impairment. For intermediate rates of viral replication, the outcome of the dynamics depends on the initial conditions: a sustained CTL response is unlikely to become established in naïve hosts, because a low initial number of CTLp allows the virus to replicate to high levels and to impair the T helper cell response before the CTL had time to act. In addition, a high initial virus load and a low initial CD4+ T cell count interfere with CTLp expansion.

If a sustained CTL response is successfully established, it is an important determinant of virus load. Virus load is suppressed to low levels by long-term persistence of CTLp in the absence of antigen (low \(b\)) and by a high activation rate of CTLp (high \(c\)). The development of such T helper cell-dependent, persistent, readily activated CTLp has been used as a criterion for defining CTL memory associated with protection from reinfection with a pathogen (27–31). However, our model suggests that these properties, traditionally associated with CTL memory, also may be required for clearance or effective containment of HIV.

Infection of CD4 cells by HIV may impair T helper function, resulting in the absence of CTLp that are long-lived in the absence of antigen. According to our models, this impairment may be the reason for persistent replication of HIV in the host, eventually leading to the development of AIDS. This notion is

Abbreviations: CTL, cytotoxic T lymphocyte; CTLp, CTL precursor.

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presence of less efficient CTL maintained mainly by persisting infection. Therefore, when our model suggests the absence of an help \( (25, 26) \), because they are predicted to lose control of the virus.

In the absence of the drug, because treatment reduces the amount of T helper cell impairment while the CTL population is expanding in response to the initial viral growth. When treatment is withdrawn, the initial conditions have been shifted so that exhaustion of the established CTL memory becomes impossible. A crucial parameter for successful therapy is the duration of treatment during the primary phase of the infection. As shown in Fig. 2, this success depends on viral, host, and medical factors, such as the time when treatment is started, the replication rate of the virus, the CTL responsiveness of the host, the initial CD4+ T cell count, and the efficacy of the drug.

Next we consider HIV infection and drug therapy during the asymptomatic period. Treatment during this phase may reduce virus load below detection limit, but when the drugs are withdrawn, virus load re-emerges to pretreatment levels (Fig. 3i). Long-term immunological control of the infection can be obtained only if the CTL memory response is re-established. According to our models this control can be attained by boosting the immune system with virus while simultaneously treating the patient to minimize the degree of immune impairment. This control can be achieved by a treatment regime that consists of four phases: first treatment, treatment window, secondary treatment, and end of treatment (Fig. 3i). The first phase of treatment reduces virus load and allows the CD4+ T cell count to increase as far as possible. This phase should continue at least until the virus is below detection limit and preferably longer so that the immune system recovers as much as possible. The treatment window involves simultaneous withdrawal of all drugs in use, minimizing the chances of resistance evolving. It allows virus load to increase for a given period of time. The increased virus load gives the CTL response a boost and is essentially a simulation of events occurring during the primary phase of the infection. As the virus population grows, the secondary treatment phase is initiated. It ensures that the degree of immune impairment is reduced while the CTL response expands, which enables the establishment of CTL memory. Once CTL memory has been generated, therapy can be stopped and the virus is maintained at a low level; the infection is in a state similar to long-term nonprogressors.

Analogous to the primary infection, the secondary phase of treatment shifts conditions in favor of CTL memory. The duration of the secondary phase of therapy is crucial for the success of this regime (Fig. 2). It depends on the length of the treatment window, the replication rate of the virus, the CTL responsiveness, the initial CD4+ T cell count, and the efficacy of the drug.

Note that after drug treatment is withdrawn, the models predict virus load to rise and oscillate before being controlled by CTL memory (Fig. 3), because the CTL effector response is short-lived and decays during drug therapy. This decay allows the virus to initially grow to a peak and oscillate before the dynamics between CTL and HIV have become more stable. A transient rise in virus load after the secondary phase of treatment therefore does not necessarily implicate failure of the treatment regime.

The principle underlying the basic drug window treatment regime is to simulate vaccination of the patient with the infecting virus, resulting in the establishment of CTL memory. Efficient CTL memory controls the virus in the long term. Modifications of this basic treatment schedule should lead to the same outcome. Especially for weak immune responders, or patients who have progressed relatively far in the disease process, repeated phases of therapy and drug windows may be necessary (Fig. 4i).
In patients with an inefficient immune response, the drug window followed by the secondary phase of treatment may only partially restore CTL memory and virus load may remain relatively high. Repeating the drug window therapy schedule may result in increased levels of CTL memory, eventually controlling the virus (Fig. 4i).

Another modification involves a combination of drug therapy and vaccination during the asymptomatic period (Fig. 4ii). Although antiretroviral drugs keep virus load at low or undetectable levels, minimizing the amount of immune impairment, the patient is vaccinated with a mixture of immunogenic HIV peptides, e.g., expressed on a recombinant virus vector. This vaccination again provides a stimulus for the expansion of CTLp, which may result in the generation of CTL memory. Once memory is established, drug therapy can be discontinued and the immune system may control HIV in the long term. This treatment schedule may be preferable, because it decreases the chances of viral resistance evolving, which may be a concern during the presence of a drug window. In addition, a combination of drug treatment and vaccination may be able to reduce virus load to extremely low levels, maximizing the chances of eradicating HIV from the patient (Fig. 4ii), because the immunological boost is given in the absence of HIV replication. The rising memory CTL response therefore may push the number of infected cells to decreasingly low values. Important for success is that the virus antigen mixture used for vaccination induces CTL clones with appropriate specificities (34). Especially advantageous would be the induction of cross-reactive immune responses (34), also including the presence of CD8+ T cells inhibiting virus replication by nonlytic mechanisms (35, 36). As before, early treatment is recommended because a patient with a low CD4+ T cell count is unlikely to re-establish CTL memory.

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Future research should be directed at elucidating the exact nature of CD4^+ T cell help for the establishment of CTL memory. Administration of the relevant factors may greatly facilitate the development of CTL memory in HIV-infected patients.

Although we have analyzed the potential for immunological control of HIV from a modeling perspective, our findings are consistent with empirical results. In long-term nonprogressors controlling viremia in the absence of therapy, extremely low viral loads are associated with a strong CTL response (19, 20) and vigorous HIV-specific CD4^+ T cell proliferative responses (13–18). Interestingly, HIV-exposed but uninfected individuals tend to show specific CTL responses detectable 34 months after the last virus exposure (21). Our predictions are also consistent with preliminary data from HIV-infected patients (37), as well as with experiments on drug treatment and rechallenge during the primary phase of simian immunodeficiency virus infection in macaques (unpublished work).

Although our models suggest that the treatment regimes described may result in long-term immunological control of the infection, this result deserves detailed empirical investigation under carefully controlled conditions. An especially important point is the potential evolution of CTL escape mutants which may result in loss of virus control (39, 40). Our models did not take into account antigenic variation and viral evolution, and this requires further detailed analysis. In particular, a comparison of the dynamics of antigenic variation and HIV-induced subversion of the immune system both under a good memory CTL response and under a less efficient response merits further mathematical investigation.

Appendix

The model describing the dynamics between HIV and the CTL response was analyzed as follows. The basic reproductive ratio of the virus is given by R_0 = \beta/\lambda. It denotes the average number of newly infected cells produced by one infected cell at the beginning of the infection. If R_0 > 1, the system may converge to one of two equilibria. The pathogen may replicate in the absence of an efficient, sustained CTL response, which is described by equilibrium E1:

\[ x^{(1)} = a/\beta, y^{(1)} = \lambda/a - d/\beta, w^{(1)} = 0, z^{(1)} = 0. \]

On the other hand, an efficient, sustained CTL response may be established, which is described by equilibrium E2:
If this condition is not fulfilled equilibrium E1 is stable. However, equilibrium E2 may or may not be stable depending on host and viral parameters. If equilibrium E2 is complex \([c(\lambda + dq) - b\beta] < 4c^2\lambda dq] \) or negative \((x(2) < q \text{ or } \beta_2(2) < a)\), a persisting CTL response can never be established. On the other hand, if equilibrium E2 is positive and real, both equilibria E1 and E2 are stable and the outcome depends on the initial conditions. A low initial number of CTLp, a high initial virus load, as well as a low initial CD4+ T cell count promote the absence of an efficient, sustained CTL response. Overall, a high replication rate of the virus as well as a low immune responsiveness of the host shift the dynamics between HIV and the immune system in favor of the virus.

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