Boosting immunity by antiviral drug therapy: A simple relationship among timing, efficacy, and success

Natalia L. Komarova1†, Eleanor Barnes5, Paul Klenerman5, and Dominik Wodarz3§

1Institute for Advanced Study, Einstein Drive, Princeton, NJ 08540; 2Department of Applied Mathematics, University of Leeds, Leeds LS2 9JT, United Kingdom; 3Nuffield Department of Medicine, University of Oxford, Peter Medawar Building, South Parks Road, Oxford OX1 3SY, United Kingdom; 4Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, MP-665, Seattle, WA 98109-1024

Communicated by Phillip A. Griffiths, Institute for Advanced Study, Princeton, NJ, December 9, 2002 (received for review September 12, 2002)

Drug therapies against persistent human infections such as hepatitis C virus, hepatitis B virus, and HIV fail to consistently eradicate the infection from the host. Hence, recent emphasis has shifted to the study of antiviral therapy aimed at boosting specific immune responses. It was argued that structured therapy interruptions were required to achieve this, because such regimes have shown promising results in early HIV infection. Using mathematical models, we show that, contrary to this notion, a single phase of drug therapy can result in the establishment of sustained immunity. We present a simple relationship between timing of therapy and efficacy of the drugs required for success. In the presence of strong viral suppression, we show that therapy should be stopped relatively early, and that a longer duration of treatment leads to failure. On the other hand, in the presence of weaker viral suppression, stopping treatment too early is detrimental, and therapy has to be continued beyond a time threshold. We discuss our modeling results primarily in the context of HCV therapy during chronic infection. Although the therapy regimes explored here also have implications for HIV, virus-mediated destruction of specific immune cells renders success unlikely during the chronic phase of the infection.

Several human pathogens have the ability to suppress immune responses, allowing them to establish a persistent and productive infection that eventually results in pathology. A potent strategy is to impair virus-specific CD4 T helper cell responses (directly or indirectly), because they are the central component orchestrating antiviral effector mechanisms. According to clinical data, the most prominent examples of this are HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV) infection (1–7). For all these viruses, drug treatment is not effective in all cases, and for HIV, lifelong therapy is generally necessary to control viral replication (8–13). An alternative strategy is to use drug treatment to boost virus-specific immunity, resulting in sustained viral suppression in the absence of drugs. In HIV infection, this has been explored in the context of early therapy and structured therapy interruptions (4, 14, 15). During the chronic phase of the infection, however, such therapy regimes are less promising, because HIV induces the destruction of specific immune cells. Although HCV and HBV have been shown to result in impairment of the specific helper cell responses, these viruses do not induce the destruction of specific immune cells. With both HCV and HBV, a boost in T cell responses during drug therapy has been observed in some chronically infected patients (5, 6, 16).

In this paper, we use a general mathematical framework to study immune response dynamics during therapy in the context of immunosuppressive infections. Contrary to previous analysis (17, 18), we focus on a single phase of treatment during chronic infection. The model suggests that a single phase of treatment can result in long-term immune-mediated control of an immunosuppressive infection. We describe a relationship between the efficacy of drugs and the timing/duration of therapy. In the presence of strong viral suppression, the model suggests that therapy should be stopped relatively early and that a longer duration of treatment can lead to failure. In contrast, with weaker viral suppression, stopping treatment too early is detrimental. Instead, therapy should be continued beyond a time threshold. The model further suggests that interruption therapy can be helpful in a restricted parameter region. We describe how timing of therapy can in principle be optimized by monitoring immune response dynamics in patients. Theoretical results are primarily discussed in the context of HCV infection, because specific immune cells are not destroyed by the virus, and a recent study of drug therapy during chronic infection supports our theoretical notions. We also discuss implications for HIV infection. Because HIV destroys immunological specificities, however, drug therapy alone is unlikely to result in a boost of immunity during chronic infection.

The Model

The dynamics between an immunosuppressive infection and antiviral immune responses can be studied at various degrees of complexity. Here we take a very general approach. We consider a model that contains two variables: the virus population, y, and a population of immune cells, z. The exact identity of the immune cells is left open. We assume that the degree of immune expansion depends on virus load, and that the response inhibits virus growth. It could thus correspond to any branch of the adaptive immune system, such as CD8 T cells, antibodies, or CD4 T cells. The model is given by the following pair of differential equations:

\[ \frac{dy}{dt} = yg(y) - yz, \]
\[ \frac{dz}{dt} = zf(y). \]

The virus population grows at a rate described by the function g(y). This is a function that depends on the amount of virus, y, and on the parameter, r, denoting the viral replication rate. The virus population becomes inhibited by the immune response at a rate zy. Immune expansion is determined by virus load, y, and is described by the function f(y). The generic shape of functions g(y) and f(y) is presented in Fig. 1. Positive values of these functions indicate growth, and negative values correspond to decay in the population. Consider the virus growth function, g(y). On the trivial side, we make the assumption that the higher the replication rate of the virus, r, the higher the viral growth rate. The only other assumption is that virus growth is density dependent: growth slows down at higher virus loads; when virus load crosses a threshold, growth stops and the virus population declines, corresponding to target cell limitation where the virus runs out of cells to infect.

Now we turn to the function describing immune expansion, f(y). We make the assumption that the presence of the virus can...
both stimulate and impair immunity, depending on virus load, \( y \). If virus load lies below a threshold, the rate of immune expansion is negative. That is, levels of antigen are too low to induce a response. If virus load lies above a threshold, the rate of immune expansion is also negative, because immune impairment outweighs antigenic stimulation. Thus, high virus loads inhibit immunity. Immune expansion is positive for intermediate virus loads, because antigenic stimulation is strong relative to immune impairment. The precise conditions \( f(y) \) and \( g_r(y) \) have to satisfy for the results to hold true are listed in the Appendix. This framework makes minimal assumptions and defines a collection of models. Hence, results derived from this framework are robust and do not depend on the particular form of the equations. For illustrative purposes, we used a particular model that fits into this framework, given in the Appendix. Here, we analyze the behavior of the whole class of models and find three outcomes:

- In the trivial case, \( S_0 \), there is no infection and no immune response.
- Alternatively, the virus can establish an infection in the absence of an immune response, \( S_r \). We will refer to the equilibrium \( S_r \) as the virus equilibrium, because the virus can grow unchecked and cause pathology directly or indirectly.
- Finally, the virus can establish an infection that is controlled by an immune response, \( S_i \). We refer to this outcome as the immune control equilibrium.

A note of clarification: The virus outcome is characterized by the absence of the immune response, \( z \). This describes failure of long-term control in the model and can correspond to an in vivo scenario where suboptimal immune responses are temporarily maintained and subsequently collapse. Such suboptimal responses are not explicitly included in the model but can be assumed to be implicit in parameters determining virus load (such as the replication rate). To use specific examples, the immune control outcome \( (S_i) \) in the model can correspond to the state of long-term nonprogression in HIV infection (19), whereas failure of long-term control in the model \( (S_r) \) corresponds to typical HIV disease progression. A similar difference can be seen in HCV infection: a small fraction of patients control the virus (or clear virus from blood) and establish long-term immunity \( (S_i) \), whereas most patients fail to do so and eventually may develop disease \( (S_r) \) (20).

**Analysis of the Model**

We seek to understand the stability properties of these equilibria as the value of \( r \) increases from low to high, because the parameter \( r \) is influenced by drug therapy. The following regimes are observed (see Appendix II, which is published as supporting information on the PNAS web site, www.pnas.org, and Fig. 1b):

(i) If the replication rate is very small, the virus cannot infect the host, and the system converges to \( S_0 \).
(ii) If the replication rate of the virus crosses a threshold, an infection can be established, but the amount of antigenic stimulation is too low to trigger sustained immunity. The system converges to \( S_r \).
(iii) If the replication rate is higher and crosses another threshold, levels of antigen are sufficient to trigger sustained immunity. The system converges to the equilibrium describing long-term immunological control, \( S_i \).
(iv) If the viral replication rate is still higher and crosses a final threshold, the immune response can be significantly impaired. In this parameter region, both the immune control \( (S_i) \) and the virus equilibrium \( (S_r) \) are stable, and the outcome of infection depends on the initial conditions.

The dependence on initial conditions in the bistable parameter region \((iv)\) is further explored in Fig. 2a. The domain of attraction for the immune control and virus equilibria is separated by a line we call line \( L \) (dashed line in Fig. 2a). This is a separatrix that divides all possible initial states of the system into two classes: above line \( L \), the system will converge to the immune control equilibrium \( (S_i) \); below line \( L \), the system will converge to the virus equilibrium \( (S_r) \). In biological terms, the initial level of the immune response, \( z \), determines whether we are above or below line \( L \). It is also influenced by virus load, although to a lesser degree. Thus, a naive host (starting with low numbers of specific immune cells) is likely to move to the virus equilibrium. This is also promoted by a high initial virus load. On the other hand, a high initial number of immune cells and also a low initial virus load promote the establishment of immune-mediated control. The reason for the occurrence of this bistability is the assumption that the virus can both stimulate and impair immunity. If virus load is high, immune impairment outweighs antigenic stimulation. If virus load is intermediate/low, antigenic stimulation can outweigh impairment. Therefore, the initial number of immune cells and also the initial virus load determine whether immune responses can expand and get the upper hand, or whether the virus wins this race.

In the following section, we analyze immune response dynamics during drug therapy, assuming that we are in the bistable parameter region \((iv)\). Thus, infection of a naive host will result in the virus/disease outcome. Because the immune control outcome is still stable, however, the model suggests that therapeutic intervention can shift the dynamics toward the immune control outcome. This is explored below.

---

**Fig. 1.** Diagram explaining the behavior of the general mathematical model. The model is defined by the virus growth function \( g_r(y) \) and the immune expansion function \( f(y) \). As explained in the text, the function \( g_r(y) \) depends on the viral replication rate, \( r \), whereas the function \( f(y) \) does not. (a) The functions \( f(y) \) and \( g_r(y) \) are plotted versus \( y \). The function \( f(y) \) has two fixed roots, \( y_1 \) and \( y_2 \). We show \( g_r(y) \) as a function of \( y \) for different values of \( r \). The parameter \( r \) determines at which value of \( y \) the function \( g_r(y) \) equals zero. If the value of \( r \) lies above a threshold so that \( g_r(y) = 0 \) for \( y > y_2 \), we are in the bistable parameter region. If the value of \( r \) is smaller so that \( g_r(y) = 0 \) for \( y_1 < y < y_2 \), the only stable outcome is immune control, \( S_i \). If the value of \( r \) is still smaller so that \( g_r(y) = 0 \) for \( 0 < y < y_1 \), only the virus equilibrium, \( S_r \), is stable. Finally, if the value of \( r \) is very small, then \( g_r(y) = 0 \) for \( y < 0 \) and the infection cannot become established in the first place, \( S_0 \). (b) This is a schematic diagram that summarizes how the outcome of infection depends on the viral replication rate, \( r \), as detailed above.
find that a single phase of therapy may indeed result in sustained viral suppression after cessation of treatment. We further find an interesting relationship between the efficacy and the duration of therapy required for success.

During therapy, the system converges toward a new equilibrium that is determined by the efficacy of the drugs. When therapy is stopped, sustained viral suppression will be achieved only if therapy has moved the level of the immune response in the domain of attraction of the immune control equilibrium. In other words, whether the treatment moves the system above line L will determine the success of therapy.

In this context, it is important to point out that there is a tradeoff between the amount of immune impairment and antigenic stimulation in the expansion of immune responses. Treatment has to be efficient enough to sufficiently reduce the degree of immune impairment, allowing the immune response to expand. However, if treatment is too efficient, not only immune impairment but also the degree of antigenic stimulation is diminished, reducing the amount of immune expansion. The following cases of increasing drug efficacy are discussed (the dynamical behavior of the model is summarized in Fig. 2, and the corresponding time series are shown in Fig. 3).

Fig. 3. Simulation of therapy assuming relatively weak and relatively strong therapy. Phases of treatment are indicated by shading. (a) With weaker therapy, immune responses are boosted and are maintained during the phase of treatment. It takes the response a relatively long time to expand, and therapy should be stopped after a time threshold, once the level of immune responses has significantly risen. If therapy is stopped too early, immunological control is not achieved. (b) With stronger therapy, virus load is reduced quickly to low levels. On initiation of treatment, the immune response expands temporarily and declines again to low levels once the amount of antigenic drive has been diminished. To achieve long-term immunological control, therapy has to be stopped early, before the transient immunological expansion has vanished. If therapy is continued for too long, sustained immune control is not achieved. Parameters were chosen as follows: \( r = 3.5, k = 10, a = 3, P = 1, c = 12, e = 5, u = 3, \) and \( b = 0.3. \) For \( a, r = 3.13 \) during therapy, for \( b, r = 3.013 \) during therapy.

**Single Phase of Therapy**

We now consider the dynamics during a single phase of drug therapy in the chronic phase of infection. We assume that the infection is in the bistable parameter region (iv), and that the virus equilibrium has been attained. We ask whether and how a single phase of therapy can establish sustained immunemediated control of the infection. During therapy, the replication rate of the virus, \( r, \) is reduced in the model. The amount of reduction corresponds to the efficacy of the drugs. On cessation of therapy, the parameter \( r \) is reset to its pretreatment value. We...
response, \( S \), (Fig. 2b). The system will move from the pretreatment equilibrium toward the treatment equilibrium. During this process, the immune response expands (Fig. 3a). After a time \( t > t_{\text{min}} \), the level of the response moves above line \( L \). Hence, in principle, after the duration of therapy has crossed this time threshold, treatment can be stopped and sustained viral suppression will be achieved (Fig. 3a). Note that the time it takes the immune response to cross line \( L \) can be long, because the system has to pass the unstable saddle equilibrium \( S \), (Fig. 2b). This time period can be shortened if, in addition to drug treatment, the number of immune cells are augmented by immunotherapeutic approaches. Note in Figs. 2b and 3a that the approach to the treatment equilibrium is oscillatory. In the Appendix II, we state conditions for when such oscillations are expected to occur. If they do occur, they may have different implications depending on the efficacy of the drugs. We have two possible scenarios. If therapy is less efficient, the treatment equilibrium \( (S_t) \) lies high above the line \( L \), and the oscillations do not pose a problem. If therapy is more efficient, the treatment equilibrium \( (S_t) \) lies above but closer to line \( L \). After the immune response has risen to a peak, the oscillations can take the response temporarily below line \( L \) before the treatment equilibrium is reached (Fig. 2b). Therapy should not be stopped in the phases when the immune response goes through troughs.

If therapy is even more efficient, the treatment equilibrium lies below line \( L \) (greatly reduced virus load cannot maintain immunity during treatment). This occurs if the replication rate of the virus is pushed from parameter region \( iv \) to region \( ii \). As shown in Fig. 2c, the only stable outcome during treatment is the presence of the virus (at reduced levels) in the absence of sustained long-term immunity, \( S \). Because the treatment equilibrium lies below line \( L \), cessation of therapy when equilibrium has been reached will result in rebound of the virus (Fig. 3b). However, on the way to this treatment equilibrium, the number of immune cells can temporarily rise above line \( L \) soon after start of therapy. Subsequently, it declines to low levels (Fig. 3b). This is because during the initial phase of treatment, immune impairment has been reduced, but levels of virus load are still high enough to stimulate immune expansion. Once virus load is reduced further by the drugs, this initial immune expansion diminishes due to lack of antigenic stimulation. Thus, to achieve sustained viral suppression in this case, therapy must not be continued for too long: treatment has to be stopped early, while the level of immune cells is still high enough and above line \( L \) (Fig. 3b). Note, however, that the peak of the response during this temporary phase of expansion can lie below line \( L \) (Fig. 2). In this case, virus rebound will always be observed when therapy is stopped. Such an outcome is promoted by very strong drug-mediated suppression of viremia and/or the absence of a sufficient number of reactive immune cells.

To summarize, our results have given rise to the insight that a single phase of drug treatment during chronic infection can result in long-term control of the virus. We have described the following relationship among efficacy, duration, and success of therapy (summarized in Fig. 3). Therapy has to be efficient enough to reduce the rate of viral replication \( r \) at least from parameter region \( iv \) to region \( iii \). Within this constraint, significant immune responses develop during therapy only if suppression of viremia is relatively weak, because this ensures the presence of sufficient antigenic drive. Control is maintained if therapy is stopped after a defined time threshold, once immunity has peaked and become established. On the other hand, if treatment is stronger, immune responses peak early after initiation of treatment and subsequently decline because the level of antigenic drive is diminished. Long-term control now requires an early stop of treatment, before immunity has significantly declined. Treating too long will result in failure. A single phase of treatment will not lead to sustained immunological control if drug-mediated suppression of viremia is too strong, or if the number of reactive immune cells is too low.

**Why Therapy Interruptions?**

An important result from the above discussion is that long-term immune control can be achieved by a single phase of therapy if the combination of timing and efficacy of treatment is optimized. This is in contrast to previous notions that suggested that special regimes, such as structured therapy interruptions, have to be used to boost immunity. According to our theoretical framework, therapy interruptions can be helpful only in a restricted parameter region. Namely, interruptions can be beneficial if the following two conditions hold: (i) drug-mediated viral suppression is too strong to allow sufficient antigenic stimulation, and (ii) the number of reactive immune cells is reduced to very low numbers (however, the number of immune cells must be above a threshold for any therapy to work). In the limited circumstances when interruptions help, the dynamics are as follows.

A single phase of therapy moves the system toward the treatment equilibrium; the immune response increases but is not sufficiently boosted to cross line \( L \). On cessation of therapy, the system moves back to the pretreatment equilibrium. However, as shown in Fig. 4, the trajectory toward the treatment equilibrium on start of therapy is different from the trajectory away from the treatment equilibrium when therapy is stopped. Namely, when treatment is stopped, the immune response expands before it declines again. The reason is as follows. On cessation of treatment, the virus population grows. During this growth phase, virus load first attains levels at which the amount of antigenic stimulation outweighs immune impairment, and this results in immune expansion (see Appendix II for a simple mathematical explanation based on Eqs. 1 and 2). Of course, as virus load grows further, immune impairment outweighs antigenic stimulation, resulting in a decline of the response.

On the basis of the above arguments, therapy interruptions can work as follows. The first phase of treatment should be stopped while the immune response is around its maximum value (peak). During the off phase, the immune response will temporarily expand, as described above. When the immune response attains the maximum level during this off phase, therapy should be reapplied, resulting in further immune expansion that can push the response above line \( L \). The second phase of treatment should, however, not be continued for too long: after the response peaks above line \( L \), it will decline and fall back below line \( L \). It is crucial that therapy is stopped while the immune response is still sufficiently high and above line \( L \) (Fig. 4). If timing and duration of treatment are suboptimal, the immune response might not be pushed above line \( L \) by a single interruption. In this case, repeated therapy interruptions can increase the chances of success if the above scheme is continued.

**Application and Discussion**

We discuss our data in the context of HCV infection. Impairment of specific helper cell responses has been clearly documented, and the virus is not thought to destroy the T cells. Therefore, it is an ideal system to consider in light of the theory presented in this paper. Data from treated HCV-infected patients (16) support the immune response dynamics suggested by theory. This study looked at the dynamics of virus and the specific CD4 T cell responses during a single phase of treatment in 15 subjects. These subjects had persistent viremia and lack of significant CD4 T cell responses to the virus before therapy. On cessation of treatment, a fraction of these subjects were characterized by virus rebound, whereas the rest showed long-term control of the infection below detectable levels. In patients with virus rebound, generally CD4 T cell responses temporarily increased and peaked after the start of treatment, followed by a decline to insignificant levels. In the light of our theoretical
framework, an earlier cessation of treatment, while immune responses were around their peaks, might have resulted in containment of the infection. Patients characterized by long-term control after treatment showed, overall, later peaks of CD4 T cell responses, and therapy was stopped while immune responses were closer to these peak levels. After cessation of therapy, the CD4 T cell responses were, in some cases, boosted to even higher levels, as suggested by our model simulations (Fig. 3). These data confirm that a single phase of treatment can indeed result in long-term immunological control of an immunosuppressive infection, and that the observed dynamics are at least consistent with our theoretical framework. There is indication that similar dynamics can occur in HBV infection (21).

Our theoretical framework is also important to consider in the context of HIV infection. Although there are some indications that with HIV-infected patients, therapy can boost long-term immunity very early after infection (4, 22–25), there are no reports indicating that a single phase of drug therapy during chronic infection could result in long-term immunological control. Also, therapy interruptions tend to fail during chronic infection (26). The reason is almost certainly that HIV infection results in the depletion of specific immune cells, leaving not enough cells to react. However, the dynamics of cytotoxic T lymphocyte responses observed during treatment (27) support patterns observed in our model. Among subjects treated relatively early, the average level of HIV-specific CD8 T cell responses during therapy was higher in patients who showed two or more viremic episodes per year compared with patients in whom drug therapy suppressed HIV replication more efficiently. A similar trend was observed in patients treated during chronic infection (27). Therefore, less efficient therapy results in higher levels of immune responses during treatment. The complications associated with immune cell destruction by HIV can be avoided to a certain degree by very early postinoculation therapy in experimental simian immunodeficiency virus infection (14, 15). Treating early ensures that a sufficient level of reactive immune cells is preserved and available. The experiments showed that a single phase of treatment early in acute infection could result in long-term immunological control as well as protection from reinfection. Longer treatment correlated with better immunity. Interestingly, these experiments have been performed with a single drug, PMPA, which is thought to be less efficient at inhibiting viral replication than in combination therapy against HIV. This is in agreement with our theoretical prediction that with weaker viral suppression, treatment has to be continued beyond a time threshold to observe success.

Finally, although we have concentrated on immunosuppressive infections, we would like to briefly put our results into a broader context. The bistable behavior as described in this paper hinges on the assumption that the virus impairs specific immune responses. Therapy can therefore shift the patient from a disease progression to a control outcome. With viruses that do not impair immunity, there is no bistability. We can still observe two outcomes; for example, with human T-lymphotrophic virus, type I infection, patients can be either asymptomatic carriers, or they may develop diseases such as HTLV-1-associated myelopathy/tropical spastic paraparesis (28). But the two outcomes happen for very different reasons. Which outcome is attained has been shown to correlate with the HLA genotype of the host, among other things (28). Therefore, different outcomes are observed across individuals; within a patient, however, drug therapy will not switch a disease state to a control state. In such cases, different approaches involving therapeutic vaccination will be necessary to improve the degree of immunological control.

Conclusion

In theory, the optimal timing of when therapy should be stopped and/or restarted can be determined by monitoring immune response and virus dynamics. After the start of treatment, we expect the immune responses to rise. The best strategy would be to stop treatment when immune responses are around their maximum value, increasing the chances that the level of immunity is above line L. On cessation of treatment, the system is expected to converge to the immune control outcome if the level of immune responses was above line L (note that the control outcome can be attained by oscillations that can involve a temporary rise in virus load). If the level of immune responses was not above line L when therapy was stopped, the system will converge to the pretreatment equilibrium, which is recognized by a sustained rise in virus load to significantly higher levels. In this case, reapplication of drugs and therapy interruptions can result in long-term virus control, as described above. Therapy should be stopped and restarted at a time when immune responses were closer to these peak levels. After cessation of therapy, the CD4 T cell responses were, in some cases, boosted to even higher levels, as suggested by our model simulations (Fig. 3). These data confirm that a single phase of treatment can indeed result in long-term immunological control of an immunosuppressive infection, and that the observed dynamics are at least consistent with our theoretical framework. There is indication that similar dynamics can occur in HBV infection (21).

**Mathematically speaking, this corresponds to the fact that at the start of treatment, z = 0, so that therapy cannot shift the system above line L.**
responses are around their peak values. Such guidelines, however, have currently limited practical meaning, because implementation would require exact knowledge of the identity of relevant responses. In addition, difficulties arise because different assays can capture different subpopulations of immune cells, giving rise to different pictures. Nevertheless, the insights created by modeling give a conceptual framework that will be important for a more rational and targeted design of therapy regimes. The model has provided previously undescribed results regarding the optimal timing and duration of antiviral therapy that have not been considered before. Although with HIV, induction of long-term control will most likely require a combination of drug therapy and therapeutic vaccination, our findings have important practical implications for the treatment of HCV and HBV infections.

Finally, we would like to point out that we have used a very general modeling framework, which makes minimal assumptions. Hence, the results do not depend on the specific forms of equations which describe processes such as virus growth and immune expansion (29). We argue that any system characterized by the basic assumptions defined in our general framework will share the bistable behavior and the therapy results described here. This also applies to higher dimensional systems that have been studied in a different context (17).

Appendix

For our results to hold, the function $g(y)$ in Eq. 1 must satisfy the following four conditions (see Fig. 1):

1. $g(0) > 0$,
2. $\frac{dg}{dy} < 0 \forall y$,
3. There exists $y^* > 0$ such that $g(y^*) = 0$,
4. $\frac{dg}{dy} > 0$ for all $r, y$.

The function $f(y)$ in Eq. 2 satisfies the following two conditions:

1. There exist only two values $y_1, y_2 > 0$ such that $f(y_1) = f(y_2) = 0$,
2. $\frac{df}{dy} > 0$ for $y = y_1$ and $\frac{df}{dy} < 0$ for $y = y_2$.

A particular example is given by the system,

$$\dot{y} = ry \left(1 - \frac{y}{k}\right) - ay - pyz,$$

$$\dot{z} = cyz \frac{1 + ey}{1 + ey} - qyz - bz,$$

See the Appendix II for details.

Appendix II

Mathematical details of the modeling framework. The model considered in our paper is given by the following pair of differential equations:

\[ \dot{y} = yg_r(y) - yz, \quad [1] \]
\[ \dot{z} = zf(y). \quad [2] \]

For our results to hold, the function \( g_r(y) \) in Eq. 1 must satisfy the following four conditions (see Fig. 1):

1. \( g_r(0) > 0. \)
2. \( \partial g_r/\partial y < 0 \ \forall y. \)
3. There exists \( y_* > 0 \) such that \( g_r(y_*) = 0. \)
4. \( \partial g_r(y)/\partial r > 0 \) for all \( r, y. \)

The function \( f(y) \) in Eq. 2 satisfies the following two conditions:

1. There exist only two values, \( y_1 > 0 \) and \( y_2 > 0 \), such that \( f(y_1) = f(y_2) = 0. \)
2. \( \partial f/\partial y > 0 \) for \( y = y_1 \), and \( \partial f/\partial y < 0 \) for \( y = y_2. \)

System 1–2 admits four equilibria:

- \( S_0: y = 0, z = 0, \)
- \( S_1: y = y_1, z = g_r(y_1), \)
- \( S_2: y = y_2, z = g_r(y_2), \)
- \( S_v: y = y_*, z = 0. \)
Linear stability of these equilibria can be investigated by looking at the eigenvalues, $\Gamma_1$ and $\Gamma_2$, of the linearized perturbation problem. We have the following results:

Equilibrium $S_0$ corresponds to eigenvalues $\Gamma_1 = g_r(0)$ and $\Gamma_2 = f(0) < 0$. It is stable if and only if $g_r(0) < 0$, which means that $r$ must be smaller than a threshold value.

Equilibrium $S_i$ has eigenvalues satisfying $L - \Gamma I = 0$ with the matrix

$$L = \begin{pmatrix}
y_1 \frac{\partial g_r}{\partial y} |_{y_1} & -y_1 \\
g_r(y_1) \frac{\partial f}{\partial y} |_{y_1} & 0
\end{pmatrix}.$$

For stability we need $g_r(y_1) > 0$, that is $r$ must be higher than a threshold. The fixed point is oscillatory if and only if we have

$$y_1 \left( \frac{\partial g_r}{\partial y} |_{y_1} \right)^2 - 4g_r(y_1) \frac{\partial f}{\partial y} |_{y_1} < 0.$$

Equilibrium $\bar{S}_i$ is stable if and only if $g_r(y_2) < 0$; the analysis is similar to the analysis of point $S_i$. We can see that equilibrium $\bar{S}_i$ is stable only in the region where $z < 0$, that is it does not describe a biologically relevant state. Equilibrium $S_v$ has eigenvalues $\Gamma_1 = y_* \frac{\partial g_r}{\partial y} |_{y_*}$, and $\Gamma_2 = f(y_*)$ and is stable if and only if $f(y_*) < 0$ and $y_* > 0$. This is the case for $y_2 < y_* $ or $0 < y_* < y_1$. These are implicit conditions for $r$ because $y_*$ is a function of $r$.

To summarize, we have the following four regimes:

(i) For $r < r_1$, where $r_1$ is found from the equation $g_{r_1}(0) = 0$, $S_0$ is the only stable fixed point.

(ii) For $r_1 < r < r_2$, where $r_2$ is found from the equation $g_{r_2}(y_1) = 0$, $S_v$ is the only biologically relevant stable fixed point. The flow lines are illustrated in Fig. 2c.

(iii) For $r_2 < r < r_3$, where $r_3$ is found from the equation $g_{r_3}(y_2) = 0$, $S_i$ is the only biologically relevant stable fixed point (illustrated in Fig. 2b).

(iv) For $r > r_3$, there are two biologically relevant stable fixed points, $S_v$ and $S_i$ (illustrated in Fig. 2a).
**Interruption therapy.** As long as the virus load, $y$, is between $y_1$ and $y_2$, applying interruption therapy will lead to an increase in the immune response. Namely, from assumptions of the model it follows that $f(y) > 0$ for $y_1 < y < y_2$, and therefore we have $\dot{z} > 0$ in this region. During treatment (regimes ii and iii), the virus load starts decreasing while the immune response increases. After the cessation of therapy (regime i), $y$ increases, and $z$ continues to increase. Now if we re-start therapy, the system will end up following a flow line with higher values of $z$ compared to the first round of treatment (see Fig. 4a). In principle, several rounds of interruption will boost $z$ to high enough levels so that the system is above line $L$.

**A particular model used for illustrations.** As the general framework, this model contains two variables: the virus population, $y$, and a sustained virus specific immune response that can control the infection in the long term, $z$. The model is given by the following pair of differential equations:

$$\dot{y} = ry\left(1 - \frac{y}{k}\right) - ay - pyz, \quad \text{[3]}$$

$$\dot{z} = \frac{cyz}{1+ey} - qyz - bz. \quad \text{[4]}$$

A similar model for the dynamics of immunosuppressive infections has been published by De Boer and Boerlijst (1) in a different context. The virus population grows at a density-dependent rate $ry(1 - y/k)$. The parameter $r$ can be considered to represent the rate of viral replication, whereas the parameter $k$ represents the “carrying capacity” (target cell limitation). The virus population dies at a rate $ay$ and becomes inhibited by the immune response at a rate $pyz$. The immune response expands at a rate $cyz/(ey + 1)$. Thus, expansion is a saturating function of the amount of virus present. The virus population also inhibits the immune response at a rate $qyz$. Finally, in the absence of antigenic stimulation, the immune response declines at a rate $bz$.

Eqs. 3 and 4 can be written in the form of 1–2 if we set $f(y) = 1/p[cy/(1 + ey) - qy - b]$ and $g_r(y) = 1/p[r(1 - y/k) - a]$ and rescale time according to $t \rightarrow pt$.

The model is characterized by three outcomes. In the trivial case, $S_0$, there is no infection and no immune response ($y = z = 0$). Alternatively, the virus can establish an infection in the absence of an immune response, $S_v$, ...
such that $y = k(1-a/r)$, $z = 0$. Finally, the virus can establish an infection that is controlled by an immune response, $S_i$, with $y = y_1$ and $z = z_1$ with

$$y_{1,2} = \frac{c - q - b\epsilon \mp \sqrt{(c - q - b\epsilon)^2 - 4qb\epsilon}}{2eq},$$

$$z_{1,2} = \frac{1}{p} \left[ r \left( 1 - \frac{y_{1,2}}{k} \right) - a \right].$$

Note that equilibrium $S_i$, given by $y = y_2$, $z = z_2$ is always unstable and therefore biologically irrelevant.

The dependency of the dynamics on the replication rate of the virus, $r$, is as follows.

(i) If $0 < r < a$, then the system converges to $S_0$.

(ii) If $a < r < a/(1 - y_1/k)$, the system converges to $S_v$ (Fig. 2c).

(iii) If $a/(1 - y_1/k) < r < a/(1 - y_2/k)$, the system converges to $S_i$ (Fig. 2b).

(iv) If $r > a/(1 - y_2/k)$, both equilibria, $S_i$ and $S_v$, are stable (Fig. 2a).

In the bistable parameter region where the outcome of infection depends on the initial conditions, the separatrix (line $L$) near point $S_i$ can be approximated by the following equation:

$$z = z_2 + \Gamma_2 \left( \frac{y}{y_2} - 1 \right),$$

where

$$\Gamma_2 = \frac{1}{2p} \left( -\frac{ry_2}{k} + \sqrt{\left(\frac{ry_2}{k}\right)^2 - 4pz_2y_2 \frac{c}{(1 + ey_2)^2} - q} \right).$$

Reference: