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The dynamics of HTLV-I and the CTL response

Dominik Wodarz, Martin A. Nowak and Charles R.M. Bangham

Human retroviruses, like other RNA viruses, can rapidly accumulate sequence variation during replication because of nucleotide substitutions made by their error-prone polymerases. Human immunodeficiency virus type 1 (HIV-1), which replicates persistently at a high level, quickly develops extensive within-isolate sequence variation. However, human T-cell leukaemia virus type 1 (HTLV-I) varies much less in sequence than does HIV-1. It has therefore been widely assumed that there is little persistent replication of HTLV-I, and that the remarkably high proviral load found in HTLV-I infection – typically 0.1–10% of peripheral blood mononuclear lymphocytes (PBMCs)

Dominik Wodarz and colleagues describe a mathematical model for the in vivo dynamics of human T-cell leukaemia virus type 1 (HTLV-I) infection and the virus-specific cytotoxic T lymphocyte response. They show that a high rate of viral replication is consistent with the relative sequence invariance of HTLV-I and might be necessary to maintain a persistent infection.

carry the provirus – is maintained largely or wholly by division of provirus-containing cells. The provirus is replicated by cellular DNA polymerases, and is therefore subject to much lower mutation rates than is infectious virus (see Fig. 1). However, a number of observations suggest that HTLV-I is not latent. (1) Tax/Rex mRNA is detectable in PBMCs in a proportion of infected people^{1,2}. (2) There is a persistently activated cytotoxic T lymphocyte (CTL) response to the Tax protein of HTLV-I (Refs 3, 4) in the majority of HTLV-I-infected individuals, regardless of disease manifestation^{4–7} (S. Navarrete and C.R.M. Bangham, unpublished). *De novo* protein production in the cytoplasm is required to stimulate an efficient CTL response, indicating that there is persistent

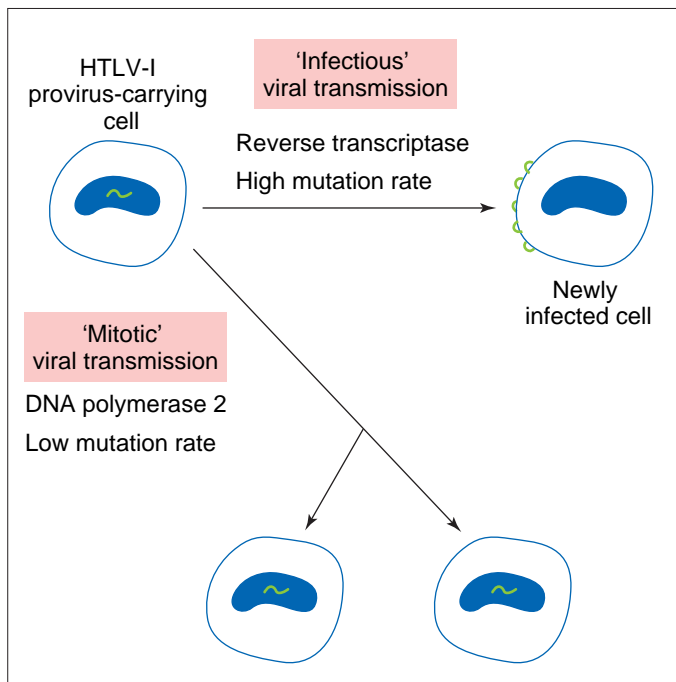


Fig. 1. Two modes of viral spread within human T-cell leukaemia virus type I (HTLV-I)-infected patients. Virion transmission to an uninfected cell is referred to as 'infectious' transmission. Similarly, proviral transmission is referred to as 'mitotic' transmission.

translation at least of the Tax protein. (3) There is persistent anti-HTLV-I IgM present in almost 50% of cases, especially in HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP)^{8–10}. Again, this strongly implies continuous antigen production.

The three observations above suggest that there is continuous expression at least of certain HTLV-I genes, which might reflect persistent viral replication. Three further observations indicate that persistent viral replication is indeed the likely explanation. (1) There is measurable sequence diversity within an isolate of HTLV-I (Refs 11–14). (2) The high ratio of nonsynonymous nucleotide substitutions to synonymous (silent) substitutions (the dN/dS ratio) within an isolate of HTLV-I shows that the virus is subject to continuous positive selection^{12,14}. If a stable equilibrium is reached in which there is no further selection pressure on the virus, the dN/dS ratio will not remain high. The virus must be replicating to be exposed to selection. Since this observation has been made in the Tax gene, which encodes the immunodominant target antigen recognized by the anti-HTLV-I CTL response, it is a reasonable inference that this positive selection is exerted by CTLs (Ref. 15). (3) Recently, five HTLV-I-infected individuals were treated with the nucleoside analogue 3TC (Lamivudine; G. Taylor *et al.*, unpublished). In the five cases there was a mean fall in the HTLV-I proviral load to approximately 10% of the pretreatment level in the six months following the start of treatment. Because Lamivudine acts by blocking reverse transcriptase, this response to treatment suggests that there is chronic reverse transcriptase activity. In one case (the only case examined with serial limiting dilution assays of CTL frequency), the fall in HTLV-I proviral load was accompanied by a similarly rapid fall in the frequency of anti-Tax CTLs, supporting the view that the high anti-Tax CTL-effector frequency was maintained by active replication of the virus^{15,16}.

Replication without sequence variation

How is it possible to reconcile this evidence for persistent HTLV-I replication with the relative constancy of the HTLV-I sequence? Here, we show that, if HTLV-I spreads within an infected person both by the 'infectious' route (i.e. by contact with a productively infected cell) and by the 'mitotic' route (by division of a provirus-carrying cell) then, even if the rate of infectious transmission is significant, at high loads most of the newly infected cells are produced by mitotic rather than infectious transmission of the virus. The mitotically transmitted provirus is replicated by cellular DNA polymerases, and so is subject to much lower mutation rates than virus transmitted by cell–cell infection. Therefore, the observation of relative sequence invariance of HTLV-I is consistent with the occurrence of abundant persistent replication of the virus.

The HTLV-I-associated chronic inflammatory diseases, such as HAM/TSP, uveitis and polymyositis, are associated with a very high HTLV-I proviral load, of around 10% PBMC (Refs 9, 17–21). Some asymptomatic carriers of HTLV-I have similarly high proviral loads: these individuals appear to have an increased risk of developing an inflammatory disease (G. Taylor *et al.*, unpublished).

The conclusion that persistent replication of HTLV-I is important for maintaining the high proviral load therefore has significant implications for the possibility of treating HTLV-I-infected people with drugs that inhibit viral replication, either before or after the development of HTLV-I-associated disease. The model also emphasizes the importance of understanding the factors, such as the immune response, that determine differences between infected individuals in the proviral load of HTLV-I.

A mathematical model for HTLV-I infection

The basic model

Here, we develop a basic model for HTLV-I infection, taking both infectious and mitotic transmission into account. Denoting uninfected CD4⁺ T helper cells by x and infected CD4⁺ T helper cells by y , the model is given by a pair of differential equations (Box 1). We assume the existence of a feedback mechanism assuring that the total number of target cells (uninfected and infected) cannot exceed a certain carrying capacity (k).

Thus, production of new target cells occurs at a density-dependent rate. In addition, the model includes a density-dependent proliferation term that includes proliferation in response to antigen and bystander proliferation. Therefore, if the overall number of target cells is well below the carrying capacity, the rate of target-cell production approaches λ and the proliferation rate approaches rx , however, these rates are diminished as the population of helper cells approaches the carrying capacity. Uninfected target cells die at a rate dx and become infected by infectious transmission at a rate βxy . The parameter β captures both the rate of production of virions and the rate of infection of susceptible cells. We assume that infectious transmission occurs by cell-to-cell contact, thus ignoring free viral particles in the model, since there is little if any cell-free HTLV-I in the plasma. Infected cells are driven to proliferate at a density-dependent rate, thus spreading the provirus by mitotic transmission. The strength of

Box 1. Basic model for infection by human T-cell leukaemia virus (HTLV-I)

Denoting uninfected cells by x and infected cells by y , the model is given by:

$$\dot{x} = (\lambda + rx) \left(1 - \frac{x+y}{k} \right) - dx - \beta xy \quad (1)$$

$$\dot{y} = \beta xy + sy \left(1 - \frac{x+y}{k} \right) - ay \quad (2)$$

The disease-free equilibrium is given by (E_0):

$$x_0 = \frac{k(r \pm d) \pm \lambda + \sqrt{[k(r \pm d) \pm \lambda]^2 + 4r\lambda k}}{2r}, y_0 = 0$$

Target cell-limited viral growth is described by equilibrium (E_1):

$$x_1 = \frac{\beta[k(a-s) - \lambda] + ra - sd + \sqrt{[\beta[k(a-s) - \lambda] + ra - sd]^2 + 4\lambda a\beta(r + \beta k - s)}}{2\beta(r + \beta k - s)}$$

$$y_1 = \frac{x_1(\beta k - s) + k(s - a)}{s}$$

The basic reproductive ratio of the virus is given by:

$$R_0 = \frac{1}{a} \left[\beta x_0 + s \left(1 \pm \frac{x_0}{k} \right) \right] \quad (3)$$

where x_0 is the equilibrium expression for uninfected target cells in the absence of an infection as defined above.

New infectious transmission occurs at a rate βxy , while new mitotic transmission occurs at a rate $s y (1 - (x + y)/k)$. We can therefore define the ratio of infectious to mitotic spread by the virus as $\alpha = (k\beta x) / [s(k - x - y)]$. If the virus-persistence equilibrium (E_1) is attained, this ratio can be rewritten as $\alpha_1 = (\beta x_1) / (\alpha - \beta x_1)$.

mitotic transmission is captured in the parameter s . Finally, infected cells die at a rate ay .

Without infection or if the viral population is not able to maintain itself, the system moves to the disease-free equilibrium (E_0 , Box 1).

produced by each infected cell at the beginning of the infection²², is greater than unity. Both infectious (β) and mitotic (s) transmission contribute additively to the basic reproductive ratio. The expression describing R_0 is given in Box 1. Another important measure that can

Box 2. Modelling a lytic cytotoxic T lymphocyte (CTL) response

CTLs (z) proliferate at a rate c and die at a rate b . We assume that CTL proliferation at high CTL densities is simply proportional to the number of infected target cells. Finally, CTLs lyse infected cells at a rate p , resulting in the following set of differential equations:

$$\dot{x} = (\lambda + rx) \left(1 - \frac{x+y}{k} \right) - dx - \beta xy \quad (4)$$

$$\dot{y} = \beta xy + sy \left(1 - \frac{x+y}{k} \right) - ay \pm pyz \quad (5)$$

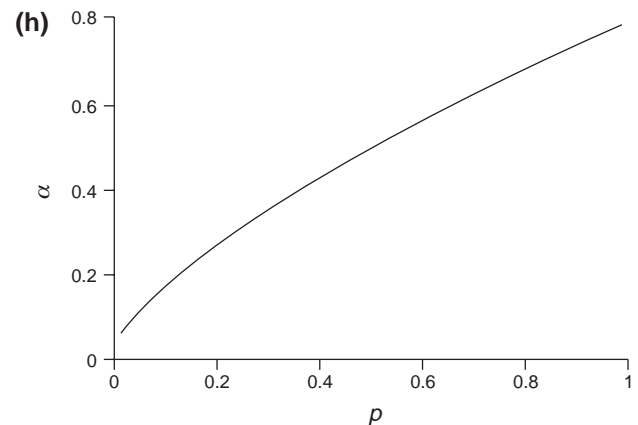
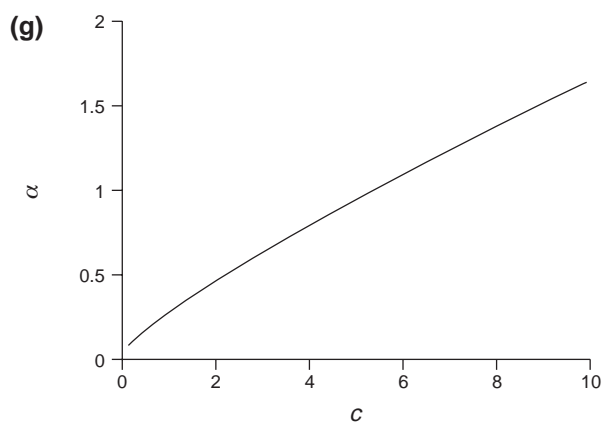
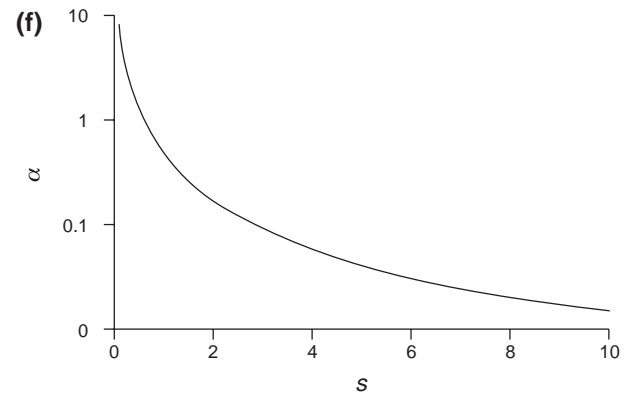
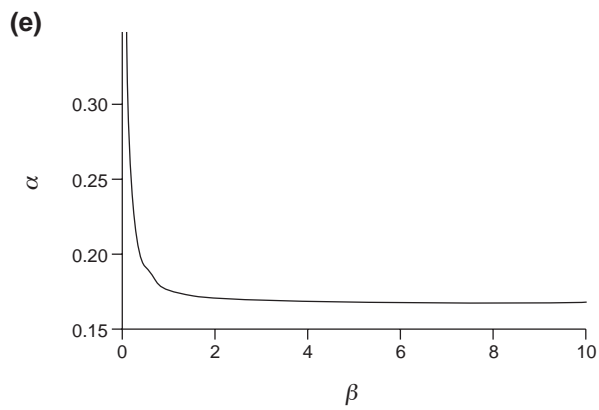
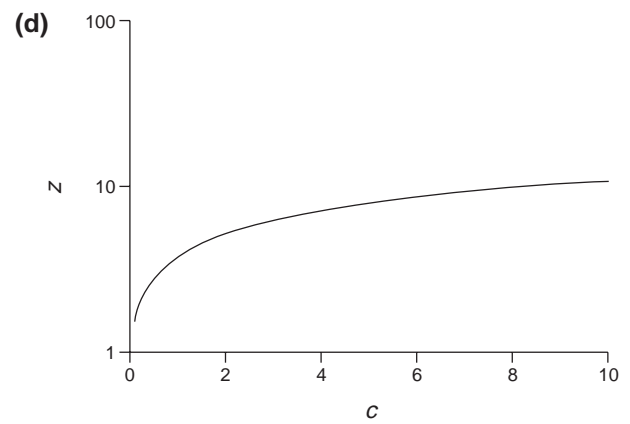
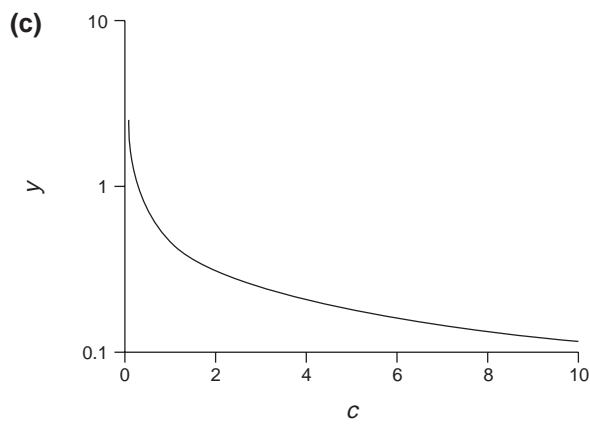
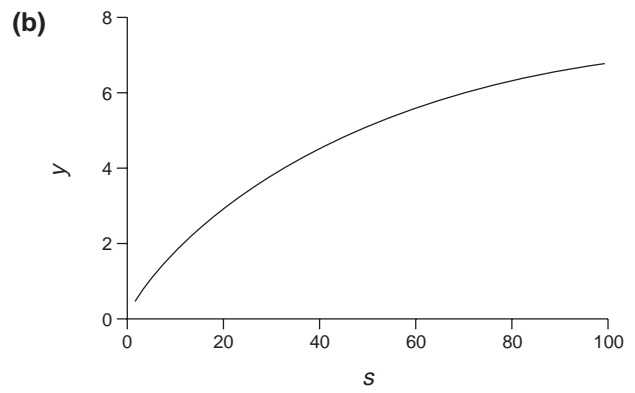
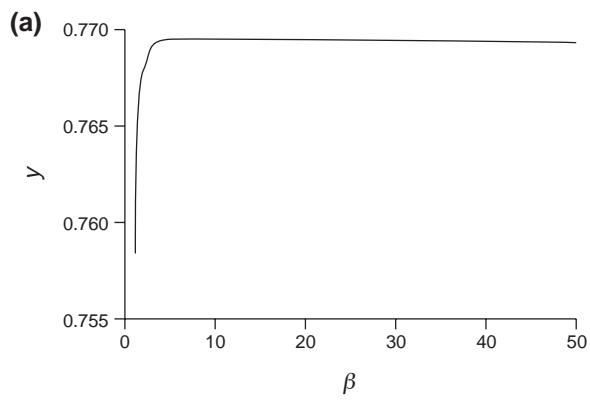
$$\dot{z} = \frac{c y z}{z + 1} - bz \quad (6)$$

Again, this model is characterized by the trivial equilibrium (E_0) and target cell-limited viral growth (E_1). If $cy_1 > b$, levels of viral load are high enough to stimulate a CTL response, leading to viral growth controlled by a combination of target-cell limitation and the immune response. However, the equilibrium expressions describing this outcome are not written out here, since they are too complicated to give any useful insights.

By contrast, if the virus successfully establishes an infection, target cell-limited viral growth will be observed (E_1 , Box 1). This equilibrium is stable and is reached by damped oscillations.

A persistent infection will be established if the basic reproductive ratio of the virus (R_0), defined as the average number of secondarily infected cells

Fig. 2. (a–d) The effect of host and viral parameters on viral load and the levels of cytotoxic T lymphocytes (CTLs) at equilibrium. (a) Above a certain value of R_0 , the rate of infectious transmission (β) is not a significant factor determining viral load. At low values of β , when the basic reproductive ratio of the virus is relatively low, an increase in this parameter leads to an increase in viral load up to a peak, which is followed by a very slight decline to an asymptote as β is further increased. Note that the y-axis has been expanded to show these patterns, since the impact of the rate of infectious transmission on viral load is very weak for the parameters chosen. (b) The rate of mitotic transmission (s) is a significant determinant of viral load. For very high values of s , viral load eventually approaches the carrying capacity (k). (c) Viral load is also significantly influenced by the immune responsiveness of the host (c). Very high values of c drive viral load towards zero. (d) The immune responsiveness of the host has no significant impact on the levels of CTLs at equilibrium (z). (e–h) The effect of host and viral parameters on the ratio of infectious to mitotic spread (α), at equilibrium. (e) As the rate of infectious transmission (β) is increased, one observes the counterintuitive pattern that the fraction of virus-containing cells acquired by infectious transmission first declines before it reaches an asymptote. (f) With increasing rates of mitotic transmission (s), the ratio α declines as expected. (g) Although the immune responsiveness of the host is a parameter unrelated to the route of viral transmission, it has a major impact on the fraction of virus-containing cells acquired by infectious transmission. An increased immune responsiveness leads to an increase in the ratio α . (h) Similarly, a higher rate of CTL-mediated killing of infected cells leads to an increase in the ratio α . The base-line values of the parameters for a–h were: $\beta = 2$, $s = 2$, $\lambda = 1$, $d = 0.1$, $a = 0.2$, $r = 0.4$, $k = 10$, $c = 1.5$, $b = 0.1$, $p = 0.1$.



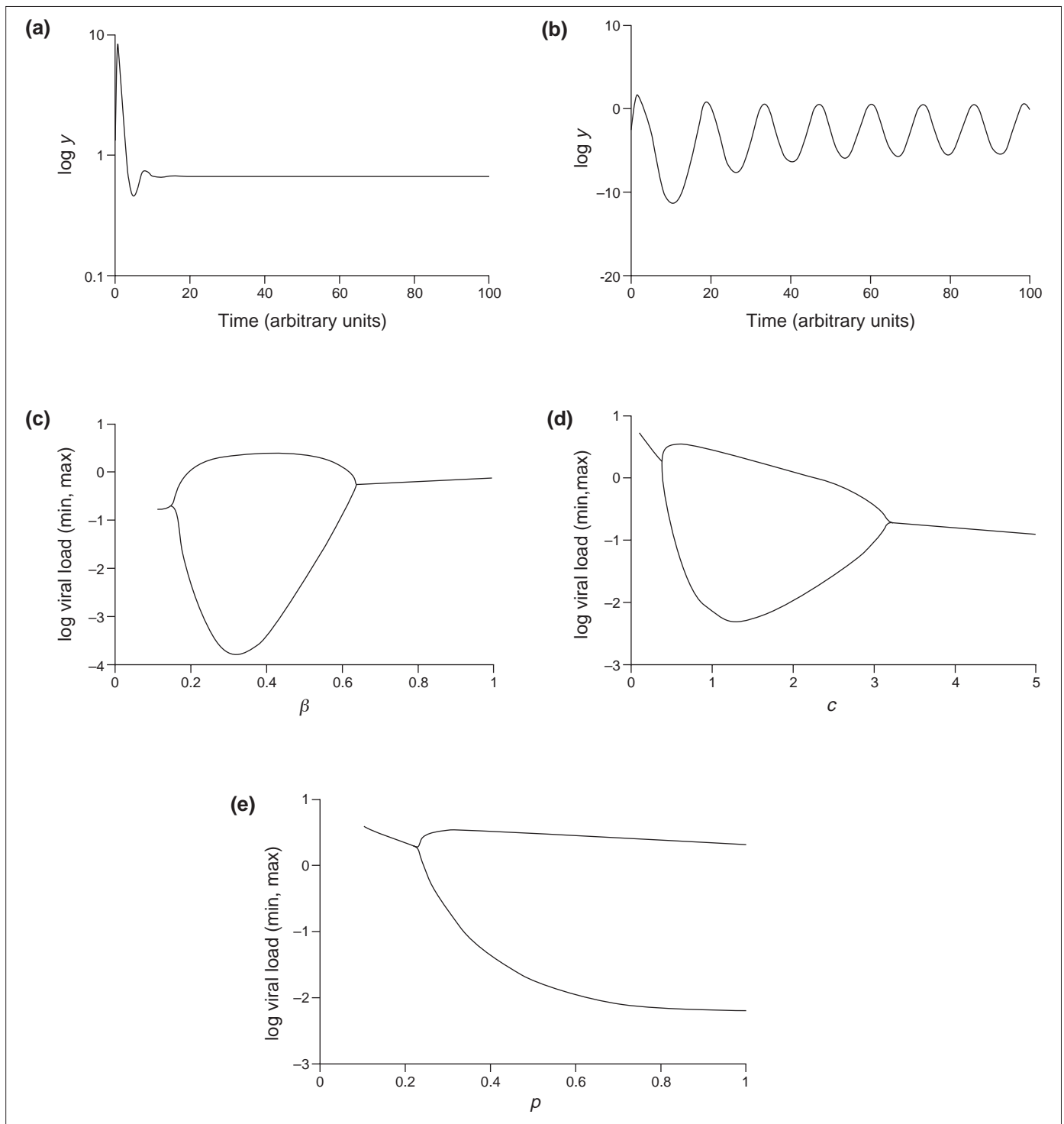


Fig. 3. (a,b) Two kinds of dynamic behaviour of the model including a cytotoxic T lymphocyte (CTL) response. The equilibrium describing the coexistence of uninfected and infected cells as well as the CTL response can either be stable, being approached by damped oscillations (a), or alternatively can show stable limit cycles (b). (c–e) The effect of relevant parameters influencing the dynamic behaviour of the model. The graphs show bifurcation diagrams in which the minimum and maximum values of viral load at equilibrium are plotted. If these coincide, the equilibrium is stable, while in the opposite case, stable limit cycles will be observed. (c) As the rate of infectious transmission (β) is decreased relative to the rate of mitotic transmission, the system moves from stable to cycling dynamics. As β is further decreased, the amplitudes of the cycles first increase, until they diminish. For very low values of β , when the basic reproductive ratio of the virus becomes relatively low, the system moves back to stable dynamics. (d) For the oscillatory behaviour to be observed, the immune responsiveness of the host (c) needs to be above a certain threshold. Above that threshold, a further increase in c leads first to an increase in the amplitude of the cycles followed by a decline until the system moves back to stable dynamics for relatively high values of c. (e) The rate of CTL-mediated killing of target cells (ρ) also needs to be above a certain threshold to induce cycling dynamics. A further increase in ρ leads to an increase in the amplitude of the cycles up to an asymptote. The base-line parameters were: (a) $\beta = 0.5$, $s = 10$, $\lambda = 1$, $d = 0.1$, $a = 0.2$, $r = 2$, $k = 10$, $c = 1.5$, $b = 0.1$, $\rho = 1$; (b–e) $\beta = 0.5$, others as for (a).

be derived from our model is the ratio of infectious to mitotically acquired cases at equilibrium, denoted by α (Box 1).

Incorporation of a lytic CTL response

The basic model described above can be extended to include a lytic CTL response (Box 2). We explore the effect of host and viral parameters on the equilibria, and on the ratio of infectious over mitotically transmitted cases (α). In addition, we investigate the stability properties of the model. Figure 2 shows the effects of host and viral parameters on the equilibrium viral load. Above a certain value, the rate of infectious transmission (β) has no significant effect on viral load, whereas the rate of mitotic transmission (s) has a significant influence on viral load, driving the system towards the carrying capacity (k) for very high values of s . The immune responsiveness of the host significantly decreases viral load but it has no strong impact on the levels of CTLs (Fig. 2). If the ratio of infectious versus mitotically transmitted cases (α) at equilibrium is analysed, Fig. 2 shows the counterintuitive observation that α initially declines with increasing rate of infectious transmission (β) until it reaches an asymptote. By contrast, high rates of mitotic transmission (s) lead to lower values of α , whereas a higher immune responsiveness as well as a higher rate of CTL-mediated lysis of infected cells leads to an increase in the frequency of infectious transmission.

Consideration of the stability properties of this equilibrium by extensive simulations shows two kinds of behaviour (Fig. 3). The equilibrium can be stable (reached by damped oscillations) or, alternatively, stable limit cycles can be observed. Simulations indicate that important factors determining the dynamics of the system at equilibrium include the relative importance of infectious compared with mitotic transmission, as well as the effectiveness of the immune response. Figure 3 shows bifurcation diagrams demonstrating how relevant parameters contribute to the change from stable dynamics to limit cycles. Lowering the rate of infectious (β) relative to mitotic transmission can lead to the transition from stable to cycling dynamics. The amplitude of the cycles first increases with decreasing rates of infectious transmission, before diminishing again until the system moves back to stable dynamics for very low values of β when the basic reproductive ratio of the virus becomes relatively low. In addition, the effectiveness of the immune response is an important factor governing the stability properties of the model: a low immune responsiveness (c) promotes stability. Increasing c can lead to the appearance of cycles with increasing amplitudes. A further increase in immune responsiveness in turn leads to a decrease in amplitudes until, for relatively high values of c , the system returns to stable dynamics. The pattern looks different for the rate of CTL-mediated target cell lysis (p). Low values of p promote stability, whereas higher values lead to a transition to cycling dynamics with the amplitude of the cycles increasing to an asymptote. Note that for all parameters, the change in amplitude of the cycles does not significantly involve the peak of the cycle rising to a higher value. Only the trough of the cycle drops to a lower value.

The model analysed above goes beyond the basic viral infection model of Nowak and Bangham¹⁶ to describe specifically infection by HTLV-I. Its properties are the result of the nonlinear interactions be-

tween uninfected and infected target cells as well as the CTL response. Several of the characteristics of this model depend on the fact that the target cells are both produced by the bone marrow and proliferate at a density-dependent rate that is characteristic of viruses infecting immune cells such as CD4⁺ T helper cells.

Experimental observations explained by the model

The sequence invariance of HTLV-I does not exclude persistent replication

The relative lack of nucleotide sequence variation of HTLV-I has been widely interpreted as showing that there is little persistent replication of the virus, and that the high proviral loads in HTLV-I infection are maintained by mitotic transmission, i.e. division of CD4⁺ T cells that carry latent HTLV-I provirus. However, a number of observations, summarized earlier, suggest that HTLV-I does replicate persistently. We have shown that the importance of infectious transmission for maintaining the viral infection might not be reflected in the proportion of proviruses at equilibrium that are acquired by the infectious route. In fact it can be demonstrated that an increase in the rate of infectious transmission leads to a decrease in the relative frequency at equilibrium of cells infected by this route. By contrast, parameters that are unrelated to the route of viral spread, such as the immune responsiveness of the host, can significantly influence the ratio of infectious to mitotic spread by the virus, at equilibrium. The reason for this is that factors that reduce the number of uninfected susceptible CD4⁺ T cells and/or increase viral load diminish the opportunity of the virus to spread by infectious transmission. Therefore, most newly infected CD4⁺ cells arise by mitotic rather than infectious transmission, and the opportunity for the virus to mutate is also diminished. It is therefore not justifiable to infer from the relative sequence invariance of HTLV-I that persistent replication is not occurring.

CTL-mediated selection on tax is stronger in healthy carriers of HTLV-I

The model also provides a simple explanation for the observation^{12,14} that the effect of CTL-mediated selection on the *tax* gene is stronger in healthy virus carriers than in patients with the inflammatory disease HAM/TSP. Healthy HTLV-I carriers have a proviral load on average only 7% that of HAM/TSP patients, although the distributions of proviral load in these two groups overlap. In individuals with a lower load, a higher proportion of the newly produced, virus-infected cells arise by infectious transmission; therefore, a greater fraction of the total viral burden is exposed to CTL-mediated surveillance, and the rate of selection for immune-escape mutations is greater, resulting in a higher proportion of nonsynonymous nucleotide substitutions, i.e. a higher dN/dS ratio. In this way, the model extends the ideas presented by Nowak and Bangham¹⁶.

Low CTL responsiveness might predispose to HAM/TSP

We have found little (if any) difference in the frequency of anti-Tax CTLs between HAM/TSP patients, who typically have a high HTLV-I

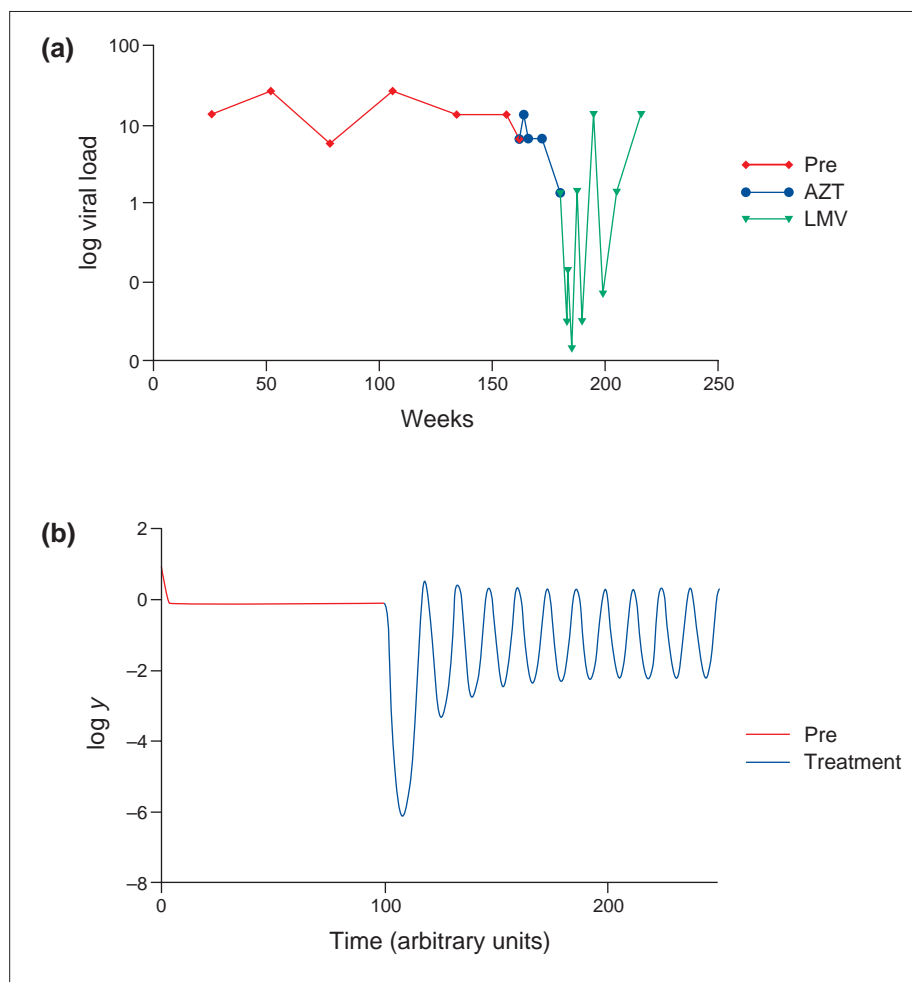


Fig. 4. The effect of drug treatment on viral load in human T-cell leukaemia virus type I (HTLV-I)-infected patients. (a) Experimental data. A healthy 39-year old woman was found to be HTLV-I seropositive in a screening programme. She remained asymptomatic during two years of observation, during which her HTLV-I proviral load varied by less than 1 log. She then began to develop symptoms of HTLV-I-associated myelopathy/tropical spastic paraparesis. AZT (3'-azido-3'-deoxythymidine) was given for three months, then discontinued because it was poorly tolerated and accompanied by little change in proviral load. Subsequent therapy with Lamivudine (LMV) was followed by a rapid and profound fall in the proviral load, which then fluctuated widely during sustained treatment with Lamivudine (G. Taylor *et al.*, unpublished). (b) Computer simulation of infection by HTLV-I, controlled by a cytotoxic T lymphocyte response, before and after the start of treatment with a drug that significantly reduces the rate of infectious transmission. Before drug treatment, levels of viral load remain stable. After the start of drug treatment, a significant fall in viral load is observed followed by sustained oscillations over several log units. Parameter values before drug treatment are identical to the ones chosen for graph (a) in Fig. 3, while parameters after the start of drug treatment were chosen as in graph (b) of Fig. 3.

proviral load, and asymptomatic HTLV-I carriers, whose proviral load is usually lower^{6,7}. The model presented here suggests that the explanation for this lies in individual differences in immune responsiveness to HTLV-I. Low-immune responders (low c) develop a high proviral load, because they cannot efficiently control viral replication. The resulting large antigenic load provides a strong stimulus to the weak CTL response. By contrast, in a high-immune responder, the smaller antigenic stimulus more efficiently elicits CTLs. Therefore, at equilibrium, there is little difference between the two groups in the abundance of anti-HTLV-I CTLs. This is illustrated by the weak effect of c on z (Fig. 2). This explanation is again consistent with the model proposed by Nowak and Bangham¹⁶.

However, the ability of the model to reconcile conflicting observations on the sequence variation and replicative ability of the virus (not reconciled in any other way) shows that it might not be necessary to invoke factors other than those already observed to explain the main features of the dynamics of this infection.

In this model, we have not attempted to describe the viral dynamics of antigenic variation^{25,26}. There is circumstantial evidence of immune-escape mutations in HTLV-I (Refs 13–15), but it is unlikely that immune escape contributes significantly to the persistence of HTLV-I because most of the variant proteins selected are impaired in function¹³. Rather, the evidence of immune selection suggests¹⁵ that

If this analysis is correct, the chief determinants of the equilibrium viral load of HTLV-I are the immune responsiveness to the virus (variables c and p in the model) and the rate of division of virus-infected cells (variable s). In more lytic viral infections such as HIV-I, the rate of virus-induced cell death might be a further important determinant of load. The rate of division of virus-infected cells is not likely to vary greatly between individuals independently of the proviral load. However, there are numerous examples, in both natural and experimental infections, of substantial individual variation in the immune responsiveness to a given pathogen, which is influenced by polymorphic genes both within²³ and outside²⁴ the major histocompatibility complex (MHC). On this interpretation, the main factor that is responsible for individual variation in the proviral load of HTLV-I is the immune responsiveness to the virus^{7,15,16}.

Anti-retroviral drug treatment-induced fluctuations in proviral load

At reduced rates of viral replication, the model predicts that the nonlinear interactions between the virus, its target cells and the CTL response might give rise to sustained fluctuations in the proviral load (Fig. 3). We have observed such fluctuations during treatment of a HAM/TSP patient with the nucleoside analogue Lamivudine (Fig. 4a; G. Taylor *et al.*, unpublished). If the drug does indeed inhibit HTLV-I reverse transcriptase, the lowered rate of viral replication could account for the onset of fluctuations in the proviral load in this patient, who previously had a high and stable load. A simulation of the effect of drug treatment on the dynamics of HTLV-I infection is shown in Fig. 4b.

The correspondence between the behaviour of the model and experimental observations does not prove the validity of the model. However, the ability of the model to reconcile conflicting observations on the sequence variation and replicative ability of the virus (not reconciled in any other way) shows that it might not be necessary to invoke factors other than those already observed to explain the main features of the dynamics of this infection.

the immune response, particularly CTLs, plays a significant part in limiting the rate of replication of this virus, as in other viral infections.

Concluding remarks

The conclusions drawn from this model parallel in many respects the conclusions drawn by Lipsitch *et al.*^{27,28} from their analysis of vertical and horizontal transmission of an infectious disease in a population. The model presented here has the added complexity of an immune response. However, the principal nonintuitive result is the same in each case, that is, in an infection transmitted both horizontally and vertically, a high equilibrium frequency of vertical transmission – here, mitotic spread – does not imply that the rate of horizontal transmission (infectious spread) is low. In fact, horizontal transmission might be a significant factor contributing to the maintenance of the infection.

We conclude that, at equilibrium, the high proviral load of HTLV-I is indeed maintained chiefly by proviral transmission, but that this is consistent with, and indeed might require, a high rate of replication of HTLV-I. This in turn implies that inhibition of viral replication might be able to lower substantially the proviral load: recent results obtained by Taylor *et al.* (unpublished) support this contention. Since a high proviral load is strongly associated with the development of HTLV-I-associated inflammatory diseases such as HAM/TSP, this analysis suggests that drug treatment of HTLV-I infection could reduce the risk of disease in HTLV-I-infected individuals.

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