Moels of Interactions Between HIV and Other Pathogens

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We investigate possible interactions between HIV and other pathogens that would arise if HIV replication were enhanced by the activation of T helper cells specific to other pathogens. Using mathematical models of the population dynamics of T helper cells, HIV and other pathogens we address three facets of the interactions between HIV and other pathogens: enhanced HIV replication due to immune stimulation by other pathogens; modified immune control of other pathogens due to immunosuppression by HIV; and the vicious circle formed by positive feedback between these two effects. The models predict that there is a correlation between higher levels of activated T helper cells and disease progression and that there is a threshold number of activated T helper cells above which the HIV infected immune system is unable to control pre-established pathogens. This threshold marks the boundary between a suppressed but still functioning immune system and the vicious circle of CD4 cell depletion that marks the final stages of AIDS.

1. Introduction

There are three facets of the interactions between HIV and other pathogens addressed in this paper: enhanced HIV replication due to immune stimulation by other pathogens; modified immune control of other pathogens due to immunosuppression by HIV; and the vicious circle formed by positive feedback between these two effects.

Several studies suggest that only activated T helper cells are permissive for HIV replication. When HIV infects a resting T helper cell viral DNA is maintained extrachromosomally suggesting that HIV infection of resting T helper cells is non-productive and that it is only upon antigen or mitogen induced activation that virus can integrate and new viruses be produced (Stevenson et al., 1990). Further evidence for the importance of T helper cell activation for the establishment of a productive infection comes from the studies of Zack et al. (1990) who show that HIV in resting T helper cells is unable to complete the reverse transcription process and that if such "infected but not integrated" cells are not stimulated within a few days levels of viral production are very low. Taken with the now well-established in vitro results that immune activation greatly enhances the rate of viral production from infected cells (Zagury et al., 1986; Zack et al., 1988) these experiments strongly suggest that immune activation of T helper cells may play an important role in determining the rate of HIV replication in an

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individual. There is also indirect evidence that immune activation plays a role in driving disease progression during HIV infection. Raised levels of beta-2-microglobulin and of neopterin [which are both markers of immune activation (Lamerton et al., 1982)] both correlate with falling CD4 levels in infected individuals (Hofman et al., 1990; Fahey et al., 1990). High levels of activated peripheral T cells are another predictor of early progression to AIDS (Levacher et al., 1990; Giogi & Detels, 1989) and are associated with acute infections with other viruses (Yu, 1980). Taken together these data indicate a need to consider the impact of immune stimulation upon the rate of HIV replication and thus of disease progression.

The destruction of immune function by HIV leads to the appearance of opportunistic infections, and for most AIDS patients death is caused by overwhelming infection with other pathogens (Poli & Masur, 1989). One can envisage two separate groupings of opportunistic infections. On the one hand are pathogens which, in an immunocompetent host would be rapidly cleared, but in AIDS patients either are only cleared very slowly, or establish persistent infections. Candida sp. (the cause of thrush) (Klein et al., 1984) and the enteropathic protozoa Cryptosporidium sp. and Isospora belli (Antony et al., 1983) are examples of such pathogens. The second group of opportunistic infections are those which are reactivations of latent persistent infections, e.g. cytomegalovirus, tuberculosis, toxoplasmosis and Pneumocystis carinii pneumonia. In immunocompetent hosts these pathogens are suppressed to very low levels, but in HIV infected individuals they can be isolated with increasing frequency as disease progresses and are frequently the eventual cause of death when they break out from weakened immune control (Macher et al., 1983; Jacobson, 1988; Brenner et al., 1987).

If HIV induced immunosuppression leads to reactivation of previously quiescent persistent infections, which in their turn, through immune activation, drive more HIV production and hence further immune suppression, a "vicious circle for further CD4 cell depletion" (Wong-Staal, 1989) may be established. In the modelling work presented below we investigate the circumstances under which such a vicious circle of positive feedback could be established. Using the models we develop we propose that there is a threshold on the size of the pool of activated T\(\text{h}1\) cells in an HIV-infected immune system. Below this threshold HIV establishes a persistent infection and other pathogens, although present at higher levels, are controlled. Beyond this threshold positive feedback between immune suppression by HIV and immune activation by other pathogens leads to the vicious circle of full blown AIDS. This pattern of model behaviour arises from the assumption that the average rate of HIV replication increases with the number of activated T\(\text{h}1\) cells.

In this paper our aim is to explore the interactions between HIV and other pathogens during the course of infection. We do not include antigenic variation, which has recently been proposed as a potential factor in disease progression (Nowak et al., 1990). A more complex model that combines the approach taken in this paper with the antigenic drift theory is in preparation.

In the first section below we present a model based on a simple set of assumptions about the immune system and use this model to obtain a threshold result on the number of other pathogens that can be controlled by an immune system infected
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with HIV. We then go on to develop a more complex model of the immune system which makes a distinction between pathogens which would normally be cleared leaving immune memory, and those which would normally persist at low levels. This is then used as the "core" of a more complex model of the infection of an immune system consisting of many different clones of $T_v$ cells.

2. Other Infections as Co-factors for HIV Progression

The first model we present explores interactions between HIV and other pathogens within the context of a minimalistic model of the immune system. This first immune model consists of a system of equations for the interaction of pathogens $A$ and $X$ with activated $T_v$ cells.

\[ \frac{dA}{dt} = rA - \gamma AX \]  
\[ \frac{dX}{dt} = aA - \xi X. \]

This shows damped oscillations to a stable equilibrium state at $A = \xi/a\gamma, X = r/\gamma$ for $a > \xi$, which represents a persistent infection. Instead all pathogens inhibit persistence of HIV and immune activation of $T_v$ cells. This pattern of behaviour is also common to the model of immune system infected with HIV and other pathogens.

To incorporate HIV into such a model requires the addition of two further equations, one to describe the amount of circulating HIV and one to describe the amount of activated $T_v$ cells specific to HIV. We also add a term describing the HIV-induced killing of activated $T_v$ cells and we enumerate different pathogens and their respective clones of $T_v$ cells with subscripted variables $i$ and $X_i$.

\[ \frac{dA_i}{dt} = rA_i - \gamma AX_i \]  
\[ \frac{dX_i}{dt} = aA_i - \xi X_i - \beta X_i V_i \]  
\[ \frac{dV_i}{dt} = \alpha V_i - \beta V_i Y_i - \gamma Y_i V_i. \]

Killing of activated $T_v$ cells by HIV is represented by the terms $-\beta X_i V_i$ in eqn (4) and $-\beta V_i Y_i$ in eqn (5), representing the assumption that it is upon activation that
\( T_n \) cells are killed by HIV. Equations (5) and (6) embody the following biological assumptions. HIV-specific activated \( T_n \) cells, \( Y \), are activated by HIV and then return to the resting state or are killed by HIV in the same way as \( T_n \) cells specific to any other pathogen. Production of HIV proceeds at some background rate \( r \), which is augmented by an amount depending on the total number of activated \( T_n \) cells \( (S_n X_n \cdot Y) \). HIV is removed at a rate depending on the number of HIV-specific activated \( T_n \) cells \( Y \). Drug treatment studies provide some indirect evidence for the relative importance of a rapidly turning over population of infected cells (e.g., CD4 cells) as the source of free virus in the circulation. Four weeks after starting AZT therapy, mean levels of circulating virus in seven patients fell to just 5% of their pretreatment levels (Hof et al., 1989). If AZT acts only to block new infections (as suggested by one in vitro study (Poli et al., 1989)) this data suggests that most circulating HIV comes from recently infected cells. The consequence of this increased importance of CD4 cells as a source of circulating virus relative to the putative tissue-based chronically infected cells of monocytic origin.

When \( n \) other pathogens \( A \), are present this model has an equilibrium at:

\[
X = \frac{e}{Y}, \quad A = \frac{r (\xi + \beta Y)}{\alpha Y}, \quad Y = \frac{\rho_r + n \alpha Y}{(Y - \lambda)} = \frac{\xi Y}{(Y - \lambda)}
\]

Consideration of the local stability properties of the sub-model accounting just for HIV and \( T_n \) cells specific to HIV shows that this equilibrium is locally stable if and only if \( \alpha - \beta Y > 0 \). There is therefore a threshold on \( n \), the number of other pathogens that can be controlled by an immune system infected with HIV:

\[
\kappa = \frac{1}{\lambda} \left[ \frac{\alpha Y (Y - \lambda)}{\beta - \rho_r} \right]
\]

We call this the "containment threshold" as it places a limit on the number of other pathogens that can be restrained by an immune system infected with HIV. If each pathogen \( A \) grows at a different rate \( r \), then instead of depending on just the total number \( n \) of other pathogens, \( n \), the containment threshold on other pathogens is expressed in terms of the sum over all \( n \) pathogens present of their respective growth rates:

\[
\sum_{i=1}^{n} r_i = \frac{1}{\lambda} \left[ \frac{\alpha Y (Y - \lambda)}{\beta - \rho_r} \right]
\]

It is perhaps more useful to rewrite this in terms of the total population of activated \( T_n \) cells:

\[
\sum_{i=1}^{n} X_i = \frac{1}{\lambda} \left[ \frac{\alpha Y (Y - \lambda)}{\beta - \rho_r} \right]
\]

Thus, the model predicts that there is a threshold on the total pool of activated \( T_n \) cells present in an HIV-infected immune system. Below this threshold HIV establishes a persistent infection and other pathogens, although present at higher levels, are
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controlled. Beyond this threshold positive feedback between immune suppression by HIV and immune activation by other pathogens leads to the vicious circle of full blown AIDS.

Figure 1 illustrates a sequence of events representing HIV infection, persistence and then breakthrough. Phase 1 represents an uninfected immune system in which just two pathogens and their specific clones of activated T_H cells are present [Fig. 1 (b) and (c)]. At the beginning of phase 2 HIV is introduced. There is an initial viremia ending when enough HIV specific, activated, T_H cells have been generated [Fig. 1(a)]. The initial burst of circulating HIV infects and kills activated T_H cells specific to the other pathogens A_1 and A_2 causing a temporary marked dip in the numbers of activated T_H cells and rise in the populations of pathogens [Fig. 1 (b) and (c)]. Phase 3 begins when a third pathogen invades. Although the containment threshold is not yet exceeded, the arrival of a new immune stimulant has effects on all model compartments. The populations of HIV and of activated T_H cells specific to HIV both grow, as do the populations of the pre-existing other pathogens. This is an illustration of how another pathogen might act as a force for disease progression without pushing the immune system over the containment threshold. The invasion of pathogen A_3 by generating more activated T_H cells allows there to be a bigger population of circulating HIV which further suppresses the immune system, allowing pathogens A_1 and A_2 to persist at higher levels. At this stage the total population of activated T_H cells is below the containment threshold, and the situation is stable until further pathogens invade. This sequence of events is repeated in phase 4—with further increases in the level of circulating HIV and other pathogens—and it is not until phase 5 that the containment threshold is finally exceeded. It is worth noting that the pathogen that triggers entry into the "vicious circle" does not have a particularly fast growth rate (see figure legend for details) nor any other special features. This is because the containment threshold depends upon the sum over all pathogens present of their growth rates [see eqn (7)] or, alternatively, the sum over all clones of the population of activated T_H cells [see eqn (8)].

This simple model generates the hypothesis that levels of T_H cell activation will correlate with disease progression, and, in particular, that there is a threshold on the size of the activated T_H cell population (given in eqn (8)) beyond which the vicious circle for further CD4 cell depletion is entered.

3. Distinguishing Between Memory and Persistent Infections

In a previous paper (McLean & Kirkwood, 1990) we described a model of the antigen driven activation and interleukin-2 driven proliferation of a clone of T_H cells. This model showed modes of behaviour akin to clearance of a replicating antigen with subsequent immune memory or, alternatively, the establishment of a persistent infection. We then went on to show how infection with HIV could perturb either of these two states, but restricted our attention to the infection of one single clone of T_H cells. We now extend those investigations to study synergistic effects when a number of T_H cells clones are simultaneously infected with HIV. Before presenting those results we give a brief summary of the behaviour of the core immune model.
FIG. 1. A minimal model of a immune system infected with HIV predicts a threshold on the number of other pathogens an HIV infected immune system can contain. Below this threshold immune control of other pathogens is diminished but their growth is still kept in check (phases 2-4) but once the containment threshold is exceeded (phase 5) HIV grows uncontrollably (a) and immune control of all other pathogens is lost (b)-(f). (a) Shows the population sizes of HIV (solid line) and T4 cells specific to HIV (broken line). (b)-(f) Show population sizes of other pathogens A-A, A, and their respective clones of T4 cells (broken line). Phase 1 establishment of an uninfected immune system. Phase 2 infection with HIV and establishment of a persistent infection. Phases 3 and 4, infection with additional pathogens which drive progression without exceeding the containment threshold. Phase 5, one pathogen too many arrive and the containment threshold is exceeded. Parameter values are: \( r_1 = 2, r_2 = 5, r_3 = 2, r_4 = 3, r_5 = 3, \gamma = 3, \alpha = 0.8, \beta = 1, r_1 = 10, \lambda = 1 \). Time 0 along the x axis and population size in arbitrary units is on the y axis. Notice that pathogens with faster replication rates have larger population sizes.
for a single clone of T<sub>4</sub> cells. We then go on to describe the full model for simultaneous infection of many different T<sub>4</sub> clones, and use this model to investigate the three aspects of HIV/other pathogen interactions discussed above.

### 3.1. SUMMARY OF SINGLE CLONE WORK

The full model for a single T<sub>4</sub> cell clone; consisting of resting T<sub>4</sub> cells, W, and activated T<sub>4</sub> cells, X, specific to another pathogen A and susceptible to killing by HIV, V is given by:

\[
\frac{dW}{dt} = \lambda - \mu W - aW + \xi X
\]

(9)

\[
\frac{dX}{dt} = aW + \frac{\alpha X^2}{1 + \kappa X^2} - \xi X - \beta VX
\]

(11)

\[
\frac{dA}{dt} = rA + \gamma AX
\]

(12)

\[
\frac{dV}{dt} = \lambda V - \rho V
\]

(13)

The single clone model arises from the following set of biological assumptions. Resting T<sub>4</sub> cells (W) migrate from the homoge at a constant rate \(\lambda\) and are depleted at rate \(\mu\) per cell unit time. T<sub>4</sub> cells are activated at rate \(a\) per resting cell—proportional to the amount of pathogen A. Activated T<sub>4</sub> cells return to the resting state at rate \(\xi\) per cell unit time. Upon activation T<sub>4</sub> cells are subjected to autocrine stimulation due to their production of both interleukin-2 and high affinity interleukin-2 receptors, but at high densities of cells this autocrine stimulation is suppressed (Fernandez-Box et al., 1988). These two processes give rise to the term \(\frac{\alpha X^2}{1 + \kappa X^2}\) in eqn (11). T<sub>4</sub> cells remain activated for about one week after which they return to the resting state (Cantrill & Smith, 1983), that is they return to being resting cells at rate \(\xi\). Activated T<sub>4</sub> cells are killed by HIV at rate \(\beta VX\). The other pathogen A grows at rate \(r\) in the absence of a specific immune response, but is removed at a rate proportional to the number of activated T<sub>4</sub> cells specific to that pathogen. Finally, HIV is assumed to be produced from activated T<sub>4</sub> cells and the removal of circulating HIV is assumed to take place at a constant rate. Thus, the assumptions about immunity to HIV are different from those in the model of section 1 where we took account of T<sub>4</sub> cells specific to HIV. We have dropped that part of the model for these investigations in order to reduce the complexity of the model.

This very brief statement of the biological assumptions inherent in the model is a summary of the more substantial treatment presented previously (McLean & Kirkwood, 1990). However, at this point our analysis diverges from that previously presented because we choose a different scheme for rendering our model to a dimensionless form, one in which the growth rate \(r\) of the other pathogen A appears in only one of the dimensionless parameters.
Choose

\[ W_i = \frac{\xi}{y}, \quad X_i = \frac{\xi}{y}, \quad A_0 = \frac{\xi}{a}, \]

\[ V_i = \frac{\xi}{\beta}, \quad b = \frac{1}{\xi}. \]

Then the model written in dimensionless form becomes

\[ \frac{dW}{dt} = p(W - W_0) - AW + X \]  
(14)

\[ \frac{dX}{dt} = AW - \frac{aX^2}{1 + bX} - X \]  
(15)

\[ \frac{dA}{dt} = A(e - X) \]  
(16)

\[ \frac{dV}{dt} = dV(e - c) \]  
(17)

where;

\[ p = \frac{u}{\xi}, \quad q = \frac{\lambda y}{\mu \xi}, \quad a = \frac{\xi}{y}, \quad b = \frac{\lambda y}{\xi}, \quad c = \frac{\xi}{y}, \quad d = \frac{\lambda}{y}, \quad e = \frac{\mu y}{\lambda \xi}. \]

The equations have been written without primes for brevity. Notice that the parameter \( r \) appears only in dimensionless parameter \( e \).

Figure 2 summarizes behaviour of the subsystem

\[ \frac{dX}{dt} = A + \frac{aX^2}{1 + bX} - X \]  
(18)

\[ \frac{dA}{dt} = A(e - X) \]  
(15)

which represents situations where there are always plenty of resting-cells, \( W \), relative to the size of the population of the pathogen \( A \). Figure 2 is a recreation of results presented in detail elsewhere, but because of the new set of dimensionless variables chosen, it is much clearer that it is the size of the composite parameter \( e \) (determined by the growth rate \( r \) of the pathogen \( A \)) that determines which of the three possible types of behaviour is displayed. For \( r \) very low [Fig. 2(a)] there are two stable states representing persistent infection or clearance of \( A \) with subsequent immune memory. Pathogens with high growth rates and thence high \( e \) also establish persistent infections which are controlled but not cleared by the immune system [Fig. 2(c)]. For intermediate values of \( e \) the system has a stable state with no pathogen \( A \) present—we shall call this state immune memory [Fig. 2(b)]. In the many-clone model that follows we
Fig. 7. Summary of the modes of behaviour of the "core" immune model: (a), (b), and (c) Are phase plane representations of the equilibrium behaviour of a two-compartment model describing the number of activated Tc cells if specific to a pathogen A (pass (18) and (19) in the text). The X nods are its conic and the y passes at the straight lines A = 0 and x = 0. Stable equilibriums are represented by filled circles and unstable equilibriums by open circles. Depending on the growth rate of the pathogen A these are three different processes which the vertical line between the cubic and those yield: (a) two stable equilibriums where a persistent infection can be perpetuated to yield human memory, (b) one stable state with pathogen A present, and (c) one stable state with no pathogen A present, but we call a persistent infection. (d) Illustrates the establishment of immune memory, from the virgin state (A = 0, X = 0), pathogen A is introduced and there is an initial burst of immunity, followed by clearance of pathogen A. The model then switches to the immune memory state where pathogen A is cleared but the memory of previous exposure is maintained. This switch is a self-perpetuating clone which immediately clears subsequent episodes of infection by A. (e) Establishment of a persistent infection with pathogen A. For faster growing pathogens the initial dynamics is followed by low level persistence.
When HIV and one clone of T\(_b\) cells are present, a number of different outcomes are possible. These have been described in detail elsewhere and are merely summarized in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Memory clone</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(e &gt; e_0)</td>
<td>HIV cannot invade</td>
</tr>
<tr>
<td>(X_e &gt; e_0)</td>
<td>HIV invades and establishes a persistent infection; the size of the memory clone is reduced to (e) and memory remains intact</td>
</tr>
<tr>
<td>(e \leq e_0)</td>
<td>HIV invades and establishes a persistent infection; the size of the memory clone is reduced to (e) and memory is destroyed, although the clone is still self-perpetuating</td>
</tr>
<tr>
<td>(1 \geq e_0 \geq 0)</td>
<td>HIV invades and establishes a persistent infection; the size of the memory clone is reduced to (e), and the clone is no longer self-perpetuating and completely disappears. After the clone has been destroyed, HIV can no longer replicate and disappear</td>
</tr>
</tbody>
</table>

### Peristent clone

| \(e < e_0\) | HIV cannot invade |
| \(e \geq e_0\) | HIV invades and the size of the T\(_b\) clone is reduced to \(e\), the persistent pathogen therefore grows without bound |

#### 3.2. Development of a Model with Many Clones

To progress from a model of infection of a single clone to a model of infection of many clones, we simply expand eqs (10-13) to cover a number of different clones of resting (\(W\)) and activated (\(X\)) T\(_b\) cell clones specific to the different pathogens (\(A_i\)) whose growth rate in the absence of specific killing is \(r_i\):

\[
\frac{dW}{dt} = A - \mu W - \alpha A_i W + \xi X_i \tag{20}
\]

\[
\frac{dX_i}{dt} = \alpha A_i W + \xi X_i - \beta X_i V \tag{21}
\]

\[
\frac{dA_i}{dt} = \gamma A_i X_i \tag{22}
\]

\[
\frac{dV}{dt} = -\nu V \sum X_i - \rho V . \tag{23}
\]

Notice, first of all, that the only difference between the pathogens \(A_i\) is their growth rates \(r_i\) (and, of course, their ability to induce a specific response from T\(_b\) cell clone \(X_i\)) and also that in the absence of HIV \((V')\) the equations for each clone and its pathogens are uncoupled, i.e., in the absence of HIV the behaviour of each clone is...
independent of the others. Finally notice that the growth rate of HIV is now determined by the size of the total pool of activated T\(_d\) cells \(\sum X_i\). The same scheme for writing the model in dimensionless variables can be used, with the single new definition \(c^* = c/\xi\).

\[
\frac{dW_j}{dt} = \alpha(q - W_j) - A_jW_j + X_i \\
\frac{dX_j}{dt} = A_j W_j + \frac{\alpha X_j^2}{1 + \beta X_j^2} - X_j - X_jV \\
\frac{dV}{dt} = dV\left(\sum X_i - e\right).
\]

(24)  
(25)  
(26)  
(27)

Figure 3 gives pictorial representation of the model, emphasizing that the different clones can only interact via a shared pool of infecting HIV. 

3.2. CONDITIONS FOR THE ESTABLISHMENT OF A PERSISTENT HIV INFECTION

The Edinburgh cohort of haemophiliacs consists of just 18 of 34 people all receiving the same batch of infected factor VIII (Ludlam et al., 1985). Why did the other 16 people not become infected? The conventional wisdom is that they received what was in some sense a "low dose" of virus. Analysis of the many clone model allows us to make formal definitions of the distinction between an infections dose and a non-infections dose. Such analysis shows that it is not always possible for HIV to invade a mixed population of T\(_d\) clones, and, furthermore, that once HIV has invaded it is not always able to establish a persistent infection. Table 2 summarises the conditions under which invasion and subsequent establishment are possible. The first possibility of Table 2 suggests an explanation for the seeming difficulty there is in infecting some people with HIV. The explanation offered here is that at the time of administration those people who did not become infected simply did not have a large enough pool of activated T\(_d\) cells to support HIV replication in the face of immune clearance mechanisms. This possibility offers some hope that vaccines that increased the HIV-specific immune response (in this model that would mean making \(\alpha\) bigger) might be protective; but on the other hand \(\xi\) raises disturbing questions about the impact of a large population of HIV-specific activated T\(_d\) cells. These questions are not considered here, but will be investigated in further work.

If there are enough activated T\(_d\) cells to enable HIV to invade, one possible outcome is that a persistent HIV infection will be established. This is illustrated in phase 2 of Fig. 4. Phase 1 of Fig. 4 represents the establishment of an imaginary immune system consisting of two "memory" clones [Fig. 4(b) and (c)] two "persistent" clones [Fig. 4 (d) and (e)] and one virgin clone [Fig. 4 (f)]. At the beginning of phase 2 HIV is introduced and establishes a persistent infection. The following
features are worth noting. There is no initial peak in viremia because the model does not account for acquired immunity specific to HIV. Levels of $T_u$ cells in the memory clones [Fig. 4 (b) and (c)] fall, both for resting cells and for activated cells, but for the persistent clones [Fig. 4(d) and (e)] a transient drop in the number of activated $T_u$ cells is followed by a return to their preinfection level. However, the number of resting $T_u$ cells specific to the persistent pathogens are permanently depressed and the levels of the persistent pathogens are slightly raised.

There are other possibilities suggested by the model which are summarized in the last two parts of Table 2. The first of these is, we feel, an artefact caused by our model's failure to account for latent infections although there has been one reported
Table 2: Possible outcomes when HIV invades a mixed population of $T_u$ cell clones consisting of $m$ memory clones of size $K_m$ and $n$ persistent clones each of size $K_p$.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sum_{i=1}^{m} K_m + \sum_{i=1}^{n} K_p &gt; \alpha$</td>
<td>HIV cannot invade</td>
</tr>
<tr>
<td>$\sum_{i=1}^{m} K_m + \sum_{i=1}^{n} K_p &lt; \alpha$</td>
<td>HIV invades and establishes a persistent infection. Each memory clone is reduced to size $\frac{K_m}{\alpha}$, which is lower than $1/K_m$ so each clone will still be present. Whether or not immune memory is acquired depends on the size of each clone relative to its pathogen's growth rate.</td>
</tr>
<tr>
<td>$\sum_{i=1}^{m} K_m + \sum_{i=1}^{n} K_p &lt; \alpha$</td>
<td>HIV invades and destroys all the memory clones. The remaining population of persistent clones is too small to sustain HIV replication and the HIV infection is therefore cleared.</td>
</tr>
</tbody>
</table>

The model accounts for three: $K_m$, and number of activated newly produced form activated $T_u$ of HIV and the only interactions used by $T_u$ cells that have been observed.  

3.4. Perturbation of a persistent HIV infection by other pathogens

If HIV is able to establish a persistent infection, it then becomes interesting to ask, "what is the impact of the activation of further clones of $T_u$ cells?" The answer depends on the growth rate $\alpha$ of this "sth" pathogen, $A_s$, relative to the size of the existing pool of activated $T_u$ cells, and the rate of clearance of HIV. The range of possibilities is summarized in Table 3. All of the possible modes of behaviour of the model are reminiscent of observed features of opportunistic infections in HIV infected individuals. In case i of Table 3 an HIV infected individual is unable to clear a pathogen which an immunocompetent host would rapidly eliminate. This is observed with opportunistic infections such as C. albicans and Cryptosporidium spp. (Klein et al., 1984; Antony et al., 1985). Figure 4 phase 3 illustrates such a situation. At the beginning of phase 3 the 5th clone's pathogen $A_5$ invades. The growth rate of this pathogen $\alpha_s$ is low and an unaffected immune system would clear the pathogen completely leaving immune memory. Because of the persistent HIV infection the pathogen can no longer be cleared and establishes a persistent infection. Notice also that after the invasion of the new pathogen levels of circulating HIV and of established persistent infections are higher than previously. We propose Fig. 4 as an illustration of how an opportunistic infection can itself drive HIV progression. This bring us back to the question of the threshold between containment of opportunistic
FIG. 4. HIV affects immune control of other pathogens, new infections enhance HIV production, but the total burden of pathogens remains below the containment threshold if immune control is maintained. In each graph time is along the x axis and population sizes (in arbitrary units) are on the y axis. (a) Shows HIV population size, (b)-(f) show sizes of populations of other pathogens \( A_i - d_i \) (dotted lines), activated \( T_i \) cells specific to those pathogens \( E_i \) - \( T_i \) (broken lines) and resting \( T_i \) cells specific to those pathogens \( W_i \) - \( W_i \) (solid lines). Phase 1 shows the setting up of a model immune system of two memory classes \( T_i \) and \( T_i \) and two persistent classes \( E_i \) and \( E_i \). In phase 2 HIV infects this immune system and establishes a persistent infection. All \( T_i \) cell population sizes are reduced and the population sizes of the persisting pathogens [dotted lines in (d) and (f)] increase. Infection with a fifth pathogen at the beginning of phase 3 leads to increased replication of HIV and these further decreases in \( T_i \) cell population sizes. The fifth pathogen \( A_5 \), which would have been completely cleared by an immune system not infected by HIV, establishes a persistent infection. Parameter values are: \( \alpha = 1.5, \beta = 1.7, \gamma = 2.6, \alpha = 0.2, \alpha = 0.3, \beta = 1, \alpha = 0.8, \beta = 1, \gamma = 1 \).
infections and their uncontrolled growth. The last possibility of Table 3 represents the breaching of this threshold, and an example of such a situation is given in Fig. 5. Phases 1 and 2 of Fig. 5 represent the same sequence of events as phases 1 and 2 of Fig. 4. At the beginning of phase 3 a further pathogen is introduced, the presence of which drives up the size of the circulating pool of HIV to such an extent that the existing memory clones are deleted. The remaining persistent clones are depressed to such an extent that their pathogens grow without bound. We propose this figure as an illustration of how the arrival of another pathogen can push an HIV infected immune system from a stable state in which HIV and all other persistent infections are controlled (albeit at higher levels than in an uninfected host) to one in which latent persistent infections can no longer be controlled and overwhelm the host.

4. Discussion and Conclusions

We have used two models to explore interactions between HIV and other pathogens. Both models predict that there is a threshold number of activated T4 cells that can be supported by an HIV infected immune system and that if this number is exceeded the immune system is tipped from stable control of HIV as a persistent infection to uncontrolled growth of pre-established pathogens. The second model is based on a "core" model of the immune system that distinguishes (according to their rates of growth) between pathogens that are cleared leaving immune memory and those that establish persistent infection; with rapidly growing pathogen establishing