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Explicitly accounting for antiretroviral drug uptake in theoretical HIV models predicts long-term failure of protease-only therapy

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Abstract

Mathematical models of HIV therapy have traditionally amalgamated the action of antiretroviral drugs, trading the complexity of the situation in favour of simpler—and hence mathematically tractable—models. However, the effects of ignoring such dynamics remain underexamined. In this paper, the traditional method of dosing (where the dose is modelled implicitly as a proportional inhibition of viral infection and production) is compared to a model that accounts for drug dynamics via explicit compartments. Four limiting cases are examined: frequent dosing of both major classes of drugs, absence of either drug, frequent dosing of one drug alone, or frequent dosing of the other drug alone. When drugs are absent, both models predict that the virus will dominate and the uninfected T cell counts will be low. When reverse transcriptase inhibitors are given frequently, both models predict that the virus will be theoretically eliminated and the uninfected T cell counts will be high; this is true regardless of whether the reverse transcriptase inhibitors act alone or in conjunction with protease inhibitors. However, if protease inhibitors alone are given frequently, then the implicit model predicts that the virus will be eliminated and the uninfected T cell counts will be high, whereas the (more realistic) explicit model predicts that the reverse situation may occur. In the latter case, critically, protease-only regimens may ultimately result in the death of the patient. It follows that the impact of drug regimens consisting only of protease inhibitors must be urgently re-examined, if such outcomes have been based on overly simplistic modelling.

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1. Introduction

Current HIV therapy consists primarily of a combination of antiretroviral drugs, primarily drawn from two major classes, reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) (Department of Health and Human Services, 2006). RTIs block transcription of viral RNA into DNA, preventing the infection of new cells, while PIs prevent protein cleavage in new virions, resulting in infected cells producing only noninfectious virus (Janeway et al., 2001). Historically, combination therapy has combined drugs from both classes. However, in the developing world, current antiretroviral rollout programs are staggering the release of drugs, with RTIs being used as first-line therapy and PIs held back for salvage therapy (Carpenter, 2006). In the developed world, the

use of PI-only therapy has been advocated as a possible alternative to current therapy, given that the over-reliance on nucleoside RTIs has led to an increase in drug resistance (Calmy et al., 2007).

Antiretroviral drugs are given frequently, with combination therapy that may result in up to 26 doses a day, as outlined in therapy groups for men living with HIV (Prior, 2005). The effects of different drug classes have typically been aggregated in mathematical models of HIV dynamics (Calloway and Perelson, 2002; Nowak and May, 2000), with some notable exceptions (Nelson and Perelson, 2002; Perelson, 2002; Smith and Wahl, 2004). Many of these models make the assumption that the drug is widely available within the body and the (average) efficacy varies between 0 (complete drug failure) and 1 (complete inhibition of the virus). See, for example, Nelson et al. (2000, 2001), Nowak and May (2000), Perelson and Nelson (1999), and Wu and Ding (1999). This has the advantage of

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making models simpler, allowing for greater generalisability. The disadvantage is that the dynamics of drug behaviour are ignored. In particular, the drug dynamics may have a significant impact on certain outcomes; ignoring these dynamics, while appealing for model simplicity, may result in misleading conclusions.

Although there have been attempts to capture the precise dynamics of drug behaviour (Huang et al., 2003; Smith and Wahl, 2004; Wu et al., 2006), such models are significantly more complex than those which approximate the drug behaviour by a constant effectiveness. In order to determine whether including drug dynamics makes a qualitative difference, in this paper the same basic model is examined, from two perspectives. The first models drug dynamics by inhibiting viral infection and production implicitly. In this model, T cells are either susceptible or infected. This will be referred to as the *implicit model*. The second model approximates drug dynamics by their long-term mean value, but with the property that the magnitude of the drug values is unbounded when the dosage is large or the dosing is frequent. In this model, T cells may be susceptible, inhibited by one or both drugs, or infected, with or without the presence of drugs. This will be referred to as the *explicit model*.

This paper is organised as follows: In Section 2, the models are introduced. In Section 3, the implicit model is analysed, demonstrating the stability of equilibria when drugs are either absent or perfectly efficacious. In Section 4, the explicit model is analysed, demonstrating the long-term behaviour when drugs are either absent or in the limiting case when the dosing interval shrinks to zero. In Section 5, the outcomes of the two models are compared. In Section 6, the predictions are illustrated with numerical simulations, for more realistic drug efficacies and dosing intervals. Finally, in Section 7, the implications with regards to treatment plans are discussed, particularly the plan to treat patients using a regimen of PIs alone.

2. The models

Let V_I represent infectious virus, V_{NI} represent non-infectious virus, T_S represent susceptible CD4⁺ T cells and T_I represent infected T cells. Then the implicit model is given by

$$\begin{aligned} \frac{dV_I}{dt} &= n_I\omega(1 - \varepsilon_P)T_I - d_V V_I - r_I T_S V_I, \\ \frac{dV_{NI}}{dt} &= n_I(1 - \omega)T_I - d_V V_{NI} + n_I\omega\varepsilon_P T_I, \\ \frac{dT_S}{dt} &= \lambda - r_I(1 - \varepsilon_R)T_S V_I - d_S T_S, \\ \frac{dT_I}{dt} &= r_I(1 - \varepsilon_R)T_S V_I - d_I T_I. \end{aligned} \quad (2.1)$$

Here, t is time in days, n_I is the number of virions produced per infected cell per day, ω is the fraction of virions produced by an infected T cell which are infectious, ε_P is the PI efficacy, d_V is the rate at which free virus is cleared,

r_I is the infection rate of noninfected T cells, d_S is the noninfected CD4⁺ T cell death rate, d_I is the infected CD4⁺ T cell death rate, λ represents a source of susceptible cells and ε_R is the RTI efficacy. All parameters are positive, except for the drug efficacies, which satisfy $0 \leq \varepsilon_P, \varepsilon_R < 1$.

The explicit model is given by

$$\begin{aligned} \frac{dV_I}{dt} &= n_I\omega T_I - d_V V_I - r_I T_S V_I - r_I T_{PNI} V_I, \\ \frac{dV_{NI}}{dt} &= n_I T_{PI} + n_I(1 - \omega)T_I - d_V V_{NI}, \\ \frac{dT_S}{dt} &= \lambda - r_I T_S V_I - d_S T_S - r_R T_S R_{av} - r_P T_S P_{av} \\ &\quad + m_R T_R + m_P T_{PNI}, \\ \frac{dT_I}{dt} &= r_I T_S V_I - d_I T_I - r_P T_I P_{av} + m_P T_{PI}, \\ \frac{dT_R}{dt} &= r_R T_S R_{av} - d_S T_R + m_P T_{RP} - m_R T_R - r_P T_R P_{av}, \\ \frac{dT_{RP}}{dt} &= r_R T_{PNI} R_{av} - d_S T_{RP} - m_P T_{RP} - m_R T_{RP} + r_P T_R P_{av}, \\ \frac{dT_{PNI}}{dt} &= r_P T_S P_{av} - d_S T_{PNI} - r_I T_{PNI} V_I - r_R T_{PNI} R_{av} \\ &\quad - m_P T_{PNI} + m_R T_{RP}, \\ \frac{dT_{PI}}{dt} &= r_I T_{PNI} V_I - d_I T_{PI} + r_P T_I P_{av} - m_P T_{PI}. \end{aligned} \quad (2.2)$$

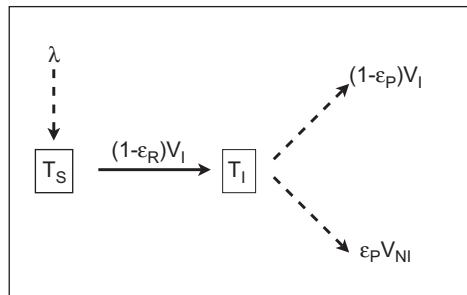
Here, additionally, T_R represents (uninfected) cells inhibited by RTIs alone, T_{RP} represents (uninfected) cells inhibited by both RTIs and PIs, T_{PNI} represents uninfected cells inhibited by PIs only, T_{PI} represents infected cells inhibited by PIs, m_R is the rate at which RTIs are cleared from the intracellular compartment, m_P is the rate at which PIs are similarly cleared, R_{av} represents RTIs and P_{av} represents PIs. All parameters are positive, except P_{av} and R_{av} , which are nonnegative.

Model (2.2) is a simplification of the impulsive differential equation model introduced in Smith and Wahl (2004). In particular, the drug concentrations are given by

$$\begin{aligned} R_{av} &= \frac{1}{2}(R(\tau^+) + R(\tau^-)) \\ &= \frac{R^i}{2} \left(\frac{1 + e^{-d_R \tau}}{1 - e^{-d_R \tau}} \right), \\ P_{av} &= \frac{1}{2}(P(\sigma^+) + P(\sigma^-)) \\ &= \frac{P^i}{2} \left(\frac{1 + e^{-d_P \sigma}}{1 - e^{-d_P \sigma}} \right), \end{aligned}$$

where r_R is the rate at which RTIs inhibit the T cells, r_P is the rate at which PIs inhibit the T cells, d_R is the rate at which RTIs are cleared, d_P is the rate at which PIs are cleared, R^i is the RTI dose, P^i is the PI dose, τ is the dosing frequency of the RTIs and σ is the dosing frequency of the PIs (At the dose times, R^i and P^i resemble delta functions,

A



B

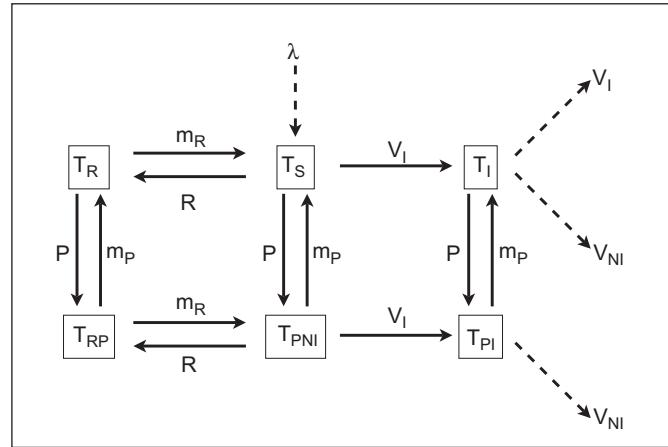


Fig. 1. Flowcharts of the models showing CD4⁺ T cell compartments. (A) The implicit model consists of susceptible (T_S) and infected (T_I) T cells. Susceptible cells can be infected and infected T cells will produce both infectious (V_I) and noninfectious (V_{NI}) virus. Drug action is implicitly modelled by the inhibition effect on new infections (ε_R) for RTIs or production of infectious virus (ε_P) for PIs. (B) The explicit model also consists of susceptible and infectious T cells, but now the compartments are divided into cells that are susceptible with no drug inhibition (T_S), susceptible and inhibited with RTIs alone (T_R), susceptible and inhibited with PIs alone (T_{PNI}), susceptible and inhibited with both drugs (T_{RP}), infected with no drug inhibition (T_I) or infected and inhibited with PIs (T_{PI}). Cells inhibited with RTIs cannot become infected, cells inhibited with PIs cannot produce infectious virus and drugs (R, P) are cleared at rates m_R, m_P . (Note that (B) was previously published in Smith and Wahl, 2004.)

due to the impulsive conditions.). The models are illustrated in Fig. 1.

The value $R(\tau^+)$ represents the value of the RTI on the impulsive periodic orbit immediately after a dose has been taken, while $R(\tau^-)$ represents the value of the RTI on the impulsive periodic orbit immediately before a dose has been taken. $P(\sigma^+)$ and $P(\sigma^-)$ are defined similarly. Note in particular that

$$\begin{aligned} \lim_{\tau \rightarrow 0} R_{av} &= \lim_{R^i \rightarrow \infty} R_{av} = \infty, \\ \lim_{\sigma \rightarrow 0} P_{av} &= \lim_{P^i \rightarrow \infty} P_{av} = \infty. \end{aligned} \quad (2.3)$$

Thus, although the drug dynamics in the explicit model are modelled in a simplified manner (i.e., by constant values

derived from the mean of the peaks and troughs of the impulsive periodic orbit from the model in Smith and Wahl, 2004), they contain the property that sufficiently frequent dosing, or a sufficiently high dose, will result in unbounded drug levels.

Models (2.1) and (2.2) are not qualitatively different; in particular, they are equivalent in the absence of drugs. Model (2.1) represents the drug effects of RTIs and PIs via the efficacy rates ε_R and ε_P , respectively. Conversely, model (2.2) reclassifies cells inhibited by drugs into different compartments, depending on whether a cell has been inhibited by RTIs, PIs, or both.

3. Analysis of the implicit model

The trivial equilibrium of model (2.1) is

$$(V_I, V_{NI}, T_S, T_I) = \left(0, 0, \frac{\lambda}{d_S}, 0 \right).$$

The nontrivial equilibrium satisfies

$$V_I = \frac{\lambda}{d_V d_I} \frac{n_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) - d_I}{1 - \varepsilon_R} - \frac{d_S}{r_I (1 - \varepsilon_R)}, \quad (3.1)$$

$$V_{NI} = \frac{n_I (1 - \omega) + n_I \omega \varepsilon_P}{d_V} \times \left\{ \frac{\lambda}{d_I} - \frac{d_V d_S}{r_I [n_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) - d_I]} \right\}, \quad (3.2)$$

$$T_S = \frac{d_V d_I}{r_I [n_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) - d_I]}, \quad (3.3)$$

$$T_I = \frac{\lambda}{d_I} - \frac{d_V d_S}{r_I [n_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) - d_I]}. \quad (3.4)$$

Note that the nontrivial equilibrium is only defined for $\varepsilon_R \neq 1$. If $\varepsilon_R = \varepsilon_P = 0$ (i.e., in the absence of drugs), then these equilibria are the same as those for model (2.2) in the absence of drugs (Smith and Wahl, 2004).

Since the production of infectious virions is high, we can assume $n_I \omega > d_I$. We also know that $d_S < d_I$ (Ho et al., 1995). Since λ and $n_I \omega$ are both large,

$$\lambda r_I [n_I \omega - d_I] > d_S d_V d_I. \quad (3.5)$$

Theorem 3.1. *In the absence of both drugs, the trivial equilibrium of model (2.1) is unstable and the nontrivial equilibrium is stable. Conversely, as either RTIs or PIs approach perfect efficacy, the trivial equilibrium becomes stable and the nontrivial equilibrium unstable.*

Proof. The Jacobian is

$$J = \begin{bmatrix} -d_V - r_I T_S & 0 & -r_I V_I & n_I \omega (1 - \varepsilon_P) \\ 0 & -d_V & 0 & n_I (1 - \omega) + n_I \omega \varepsilon_P \\ -r_I (1 - \varepsilon_R) T_S & 0 & -r_I (1 - \varepsilon_R) V_I - d_S & 0 \\ r_I (1 - \varepsilon_R) T_S & 0 & r_I (1 - \varepsilon_R) V_I & -d_I \end{bmatrix}.$$

At the trivial equilibrium,

$$J|_{(0,0,\lambda/d_S,0)} = \begin{bmatrix} -d_V - r_I T_S & 0 & 0 & n_I \omega (1 - \varepsilon_P) \\ 0 & -d_V & 0 & n_I (1 - \omega) + n_I \omega \varepsilon_P \\ -r_I (1 - \varepsilon_R) T_S & 0 & -d_S & 0 \\ r_I (1 - \varepsilon_R) T_S & 0 & 0 & -d_I \end{bmatrix}.$$

Thus, at the trivial equilibrium,

$$\begin{aligned} \det(J - \lambda I) &= -(d_V + \lambda) \\ &\times \det \begin{bmatrix} -d_V - r_I T_S - \lambda & 0 & n_I \omega (1 - \varepsilon_P) \\ -r_I (1 - \varepsilon_R) T_S & -d_S - \lambda & 0 \\ r_I (1 - \varepsilon_R) T_S & 0 & -d_I - \lambda \end{bmatrix} \\ &= (d_V + \lambda)(d_S + \lambda) \det \begin{bmatrix} -d_V - r_I T_S - \lambda & n_I \omega (1 - \varepsilon_P) \\ r_I (1 - \varepsilon_R) T_S & -d_I - \lambda \end{bmatrix}. \end{aligned}$$

This last determinant satisfies

$$\begin{aligned} \lambda^2 + (d_V + r_I T_S + d_I)\lambda + d_V d_I \\ + r_I [d_I - n_I \omega (1 - \varepsilon_R)(1 - \varepsilon_P)] T_S = 0. \end{aligned}$$

Clearly, if $\varepsilon_R = 1$ or $\varepsilon_P = 1$, then the constant term of the equation is positive and all eigenvalues will be negative. Thus, if either drug is perfectly efficacious, then the trivial equilibrium is stable. Conversely, if $\varepsilon_R = \varepsilon_P = 0$, then (since $n_I \omega > d_I$) the constant term of the equation is negative. It follows that the trivial equilibrium will be unstable in the absence of both drugs.

At the nontrivial equilibrium,

$$\begin{aligned} \det(J - \lambda I) &= -(d_V + \lambda) \\ &\times \det \begin{bmatrix} -d_V - r_I T_S - \lambda & -r_I V_I & n_I \omega (1 - \varepsilon_P) \\ -r_I (1 - \varepsilon_R) T_S & -r_I (1 - \varepsilon_R) V_I - d_S - \lambda & 0 \\ r_I (1 - \varepsilon_R) T_S & r_I (1 - \varepsilon_R) V_I & -d_I - \lambda \end{bmatrix}. \end{aligned}$$

The characteristic equation of this last determinant is

$$-\lambda^3 - a\lambda^2 - b\lambda + c = 0,$$

where

$$a = d_I + d_V + r_I T_S + r_I (1 - \varepsilon_R) V_I + d_S, \quad (3.6)$$

$$\begin{aligned} b &= d_I d_V + d_I r_I T_S + d_I r_I (1 - \varepsilon_R) V_I \\ &\quad + d_I d_S + d_V r_I (1 - \varepsilon_R) V_I + d_V d_S + r_I d_S T_S \\ &\quad - n_I r_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) T_S, \end{aligned} \quad (3.7)$$

$$\begin{aligned} c &= -d_I d_V r_I (1 - \varepsilon_R) V_I - d_I d_S d_V - d_I d_S r_I T_S \\ &\quad + n_I \omega r_I d_S (1 - \varepsilon_P)(1 - \varepsilon_R) T_S. \end{aligned} \quad (3.8)$$

Substituting (3.1) and (3.3) into (3.6) gives

$$a = d_I + d_V + \frac{d_V d_I}{n_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) - d_I} + \frac{r_I \lambda [n_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) - d_I]}{d_V d_I}.$$

Thus,

$$\begin{aligned} \lim_{\varepsilon_R \rightarrow 0} a &= d_I + d_V + \frac{d_I d_V}{n_I \omega - d_I} + \frac{\lambda r_I}{d_V d_I} [n_I \omega - d_I] \\ &> 0, \end{aligned}$$

since $n_I \omega > d_I$.

Substituting (3.1) and (3.3) into (3.7) gives

$$\begin{aligned} b &= d_I d_V + \frac{d_I^2 d_V}{n_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) - d_I} \\ &\quad + \frac{\lambda r_I}{d_V} [n_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) - d_I] \\ &\quad + \frac{\lambda r_I}{d_I} [n_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) - d_I] \\ &\quad + \frac{d_S d_V d_I}{n_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) - d_I} \\ &\quad - \frac{n_I \omega (1 - \varepsilon_R)(1 - \varepsilon_P) d_V d_I}{n_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) - d_I}. \end{aligned}$$

Thus,

$$\begin{aligned} \lim_{\varepsilon_R \rightarrow 0} b &= d_V d_I + \frac{d_I^2 d_V}{n_I \omega - d_I} + \frac{\lambda r_I}{d_V} [n_I \omega - d_I] + \frac{d_S d_V d_I}{n_I \omega - d_I} \\ &\quad + \frac{\lambda r_I}{d_I} [n_I \omega - d_I] - \frac{n_I \omega d_V d_I}{n_I \omega - d_I} \\ &= \frac{\lambda r_I}{d_V} [n_I \omega - d_I] + \frac{d_S d_V d_I}{n_I \omega - d_I} + \frac{\lambda r_I}{d_I} [n_I \omega - d_I] \\ &> 0, \end{aligned}$$

since $n_I \omega > d_I$.

Furthermore,

$$\lim_{\substack{\varepsilon_R \rightarrow 1 \\ \varepsilon_P \rightarrow 1}} b = \lim_{\substack{\varepsilon_R \rightarrow 1 \\ \varepsilon_P \rightarrow 0}} b = \lim_{\substack{\varepsilon_R \rightarrow 0 \\ \varepsilon_P \rightarrow 1}} b = -\frac{\lambda r_I d_I}{d_V} - \lambda r_I - d_S d_V < 0.$$

Substituting (3.1) and (3.3) into (3.8) gives

$$\begin{aligned} c &= -\lambda r_I [n_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) - d_I] \\ &\quad - \frac{d_I^2 d_S d_V}{n_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) - d_I} \\ &\quad + \frac{n_I \omega d_S d_V d_I (1 - \varepsilon_P)(1 - \varepsilon_R)}{n_I \omega (1 - \varepsilon_P)(1 - \varepsilon_R) - d_I}. \end{aligned}$$

Thus,

$$\begin{aligned} \lim_{\substack{\varepsilon_R \rightarrow 0 \\ \varepsilon_P \rightarrow 0}} c &= -\lambda r_I [n_I \omega - d_I] - \frac{d_I^2 d_S d_V}{n_I \omega - d_I} + \frac{n_I \omega d_S d_V d_I}{n_I \omega - d_I} \\ &= -\lambda r_I [n_I \omega - d_I] + d_S d_V d_I < 0 \end{aligned}$$

using (3.5).

Finally,

$$\lim_{\substack{\varepsilon_R \rightarrow 1 \\ \varepsilon_P \rightarrow 1}} c = \lim_{\substack{\varepsilon_R \rightarrow 1 \\ \varepsilon_P \rightarrow 0}} c = \lim_{\substack{\varepsilon_R \rightarrow 0 \\ \varepsilon_P \rightarrow 1}} c = r_I \lambda d_I + d_I d_V d_S > 0.$$

Thus, in the absence of both drugs, the characteristic polynomial has only roots with negative real part (since $a, b > 0, c < 0$), whereas if either drug is perfectly efficacious, then the characteristic polynomial has a root with positive real part (since $b < 0$ and $c > 0$). It follows that the nontrivial equilibrium is stable in the absence of both drugs and unstable if either drug is perfectly efficacious. \square

Remarks. 1. Theorem 3.1 suggests that the virus could be theoretically eliminated if either drug is perfectly efficacious. However, it should be noted that this applies to free virus in plasma only; HIV has other reservoirs of virus, such as follicular dendritic cells and latently infected cells. While actual elimination is not possible using drug therapy, elimination of free virus (or, in practice, reduction below the level of detection) is obviously the most desirable situation.

2. Perelson and Nelson (1999) analysed a similar model, although they (usually) assumed T_S was constant and did not examine the limiting effects of drugs. However, they reached similar conclusions; namely, that there is eradication if either ε_R or ε_P are sufficiently close to one.

4. Analysis of the explicit model

The following initial conditions are assumed: $V_I(0) = V_0 > 0$, $V_{NI}(0) = 0$, $T_I(0) = 0$, $T_R(0) = T_{RP}(0) = T_{PNI}(0) = T_{PI}(0) = 0$. It is also assumed that (a) V_0 is small compared to the product $n_I \lambda$ and (b) $T_S(0) \leq \lambda/d_S$, which includes the possibility that the immune system may not be operating at peak capacity when infection begins. These initial conditions correspond to the very earliest stages of infection, when the system is at the disease-free equilibrium except for a small population of infectious virus. It is therefore assumed that (1) the initial viral load is low compared to the total viral load as the infection progresses, (2) the initial (susceptible) T cell count is usually at the uninfected equilibrium value before infection (see Schacker et al., 1998), although the possibility that it may be less is allowed for, and (3) no drugs are taken before diagnosis.

The following lemma is straightforward, but will be used quite frequently.

Lemma 4.1. Suppose x is a variable satisfying

$$x'(t) < c - q(\phi)x(t),$$

where c is a constant and $q(\phi)$ is independent of x and t . Then

(a) If $x(0) < (c/q(\phi))$, it follows that

$$x(t) < \frac{c}{q(\phi)}$$

for all t .

- (b) If $x(0) < (c/q(\phi))$ and $\lim_{\phi \rightarrow 0} q(\phi) = \infty$, it follows that
 $x(t) \rightarrow 0$
as $\phi \rightarrow 0$ for all t .

Proof. See Smith and Wahl (2004, Lemma 4.1). \square

Remark. Lemma 4.1(a) also holds if the inequalities are reversed.

Let $T_{tot} \equiv T_S + T_R + T_{RP} + T_{PNI} + T_I + T_{PI}$. Then, using Lemma 4.1,

$$\begin{aligned} T'_{tot} &= \lambda - d_S(T_S + T_R + T_{RP} + T_{PNI}) - d_I(T_I + T_{PI}) \\ &\leq \lambda - d_S T_{tot}, \end{aligned}$$

$$T_{tot}(t) \leq \frac{\lambda}{d_S} \quad (4.1)$$

for all t , since $T_{tot}(0) \leq \lambda/d_S$ and $d_S < d_I$. Thus, the limiting value of the total number of T cells with infection is less than or equal to the number of T cells in the uninfected immune system. If there is no infection, then $T_I = T_{PI} = 0$ and there is equality in (4.1). In practice, $T_{tot}(t)$ will be less than λ/d_S when infection is present. By similar reasoning,

$$\begin{aligned} T'_{tot} &= \lambda - d_S(T_S + T_R + T_{RP} + T_{PNI}) - d_I(T_I + T_{PI}) \\ &\geq \lambda - d_I T_{tot}, \end{aligned}$$

$$T_{tot}(t) \geq \frac{\lambda}{d_I}.$$

Thus,

$$\frac{\lambda}{d_I} \leq T_{tot}(t) \leq \frac{\lambda}{d_S}. \quad (4.2)$$

Lemma 4.2. The infectious virions in model (2.2) satisfy

$$V_I < \frac{n_I \omega \lambda}{d_S d_V}.$$

Proof. See Smith and Wahl (2004, Lemma 5.1). \square

Lemma 4.3. The susceptible T cells in model (2.2) satisfy

$$T_S(t) > \frac{\lambda}{\alpha(\tau, \sigma)},$$

where $\alpha(\tau, \sigma) \rightarrow \infty$ as $\tau \rightarrow 0$ or $\sigma \rightarrow 0$.

Proof. Using (2.3) and Lemma 4.2,

$$\begin{aligned} T'_S &> \lambda - r_I T_S \frac{n_I \omega \lambda}{d_S d_V} - d_S T_S - r_R T_S R_{av}(\tau) - r_P T_S P_{av}(\sigma) \\ &= \lambda - \alpha(\tau, \sigma) T_S, \end{aligned}$$

where

$$\begin{aligned} \alpha(\tau, \sigma) &= \frac{r_I n_I \omega \lambda}{d_S d_V} + d_S + r_R R_{av}(\tau) + r_P P_{av}(\sigma) \\ &\rightarrow \infty \end{aligned}$$

as $\tau \rightarrow 0$ or $\sigma \rightarrow 0$.

Since λ and n_I are large compared to the other constants, it follows that $(\lambda/\alpha(\tau, \sigma))$ is small in general. It is thus reasonable to expect that $T_S(0) > (\lambda/\alpha(\tau, \sigma))$, since the body already has a sizable number of T cells when initially infected. Thus, by the remark following Lemma 4.1:

$$T_S(t) > \frac{\lambda}{\alpha(\tau, \sigma)}. \quad \square$$

Remark. This establishes a lower limit on the number of susceptible T cells, which approaches zero as treatment becomes more effective.

For simplicity of notation, define $m \equiv m_R + m_P$.

Lemma 4.4. 1. If $R_{av} \neq 0$, then, in model (2.2),

$$T_S(t) < \frac{\lambda \left(1 + \frac{m}{d_S}\right)}{r_R R_{av}} + \delta(t, \tau, \sigma),$$

where $\delta(t, \tau, \sigma) \rightarrow 0$ as $t \rightarrow \infty$ or $\tau \rightarrow 0$ or $\sigma \rightarrow 0$.

2. If $P_{av} \neq 0$, then, in model (2.2),

$$T_S(t) < \frac{\lambda \left(1 + \frac{m}{d_S}\right)}{r_P P_{av}} + \delta(t, \tau, \sigma).$$

Thus, $T_S \rightarrow 0$ as $\tau \rightarrow 0$ or $\sigma \rightarrow 0$.

Proof. 1. Using (4.1),

$$\begin{aligned} T'_S &< \lambda - d_S T_S - r_R T_S R_{av} - r_P T_S P_{av} + \frac{\lambda m_R}{d_S} + \frac{\lambda m_P}{d_S} \\ &= \lambda \left(1 + \frac{m}{d_S}\right) - \beta(\tau, \sigma) T_S, \end{aligned}$$

where

$$\beta(\tau, \sigma) = d_S + r_R R_{av} + r_P P_{av} > r_R R_{av}.$$

Thus,

$$\begin{aligned} \frac{d}{dt}(e^{\beta(\tau, \sigma)t} T_S) &< \lambda \left(1 + \frac{m}{d_S}\right) e^{\beta(\tau, \sigma)t} \\ T_S(t) &< \left[T_S(0) - \frac{\lambda \left(1 + \frac{m}{d_S}\right)}{\beta(\tau, \sigma)} \right] e^{-\beta(\tau, \sigma)t} + \frac{\lambda \left(1 + \frac{m}{d_S}\right)}{\beta(\tau, \sigma)}. \end{aligned}$$

Hence,

$$T_S(t) < \delta(t, \tau, \sigma) + \frac{\lambda \left(1 + \frac{m}{d_S}\right)}{r_R R_{av}},$$

where

$$\delta(t, \tau, \sigma) \equiv \left[T_S(0) - \frac{\lambda \left(1 + \frac{m}{d_S}\right)}{\beta(\tau, \sigma)} \right] e^{-\beta(\tau, \sigma)t}.$$

Using (2.3), $\beta(\tau, \sigma) \rightarrow \infty$ as $\tau \rightarrow 0$ or $\sigma \rightarrow 0$ and $\delta(t, \tau, \sigma) \rightarrow 0$ as $t \rightarrow \infty$ or $\tau \rightarrow 0$ or $\sigma \rightarrow 0$. Thus, $T_S \rightarrow 0$ as $\tau \rightarrow 0$ or $\sigma \rightarrow 0$.

The proof of part 2 is similar. \square

Remark. This establishes upper limits on the number of susceptible cells, which approach zero as treatment becomes more effective. Thus, when either RTIs or PIs (or both) are used frequently, the number of susceptible cells is driven to zero (since such cells are either infected or converted into drug-inhibited cells).

Theorem 4.1. If $R_{av} \neq 0$, then, in model (2.2), $T_I \rightarrow 0$, $T_{PNI} \rightarrow 0$, $T_{PI} \rightarrow 0$ and $T_R + T_{RP} \rightarrow (\lambda/d_S)$ as $t \rightarrow \infty$ and $\tau \rightarrow 0$, for any fixed σ .

Proof. Using part 2 of Lemma 4.4 and (4.1),

$$T'_{PNI} \leq \lambda \left(1 + \frac{m}{d_S}\right) + r_P \delta(t, \tau, \sigma) P_{av} - r_R R_{av} T_{PNI} + \frac{\lambda m_R}{d_S}.$$

Thus, using Lemma 4.1,

$$\begin{aligned} T_{PNI} &\leq \frac{\lambda \left(1 + \frac{m}{d_S}\right) + r_P \delta(t, \tau, \sigma) P_{av} + \left(\frac{\lambda m_R}{d_S}\right)}{r_R R_{av}} \equiv \gamma(t, \tau, \sigma) \\ &\rightarrow 0 \end{aligned}$$

as $t \rightarrow \infty$ and $\tau \rightarrow 0$, for each fixed σ .

Using Lemma 4.2, part 1 of Lemma 4.4 and the first part of Theorem 4.1,

$$\begin{aligned} T'_I + T'_{PI} &= r_I (T_S + T_{PNI}) V_I - d_I (T_I + T_{PI}) \\ &\leq \frac{r_I n_I \omega \lambda}{d_S d_V} \left[\frac{\lambda \left(1 + \frac{m}{d_S}\right)}{r_R R_{av}} + \delta(t, \tau, \sigma) + \gamma(t, \tau, \sigma) \right] \\ &\quad - d_I (T_I + T_{PI}), \\ T_I + T_{PI} &\leq \frac{r_I n_I \omega \lambda}{d_S d_V d_I} \left[\frac{\lambda \left(1 + \frac{m}{d_S}\right)}{r_R R_{av}} + \delta(t, \tau, \sigma) + \gamma(t, \tau, \sigma) \right] \\ &\rightarrow 0 \end{aligned}$$

as $t \rightarrow \infty$ and $\tau \rightarrow 0$, for each fixed σ .

Using Lemma 4.2 and part 1 of Lemma 4.4,

$$\begin{aligned} T'_S + T'_R + T'_{RP} + T'_{PNI} &= \lambda - r_I (T_S + T_{PNI}) V_I \\ &\quad - d_S (T_S + T_R + T_{RP} + T_{PNI}) \\ &> \lambda - \frac{r_I n_I \omega \lambda}{d_S d_V} \left[\frac{\lambda \left(1 + \frac{m}{d_S}\right)}{r_R R_{av}} + \delta(t, \tau, \sigma) + \gamma(t, \tau, \sigma) \right] \\ &\quad - d_S (T_S + T_R + T_{RP} + T_{PNI}). \end{aligned}$$

Using a similar argument to the proof of Lemma 4.4,

$$\begin{aligned} T_R + T_{RP} &> \frac{\lambda}{d_S} - \frac{r_I n_I \lambda}{d_S^2 d_I} \left[\frac{\lambda \left(1 + \frac{m}{d_S}\right)}{r_R R_{av}} + \delta(t, \tau, \sigma) + \gamma(t, \tau, \sigma) \right] \end{aligned}$$

$$-T_S - T_{PNI} + \left\{ T_S(0) - \frac{\lambda}{d_S} + \frac{r_I n_I \lambda}{d_S^2 d_I} \right. \\ \times \left[\frac{\lambda \left(1 + \frac{m}{d_S} \right)}{r_R R_{av}} + \delta(t, \tau, \sigma) + \gamma(t, \tau, \sigma) \right] \right\} e^{-d_S t}$$

$\rightarrow (\lambda/d_S)$ as $t \rightarrow \infty$ and $\tau \rightarrow 0$, for any fixed σ , using the first part of this proof and Lemma 4.4. \square

Remark. Thus, if RTIs are taken with sufficient frequency (with or without PIs), cells inhibited with RTIs do the work of maintaining the immune system at pre-infection levels and all other cells are driven to zero.

5. Comparison of the implicit and explicit model

For the purposes of comparison with the explicit model, it is assumed that the efficacy of the drugs is directly related to the frequency of drug dosing; that is, as the frequency of doses approaches infinity, the efficacy approaches 100%.

In the absence of both drugs, the implicit and explicit models are equivalent. In this case, both models predict that the disease-free equilibrium is unstable and the endemic equilibrium is stable. It follows that the virus dominates in the absence of drugs.

When both drugs are taken frequently, Theorems 3.1 and 4.1 predict that the virus will be eliminated and the infected T cell count will be low.

When PIs are absent, but RTIs are taken frequently, Theorems 3.1 and 4.1 also predict that the virus will be eliminated and the infected T cell count will be low.

However, when RTIs are absent, but PIs are taken frequently, the outcome may not be consistent. In particular, Theorem 3.1 always predicts that the disease-free equilibrium will be stable and the endemic equilibrium will be unstable in the implicit model. For the explicit model in this case, $T_S \rightarrow 0$ (from Lemma 4.4) and $T_{RP} = T_R = 0$

(since the RTIs are absent). Applying (4.2), we have

$$\frac{\lambda}{d_I} \leq T_I + T_{PNI} + T_{PI} \leq \frac{\lambda}{d_S}.$$

However, typically $1/d_I \ll 1/d_S$. Let μ_0 denote the minimum number of T cells required to maintain the immune system. If μ_0 satisfies

$$\frac{\lambda}{d_I} \leq \lim_{t \rightarrow \infty} (T_I + T_{PNI} + T_{PI}) < \mu_0 < \frac{\lambda}{d_S}, \quad (5.1)$$

then there is no dosing schedule that will sustain a healthy immune system. That is, if the number of nonzero T cells is too low, then the effect of treatment with PIs, no matter how frequently taken or how large the dose is, ultimately may be no better than no treatment at all. Thus, in this case, the outcome depends on the model.

The results are summarised in Table 1.

6. Numerical simulations

Section 4 does not demonstrate what happens as $\sigma \rightarrow 0$ if $R_{av} = 0$ and $P_{av} \neq 0$. In this case, the result may be identical to the implicit model (namely, eradication), it might satisfy (5.1) (in which case treatment with PIs is effectively similar to no treatment at all) or there may be a limiting value that exceeds μ_0 but is still low (see Calloway and Perelson, 2002). Consequently, the outcome must be illustrated numerically.

While drugs are never perfectly efficacious, results in Sections 3 and 4 are an idealisation of the case where one or both drugs are highly efficacious. In this section, the results are illustrated for realistic parameters, where the drugs are moderately efficacious. The parameters describing T cell and virus dynamics are largely straightforward and were taken from the literature; the reader is referred to Haase et al. (1996), Nelson and Perelson (2002), and Wahl and Nowak (2000) for details and to the figure legends for specific values (Figs. 2 and 3).

To illustrate the differences in the implicit versus the explicit models, PI-only therapy was simulated. In Fig. 2, the PI efficacy was 75%. Even this moderate efficacy led to low viral load for infectious virus (approximately

Table 1
Comparison of implicit and explicit dosing for both major classes of drugs

RTI	PI	Implicit dosing	Explicit dosing	Result
Infrequent	Infrequent	Infected T cell counts high, Uninfected T cell counts low	Infected T cell counts high, Uninfected T cell counts low	Virus dominates
Frequent	Frequent	Infected T cell counts low, Uninfected T cell counts high	Infected T cell counts low, Uninfected T cell counts high	Virus eliminated
Frequent	Infrequent	Infected T cell counts low, Uninfected T cell counts high	Infected T cell counts low, Uninfected T cell counts high	Virus eliminated
Infrequent	Frequent	Infected T cell counts low, Uninfected T cell counts high	Infected T cell counts may be high, Uninfected T cell counts may be low	Depends on method!

If both drugs are taken infrequently, then the virus dominates. If RTIs are taken sufficiently frequently, then the virus is theoretically eliminated, regardless of PI frequency. However, if PIs are taken frequently, but RTIs are taken infrequently, then the implicit and explicit models may produce different results.

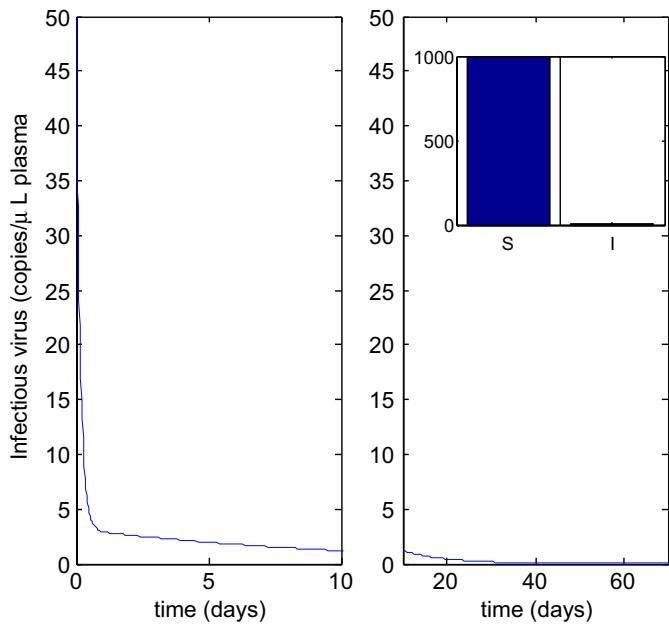


Fig. 2. PI-only therapy, using the implicit model, with efficacy $\varepsilon_P = 0.75$. Other parameters were $n_I = 62.5 \text{ day}^{-1}$, $\omega = 0.05$, $d_V = 3 \text{ day}^{-1}$, $r_I = 0.0032 \text{ day}^{-1}$, $\lambda = 100 \text{ cells } \mu\text{L}^{-1} \text{ day}^{-1}$, $\varepsilon_R = 0$, $d_S = 0.1 \text{ day}^{-1}$, $d_I = 0.5 \text{ day}^{-1}$ (taken from Smith and Wahl, 2004 where appropriate). Initial conditions were $V_I(0) = 50 \text{ virions } \mu\text{L}^{-1}$, $T_S(0) = 1000 \text{ cells } \mu\text{L}^{-1}$ and all other initial conditions zero. In this case, high-efficacy PI-only therapy leads to theoretical elimination of the virus. Inset: equilibrium CD4^+ T cell counts are high for susceptible and low for infected cells.

0.0043 copies μL^{-1}) and a high T cell count for noninfected cells (approximately 999.2 cells μL^{-1} , compared to a baseline of 1000 cells μL^{-1} for the uninfected patient).

In Fig. 3, the same parameters were used where equivalent, and the PI was given three times daily (the maximum daily dosage for any single drug or fixed-dose combination; see Calmy et al., 2007), resulting in a value of $P_{av} = 6.57$. Unlike the implicit model, the infectious viral load was significant (approximately 130 copies μL^{-1} , similar to the viral load without treatment) and the uninfected T cell counts were low (approximately 200 cells μL^{-1}).

Fig. 4 demonstrates how the stable viral load in the implicit model depends on the efficacy of the drugs. The nontrivial steady state is positive for a range of values of ε_R and ε_P , but as either $\varepsilon_R \rightarrow 1$ or $\varepsilon_P \rightarrow 1$, the nontrivial steady state exchanges stability with the trivial steady state and thereafter becomes negative.

Fig. 5 demonstrates how the stable viral load in the explicit model depends on the mean concentration of the drugs. In this case, the virus is eliminated as R_{av} increases, regardless of whether PIs are present or not. However, if RTIs are absent, then the virus remains at untreated levels, even if P_{av} becomes large.

7. Discussion

Implicitly modelling the uptake of antiretroviral drugs may result in an overconfidence in the ability of PI-only

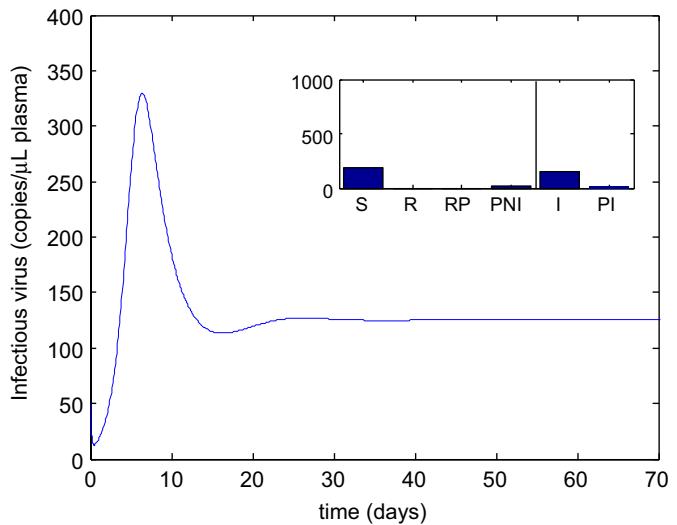


Fig. 3. PI-only therapy, using the explicit model. All equivalent parameters were as in Fig. 2. Remaining parameters were $r_P = 0.127 \mu\text{M}^{-1} \text{ day}^{-1}$, $r_R = 56.1 \mu\text{M}^{-1} \text{ day}^{-1}$, $m_R = 4.16 \text{ day}^{-1}$, $m_P = 8.52 \text{ day}^{-1}$, $d_P = 8.32 \text{ day}^{-1}$, $P^i = 11.6 \mu\text{M}$ (taken from Smith and Wahl, 2004), resulting in a mean PI concentration value of $P_{av} = 6.57$. Initial conditions were as in Fig. 2. Unlike Fig. 2, high-frequency PI-only therapy does not lead to elimination of the virus. Inset: equilibrium CD4^+ T cell counts are low for susceptible and infected cells and zero for all other cells.

therapy to combat HIV. Altering the traditional models only slightly, to include the explicit compartments of drug-inhibited T cells, results in a qualitative change in outcome for this line of therapy. Whereas RTIs prevent infection of a cell (whether used in conjunction with PIs or alone), PIs allow a cell to become infected. When the RTI wears off, the cell can only return to a noninfected state, but when the PI wears off, the cell may have already become infected. This is a consequence of the RTI and PI drug mechanisms. In particular, if RTIs are absent, then the only nonzero, noninfected cells are P_{NI} , which are themselves entirely susceptible to infection.

Intuitively, for the implicit model, as the efficacy of PIs approach 1 (in the absence of RTIs), the production of infectious virions (and hence infected T cells) is significantly reduced, but the susceptible cells are not driven towards zero. Conversely, for the explicit model, as PI dosing approaches infinity (in the absence of RTIs), most T cells become inhibited with the PI, but it only takes one virus particle to infect them. Once infected, these cells will oscillate between cells that produce infectious virions and cells that produce noninfectious virions, depending on the uptake and waning rates of the PI. This drives the noninfected cells towards zero. Once infected, the death rate of a such a cell—whether inhibited with PIs or not—is high. It follows that highly efficacious PI-only therapy may result in an abundance of susceptible cells in the implicit model, but an abundance of infected cells in the explicit model.

Thus, the traditional (implicit) method of modelling the efficacy of drugs may lead to an overconfidence in the

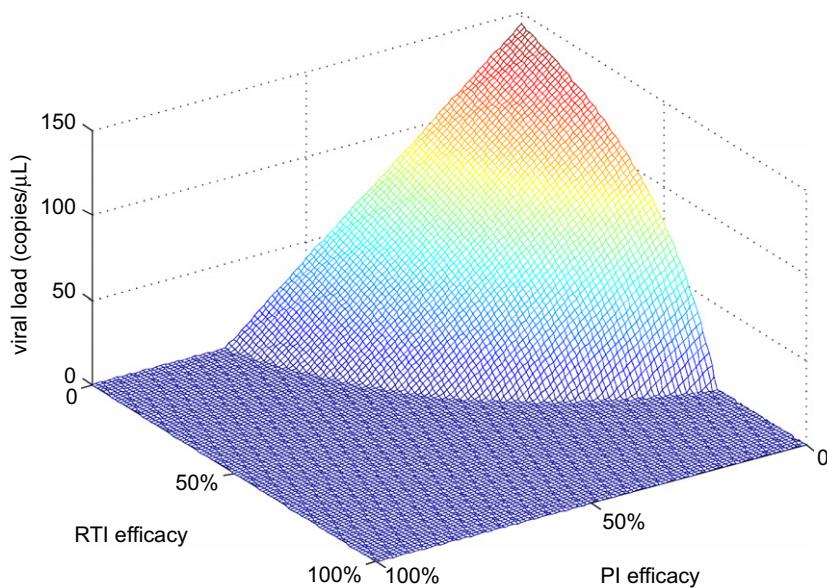


Fig. 4. Steady state viral load for the implicit model, as the efficacy of each drug varies. If both drugs are nonefficacious, then the nontrivial equilibrium is stable and the viral load is high. As the efficacy of each drug rises, the magnitude of the stable viral load decreases until the virus is eliminated. There is a critical value of each efficacy where a transcritical bifurcation occurs; at these points, the nontrivial equilibrium loses its stability and the trivial equilibrium becomes stable. The viral load at this point coalesces with the disease-free steady state; thereafter, the nontrivial viral load is negative. Parameters are as in Fig. 2. Note that this graph measures only the infectious viral load.

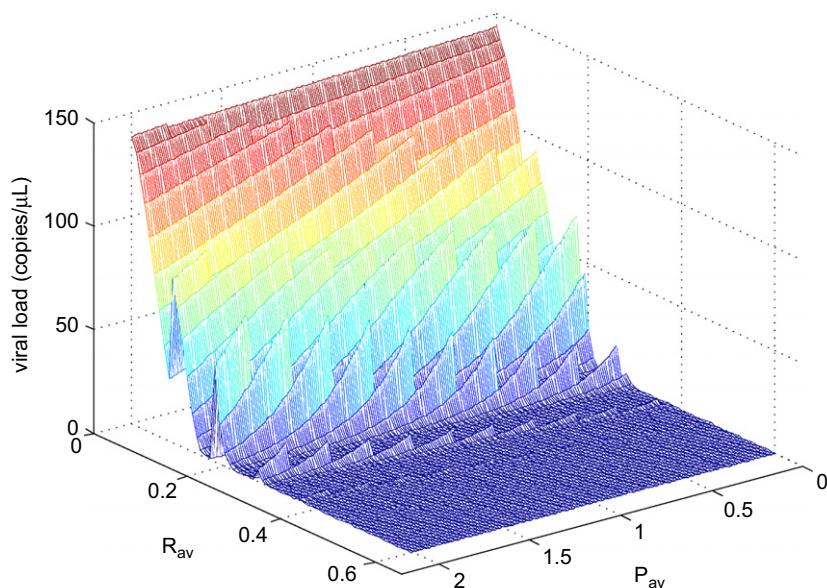


Fig. 5. Steady state viral load for the explicit model, as the mean concentration of each drug varies. If both drugs are absent, then the nontrivial equilibrium is stable and the viral load is high. As the concentration of RTIs increases, the magnitude of the stable viral load decreases until the virus is eliminated; this occurs whether PIs are present or absent. However, if RTIs are absent, the resulting viral load will be high, regardless of PI concentration and in contrast to Fig. 4. Parameters are as in Fig. 3. Note that this graph measures only the infectious viral load. (The jagged edges are due to limitations in the numerical software.)

ability of PIs to deal with the virus. While it is possible to choose parameters to ensure that PI-only therapy does lead to theoretical elimination of the virus in the explicit model (see [Smith and Wahl, 2004](#)), PI-only therapy will not eliminate the virus in all cases and, in fact, may not lead to CD4⁺ T cell counts much larger than that of no therapy at

all (Figs. 3 and 5). Critically, this means that the traditional model predicts a long-term beneficial outcome for the patient, whereas the explicit model predicts that such therapy may ultimately kill the patient.

Mathematically, the implicit model determines the stability, or not, of the trivial (disease-free) equilibrium,

compared to the endemic equilibrium. Conversely, in the explicit model, the trivial equilibrium is always unstable, for all realistic parameters, but when $\tau \rightarrow 0$, a new, stable, disease-free equilibrium (with $T_S = 0$) is approached. However, as $\sigma \rightarrow 0$, no such disease-free equilibrium may be approached. Thus, while results in Section 3 are independent of parameter estimates, results in Section 4 are independent of parameter estimates only when RTIs are involved (see Theorem 4.1). If RTIs are absent, then results depend enormously on the choice of parameters; while sample parameters from the literature illustrate treatment failure (Section 6), other parameter choices will lead to treatment success (see Smith and Wahl, 2004 for more discussion).

While neither model is an exact representation of the drug dynamics in question, the explicit model captures more of the reality of the situation than the implicit model and approximates more complex models from the literature. The two models are equivalent in the absence of drugs and have similar outcomes when the RTI is included (with or without the presence of the PI), but they produce qualitatively different results when the PI acts alone. Since the explicit model captures more (although not all) of the dynamics, this suggests that models that explicitly account for the impact of drug dynamics on T cells are more reliable predictors of therapy outcomes.

Even with a relatively low efficacy of 75%, the implicit model predicts that PI-only therapy will lead to near-total reduction in the viral load (less than 0.0043 copies μL^{-1}), with high noninfected CD4 $^{+}$ T cell counts (Fig. 2). However, the same basic model using the same parameters but with explicit drug dynamics produced high viral load (approximately 130 copies μL^{-1}) and low CD4 $^{+}$ counts for both infected and noninfected cells (Fig. 3). Fortunately, PI-sparing therapy has recently been advocated, in both the developing and developed world (Moyle, 2003). In particular, RTI-only therapy is underway in antiretroviral rollout programs in Africa, with PIs held back for second-line therapy (Carpenter, 2006).

These theoretical predictions may appear to be at odds with clinical evidence that PIs control HIV more effectively (Ghani et al., 2001). This is because this result pertains to all possible drugs which either prevent infection or prevent virion production and compares these two strategies of defense, in the absence of resistance. The effects of resistance should not be discounted, but the development of new drugs allows for the fact that mutation-resistant cocktails may now consist of numerous RTIs, numerous PIs or a combination of both. Side effects are also an important issue (Krakovska and Wahl, 2007; Moyle, 2003) that may lead to one regimen being chosen over another.

Preliminary experimental studies of PI-only therapy have been carried out in the developed world (Calmy et al., 2007) to reduce drug resistance in the short term, but such therapy has not yet been approved. In that study, 42 patients taking one or two PIs were monitored for 105 weeks as part of a larger cohort of patients assessing

virological and immunological safety and activity of nucleoside-RTI-sparing regimens. Other studies have assessed preliminary 24-week trials, demonstrating that immune reconstitution and median viral load decreased (Staszewski et al., 2003a, b; Raguin et al., 2004), although these studies were mostly performed on subjects who had a heavy history of treatment before undertaking this regimen. Such experiments were devised only for short time periods and did not assess the long-term impact of PI-only therapy. Furthermore, it should be stressed that model (2.2) does not necessarily predict treatment failure for PI-only therapy, only that it is a possibility, whereas model (2.1) does not allow for such a possibility.

The explicit model examined here is a continuous version of the previously published model in Smith and Wahl (2004). This was chosen to deliberately avoid the use of impulsive differential equations, partly for clarity of argument and partly to illustrate the robustness of the results with respect to model choice (thus, the implicit model here also differs slightly from similar models in the literature; see Perelson and Nelson (1999), Wu and Ding (1999), Nelson et al. (2001, 2000), and Nowak and May (2000)). The difference lies in the structuring of the drug-inhibited cells via compartment modelling, compared to parameter variation in the implicit model. The inclusion of the $-r_1 T_S V_I$ term accounts for the loss of virions due to infection; however, it makes little overall difference in the qualitative results. While the analysis in Section 4 is similar to the analysis in Smith and Wahl (2004), the model was simplified to a continuous version to (a) avoid the complications added by imposing discontinuities into the model and (b) examine the underlying dynamics in the model. Thus, the implicit and explicit models are both new and the analysis of each model is also new, although similar analyses of similar models have also been carried out in other works.

Generalising the explicit model, similar results will occur for any model that has unbounded drug levels as either the dosage or dosing frequency increases without bound and where the susceptible cells are driven towards zero, but cells inhibited with RTIs (both with and without PIs) approach the levels in the uninfected immune system. In such cases, RTIs could theoretically eliminate the virus, with or without PIs. Conversely, PIs alone may not control the virus without further restrictions on the parameters.

In summary, mathematical models of HIV should account for the explicit dynamics of T cells. In particular, the clinical impact of PI-only therapy must be urgently re-examined to determine long-term therapy outcomes, if such outcomes have been based on overly simplistic modelling.

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