



# Paradoxical suppression of poly-specific broadly neutralizing antibodies in the presence of strain-specific neutralizing antibodies following HIV infection

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## ABSTRACT

One of the first immunologic responses against HIV infection is the presence of neutralizing antibodies that seem able to inactivate several HIV strains. Moreover, *in vitro* studies have shown the existence of monoclonal antibodies that exhibit broad crossclade neutralizing potential. Yet their number is low and slow to develop *in vivo*. In this paper, we investigate the potential benefits of inducing poly-specific neutralizing antibodies *in vivo* throughout immunization. We develop a mathematical model that considers the activation of families of B lymphocytes producing poly-specific and strain-specific antibodies and use it to demonstrate that, even if such families are successful in producing neutralizing antibodies, the competition between them may limit the poly-specific response allowing the virus to escape. We modify this model to account for viral evolution under the pressure of antibody responses in natural HIV infection. The model can reproduce viral escape under certain conditions of B lymphocyte competition. Using these models we provide explanations for the observed antibody failure in controlling natural infection and predict quantitative measures that need to be satisfied for long-term control of HIV infection.

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## 1. Introduction

The ability of human immunodeficiency virus (HIV) to persist in an infected individual and eventually cause AIDS is dependent on its ability to avoid immune responses. Many factors facilitate virus persistence, from high genetic diversity and evolution (Walker and Korber, 2001) to the ability to stay latent in the body (Blankson et al., 2002), to the infection of immune cells, whose activation by vaccine candidates leads to an increase in the target cell population (Stebbing et al., 2004). The large-scale vaccine clinical trials (AIDSVax (Gilbert et al., 2005), STEP (Priddy et al., 2008) and RV144 (Rerks-Ngarm et al., 2009) that were aimed at stimulating both arms of the adaptive immune system: the antibody-mediated, the cell-mediated and combined antibody and cell-mediated immunity showed limited clinical efficacy (Fauci et al., 2008).

We study the roles of antibodies in limiting virus replication during HIV infection. Antibodies directed against HIV structural proteins are detected in the body within a few weeks following a

natural infection (Aasa-Chapman et al., 2004; Richman et al., 2003). Only a small fraction of them, however, neutralize the virus, which escapes recognition by ensuing reduced accessibility to antibody-binding sites, heavy glycosylation of the envelope proteins and rapid mutation (Douek et al., 2006; Parren et al., 1999; Richman et al., 2003; Wyatt and Sodroski, 1998). Despite the hurdles the immune system has to overcome, neutralizing antibodies do develop during natural infection (Burton et al., 2005; Haynes and Montefiori, 2006; Pantophlet and Burton, 2006). Most of them are strain-specific and preferentially recognize and inhibit preceding but not current viral strains (Burton et al., 2004; Richman et al., 2003; Wei et al., 2003). To completely control infection, the immune system has to find ways to elicit potent, high affinity antibody responses capable of broad neutralization, viral inactivation and protection against current infection and/or disease (Hone et al., 2002). A limited number of known broadly neutralizing human monoclonal antibodies (2F5, 4E10, b12, 2G12, PG9, PG16 and VRC01) have been identified (Burton et al., 2004; Zhou et al., 2010). They neutralize primary isolates of HIV from different genetic subtypes *in vitro* (Buchacher et al., 1994; Burton et al., 2004; Li et al., 2007), but are very rarely produced *in vivo* (Dhillon et al., 2007), and are, therefore, difficult

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to induce through vaccination. The failure may be due to host regulatory constraints (Haynes et al., 2005), incorrect epitope conformation (Moore et al., 2006), HIV induction of polyclonal B cell activation and terminal differentiation (Levesque et al., 2009), and/or B cell competition (Deem and Lee, 2003; Heyman, 2003).

While many different B cells clones can recognize a given HIV virus strain, only those of high affinity (strain-specific) respond in large numbers to produce neutralizing antibodies. For a series of discrete random infections over time (continuous immunization), competition among B cell clones may lead to the phenomenon of original antigenic sin, where B cells produced in response to a first viral infection can suppress the creation of new immune cells in response to a second infection with a related strain (Deem and Lee, 2003). For a chronic infection with a mutating virus, the original antigenic sin may be limited, since there is enough time for the immune system to create B cells against the new strain. However, there is a time delay in the production of each strain-specific neutralizing antibody that may cause that virus strain to expand at high levels before the antibody can control it (Burton et al., 2004; Richman et al., 2003). Most importantly, the continuous presence of strain-specific antibodies may lead to suppression of the less fit poly-specific B cell clones capable of producing broad neutralizing antibodies. The limitation in number of broadly neutralizing antibodies may represent the greatest weakness of the immune system.

Antibody-mediated immune suppression has been observed during passive administration of antibodies as well. In this situation, B cells are prevented from stimulation through a reduction of available antigenic determinants (Heyman, 2003). Finally, studies of Hepatitis C chronic infections have shown that strain-specific antibodies may inhibit the development of poly-specific antibodies by preventing them from recognizing antigen (Zhang et al., 2004).

To investigate the competition among strain-specific and poly-specific antibodies, we developed mathematical models of virus-antibody interactions during both immunization and natural infection with HIV. We start with the assumption that the immune system produces both strain-specific and poly-specific, cross reactive, neutralizing antibodies. The strain-specific and poly-specific neutralizing antibodies target variable (unique to each variant) or conserved (shared among variants) epitopes, respectively, on the virus envelope. The governing hypothesis is that while B cells producing both (strain-specific and poly-specific) neutralizing antibodies are activated during the infection, those producing poly-specific broadly neutralizing antibodies are made inefficient and consequently kept at undetectable levels. This process is mediated by their competition with the B cells that produce more fit strain-specific antibodies with which they share antigenic stimulation, kinetic prolongation, space in the lymph nodes and T cell conjugates.

We use information from previous modeling studies of HIV viral infection (Ho et al., 1995; Nowak and May, 2000; Perelson et al., 1996, 1997), cellular immune responses (Ciupe et al., 2006; Stafford et al., 2000), antibody formation (Oprea and Perelson, 1996; Tomaras et al., 2008) and competition (Antia et al., 1998; Boer et al., 2001; Borghans et al., 1999; Leenheer and Pilyugin, 2008) to derive and analyze models of the interaction between virus and neutralizing antibodies. Our aim is to determine the parameter regimes that lead to antibody failure and viral persistence, and to predict ways to reverse these phenomena.

The paper is structured as follows. In Section 2 we develop and analyze the mathematical model describing the interaction between families of B lymphocytes producing poly-specific and strain-specific neutralizing antibodies following continuous immunization with several HIV variants. In Section 3 we expand the model to account for natural infection and viral evolution; their analysis is presented in two appendices. In Section 4 we

present numerical results of the two models. We conclude with a discussion.

## 2. Model of antibody responses following continuous immunization

Let  $V = (V_1, V_2, \dots, V_n)^T$  be viruses of specificity  $1 \leq i \leq n$ ,  $A = (A_1, A_2, \dots, A_n)^T$  be strain-specific neutralizing antibodies of specificity  $1 \leq i \leq n$ , and  $A_0$  be the poly-specific broadly neutralizing antibody. Viruses are introduced into the body at times  $t_i$ ,  $V_i(t_i) = V_{i,0}$ , and do not mutate. We coarse-grain the viral life-cycle, aggregating the processes of infection, integration and host-cell viral production into a simple replication model in which viruses replicate with different viral fitness per-capita rates  $r_i$ . We treat the dynamics of antibody production similarly, assuming that antibody concentration is in quasi-equilibrium with the B cell population that produces them, and without representing the component subprocesses such as activation, differentiation and antibody secretion. The concentration of antibody specific to viral strain  $i$  is denoted  $A_i$ , and that of poly-specific antibody  $A_0$ . We only consider the fraction of the produced antibodies that has neutralizing function. In the presence of neutralizing antibodies viruses are removed at rates  $K$  and  $K_0$  by the strain-specific and poly-specific neutralizing antibodies, respectively. We assume that the removal rates are independent of strain and that  $K > K_0$ .

Strain-specific neutralizing antibodies are elicited at rate  $\lambda$  by the viral strain to which they are specific. Poly-specific neutralizing antibodies are elicited at rate  $\lambda_0$  by all viral strains. We denote by  $a$  the differences between B cells proliferation and death rates, effectively treating the antibody at quasi-equilibrium with these cells as surviving at that rate. Finally, all B cells compete with each other (within and between clones) for antigen, space in the lymph nodes, and conjugate T-cell help. The strength of this competition is governed by parameter  $\beta$ .

The dynamics of the system is described by the following equations:

$$\begin{aligned} \frac{dV_i}{dt} &= (r_i - KA_i - K_0A_0)V_i, \\ \frac{dA_i}{dt} &= \lambda V_i + A_i(a - \beta A_T), \\ \frac{dA_0}{dt} &= \lambda_0 T + A_0(a - \beta A_T), \end{aligned} \quad (1)$$

with  $V_i(t_i) = V_{i,0}$ ,  $A_i(t_i) = 0$ ,  $A_0(t_1) = 0$ ,  $T = 1^T V$  and  $A_T = A_0 + 1^T A$ .

In Section 2.1 we investigate the system dynamics for the case where strain-specific B cells are absent. In Section 2.2 we explore the dynamics when both poly-specific and strain-specific antibodies are produced in response to infection.

### 2.1. Virus dynamics during poly-specific antibody responses

Let us consider the case where viruses  $V = (V_1, V_2, \dots, V_n)^T$  are introduced into the body at times  $t = (t_1, t_2, \dots, t_n)^T$ , independent of each other. The immune system reacts by producing poly-specific antibodies,  $A_0$ , at rate  $\lambda_0$ , which neutralize all virus strains at rate  $K_0$ . For simplicity, we assume that all viral strains are equally adapted to the host and they replicate at the same rate  $r_i = r$  independent of the strain  $i$ . System (1) becomes

$$\begin{aligned} \frac{dV}{dt} &= (r - K_0A_0)V, \\ \frac{dA_0}{dt} &= \lambda_0 T + A_0(a - \beta A_0), \end{aligned} \quad (2)$$

with  $V_i(t_i) = V_{i,0}$  and  $A_0(t_1) = 0$ .

2.1.1. Steady-state analysis

We investigate the long-run behavior of system (2) when all viruses are present in the population. To eliminate the discontinuities in the model, we consider that the system starts at time  $t=t_n$  leading to initial conditions  $V_i(t_n)=V_{i,n} > 0$  and  $A_0(t_n) > 0$ . The steady-states of system (2) can be divided into three classes:

1. The no-infection steady-state  $S_1^1 = (0, 0, \dots, 0)$ .
2. The viral clearance steady-state  $S_2^1 = (0, 0, \dots, 0, a/\beta)$ .
3. The chronic infection hyperplane  $S_3^1 = (\bar{V}_1, \bar{V}_2, \dots, \bar{V}_n, r/K_0)$ ,

which exists for  $r > K_0 a/\beta$  and

$$\bar{T} = \sum_{i=1}^n \bar{V}_i = \frac{r}{K_0 \lambda_0} \left( \beta \frac{r}{K_0} - a \right). \tag{3}$$

Let us study the asymptotic behavior of the steady-states. The Jacobian matrix corresponding to our system is

$$J = \begin{pmatrix} r - K_0 \bar{A}_0 & 0 & \dots & 0 & -K_0 \bar{V}_1 \\ 0 & r - K_0 \bar{A}_0 & \dots & 0 & -K_0 \bar{V}_2 \\ \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & r - K_0 \bar{A}_0 & -K_0 \bar{V}_n \\ \lambda_0 & \lambda_0 & \dots & \lambda_0 & a - 2\beta \bar{A}_0 \end{pmatrix}. \tag{4}$$

**Proposition 1.** (a) The infection free steady-state  $S_1^1$  is always unstable.

(b) The viral clearance steady-state  $S_2^1$  is asymptotically stable if

$$r < K_0 \frac{a}{\beta} \tag{5}$$

and unstable if the inequality is reversed.

(c) If

$$r > K_0 \frac{a}{\beta} \tag{6}$$

the chronic infection hyperplane  $S_3^1$  exists and each of its steady-states has zero eigenvalues.

**Proof.** (a) The characteristic equation for the steady-state  $S_1^1$ ,

$$(r - \lambda)^n (a - \lambda) = 0, \tag{7}$$

has positive eigenvalues  $\lambda_{1,2,\dots,n} = r$  and  $\lambda_{n+1} = a$ . Therefore, the infection free steady-state is always unstable.

(b) The characteristic equation for the steady-state  $S_2^1$ ,

$$\left( r - K_0 \frac{a}{\beta} - \lambda \right)^n (\lambda + a) = 0 \tag{8}$$

has eigenvalues

$$\lambda_{1,2,\dots,n} = r - K_0 \frac{a}{\beta} \tag{9}$$

and

$$\lambda_{n+1} = -a. \tag{10}$$

When  $r < K_0 a/\beta$ , the eigenvalues are negative and the viral clearance steady-state is asymptotically stable. If the inequality is reversed, the eigenvalues are positive and the viral clearance steady-state is unstable. In other words, when the antibody response at steady-states exceeds the viral production, the virus will be cleared otherwise the virus persists.

(c) The characteristic equation for the steady-state  $S_3^1$ ,

$$A^{n-1} \left( A^2 - \left( a - 2\beta \frac{r}{K_0} \right) A + r \left( \beta \frac{r}{K_0} - a \right) \right) = 0 \tag{11}$$

has eigenvalues

$$\lambda_{1,\dots,n-1} = 0,$$

$$\lambda_{n,n+1} = \frac{a - 2\beta \frac{r}{K_0} \pm \sqrt{\left( a - 2\beta \frac{r}{K_0} \right)^2 - 4r \left( \beta \frac{r}{K_0} - a \right)}}{2}. \tag{12}$$

Although the latter pair of eigenvalues are negative for  $r > K_0 a/\beta$ , there are always zero eigenvalues, and hence we cannot decide stability of the chronic hyperplane based on linear analysis.  $\square$

2.1.2. Global stability

**Proposition 2.** When  $r < K_0 a/\beta$ ,  $S_2^1$  is globally asymptotically stable.

**Proof.** Consider the function

$$W(V_1, V_2, \dots, V_n, A_0) = \sum_{i=1}^n \int_0^{V_i} d\tau + \frac{K_0 \bar{A}_0^{-2}}{\lambda_0} \int_{\bar{A}_0}^{A_0} \left( \frac{1}{\bar{A}_0} - \frac{1}{\tau} \right) d\tau. \tag{13}$$

Note that for positive  $(V_1, \dots, V_n, A_0) > 0$ ,  $W$  is positive semi-definite and zero only if  $(V_1, V_2, \dots, V_n, A_0) = (0, 0, \dots, 0, a/\beta)$ . Moreover,

$$\begin{aligned} \dot{W} &= \sum_{i=1}^n V_i \left( r - K_0 A_0 + K_0 \bar{A}_0 - K_0 \frac{\bar{A}_0^2}{A_0} \right) - \frac{K_0 \bar{A}_0}{\lambda_0} \beta (A_0 - \bar{A}_0)^2 \\ &= \sum_{i=1}^n V_i \left( r - K_0 \bar{A}_0 - K_0 \left( A_0 - 2\bar{A}_0 + \frac{\bar{A}_0^2}{A_0} \right) \right) - \frac{K_0 \bar{A}_0}{\lambda_0} \beta (A_0 - \bar{A}_0)^2 \\ &= \sum_{i=1}^n V_i (r - K_0 \bar{A}_0) - \sum_i V_i \frac{K_0}{A_0} (A_0 - \bar{A}_0)^2 - \frac{K_0 \bar{A}_0}{\lambda_0} \beta (A_0 - \bar{A}_0)^2. \end{aligned} \tag{14}$$

When  $r < K_0 a/\beta$  is satisfied  $\dot{W}$  is negative semi-definite, and the largest invariant set where  $\dot{W} = 0$  is  $\{(0, 0, \dots, 0, a/\beta)\}$ . Since  $\dot{W} \leq 0$ , and  $W$  is a proper function (i.e. for each  $c$ , the set  $\{x \geq 0 | W(x) \leq c\}$  is compact) we have that all solutions of (2) are bounded. Therefore, from Lasalle's invariance principle,  $S_2^1$  is globally asymptotically stable.  $\square$

**Proposition 3.** When  $r > K_0 a/\beta$ ,  $S_3^1$  is globally asymptotically attractive.

**Proof.**  $T = \sum_{i=1}^n V_i$  satisfies system

$$\frac{dT}{dt} = T(r - K_0 A_0),$$

$$\frac{dA_0}{dt} = \lambda_0 T + A_0(a - \beta A_0). \tag{15}$$

Consider the function

$$W(T, A_0) = \lambda_0 \bar{T} \int_{\bar{T}}^T \left( \frac{1}{\bar{T}} - \frac{1}{\tau} \right) d\tau + \int_{\bar{A}_0}^{A_0} (K_0 \tau - r) d\tau, \tag{16}$$

where  $\bar{A}_0 = r/K_0$  and  $\bar{T} = (r/\lambda_0 K_0)(\beta r/K_0 - a)$ .

Note that  $W$  is positive semi-definite for  $(T, A_0) > 0$ , and zero at  $(\bar{T}, \bar{A}_0)$ . Moreover,

$$\begin{aligned} \dot{W} &= \lambda_0 (r - K_0 A_0)(T - \bar{T}) + (\lambda_0 T + A_0(a - \beta A_0))(K_0 A_0 - r) \\ &= (K_0 A_0 - r)(\lambda_0 \bar{T} + A_0(a - \beta A_0)) \\ &= (K_0 A_0 - r)(-\bar{A}_0(a - \beta \bar{A}_0) + A_0(a - \beta A_0)), \end{aligned} \tag{17}$$

where we used that  $\lambda_0 \bar{T} + \bar{A}_0(a - \beta \bar{A}_0) = 0$ . Notice that  $\dot{W}$  is a product of two factors, each of which has a single root at  $A_0 = \bar{A}_0$ . For  $A_0 \neq \bar{A}_0$ , these factors have opposite signs, and thus  $\dot{W} \leq 0$ . Moreover, the largest invariant set where  $\dot{W} = 0$  is  $\{(\bar{T}, \bar{A}_0)\}$ . Since  $\dot{W} \leq 0$ , and  $W$  is a proper function (i.e. for each  $c$ , the set  $\{x \geq 0 | W(x) \leq c\}$  is compact) we have that all solutions of (15) are bounded. From Lasalle's invariance principle, the hyperplane  $S_3^1$  is globally attractive.  $\square$

2.2. Virus dynamics in the presence of competition between strain-specific and poly-specific antibody responses

Let us consider the general case given by the system (1) where immunization with viruses  $V = (V_1, V_2, \dots, V_n)^T$  at times  $t = (t_1, t_2, \dots, t_n)^T$  leads to production of both poly-specific and strain-specific neutralizing antibodies,  $A_0$  and  $A = (A_1, \dots, A_n)^T$  respectively. As before, we assume that all viral strains replicate at the same rate  $r_i = r$  independent of the strain  $i$ . We study the viruses' long term behavior as strain-specific and poly-specific neutralizing antibodies compete with each other for resources.

2.2.1. Steady-state analysis

As before, we eliminate the discontinuities in the model, by considering system's initial condition for time  $t = t_n$ , where all viruses are already present in the population. The steady-states can be divided into three classes:

1. The infection free steady-state  $S_1^2 = (0, 0, \dots, 0, 0, 0, \dots, 0, 0)$ .
2. The clearance hyperplane  $S_2^2 = (0, 0, \dots, 0, \bar{A}_1, \bar{A}_2, \dots, \bar{A}_n, \bar{A}_0)$ , where  $\bar{A}_i \geq 0$  for  $i = 1, \dots, n$ , and  $\bar{A}_0 \geq 0$  are any vector, respectively number, such that  $\bar{A}_T = a/\beta$ . This set of steady-states is the intersection of a hyperplane of dimension  $(2n+1) - n - 1 = n$  in  $\mathbb{R}^{2n+1}$ , and the non-negative orthant  $\mathbb{R}_+^{2n+1}$ .
3. Let  $\emptyset \neq I \subset \{1, 2, \dots, n\}$ , and assume that  $\#(I) = m \geq 1$ . Then there are chronic steady-states  $S_3^2 = (\bar{V}_1, \bar{V}_2, \dots, \bar{V}_n, A_1, A_2, \dots, \bar{A}_n, \bar{A}_0)$  with  $(\bar{V}_i, \bar{A}_i) > 0$  for all  $i \in I$  and  $\bar{V}_j = \bar{A}_j = 0$  for all  $j \notin I$  if and only if

$$r > \left( \frac{mK_0\lambda_0 + K\lambda}{m(\lambda + \lambda_0)} \right) \frac{a}{\beta}. \tag{18}$$

The nonzero components of such steady-states are given by

$$\bar{A} = \bar{A}_i = \frac{\lambda r}{mK_0\lambda_0 + K\lambda}, \quad \bar{V}_i = \frac{r}{mK_0\lambda_0 + K\lambda} \left( \beta \frac{mr(\lambda + \lambda_0)}{mK_0\lambda_0 + K\lambda} - a \right) \text{ for all } i \in I, \tag{19}$$

$$\bar{A}_0 = \frac{m\lambda_0 r}{mK_0\lambda_0 + K\lambda}.$$

**Proposition 4.** (a) The infection free steady-state  $S_1^2$  is always unstable.

(b) The viral clearance hyperplane  $S_2^2$  has zero eigenvalues.

(c) For every  $m = 1, 2, \dots, n-1$  for which (18) holds, there are  $\binom{n}{m}$  corresponding steady-states  $S_3^2$  of form (19) having exactly  $m$  virus strains and corresponding antibodies present, and they are all unstable. Moreover, there is a unique steady-state of form (19) having exactly  $m=n$  virus strains and corresponding antibodies present, and it is asymptotically stable.

**Proof.** The Jacobian matrix corresponding to the linearized system is

$$J = \begin{pmatrix} X_1 & 0 & \dots & 0 & -K\bar{V}_1 & 0 & \dots & 0 & -K_0\bar{V}_1 \\ 0 & X_2 & \dots & 0 & 0 & -K\bar{V}_2 & \dots & 0 & -K_0\bar{V}_2 \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & X_n & 0 & 0 & \dots & -K\bar{V}_n & -K_0\bar{V}_n \\ \lambda & 0 & \dots & 0 & Y_1 & -\beta\bar{A}_1 & \dots & -\beta\bar{A}_1 & -\beta\bar{A}_1 \\ 0 & \lambda & \dots & 0 & -\beta\bar{A}_2 & Y_2 & \dots & -\beta\bar{A}_2 & -\beta\bar{A}_2 \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & \lambda & -\beta\bar{A}_n & -\beta\bar{A}_n & \dots & Y_n & -\beta\bar{A}_n \\ \lambda_0 & \lambda_0 & \dots & \lambda_0 & -\beta\bar{A}_0 & -\beta\bar{A}_0 & \dots & -\beta\bar{A}_0 & Z \end{pmatrix}, \tag{20}$$

where for  $i = 1, 2, \dots, n$ ,

$$X_i = r - (K_0\bar{A}_0 + K\bar{A}_i),$$

$$Y_i = a - \beta(\bar{A}_T + \bar{A}_i),$$

$$Z = a - \beta(\bar{A}_T + \bar{A}_0). \tag{21}$$

(a) The characteristic equation of the steady-state  $S_1^2$ ,

$$(r - \lambda)^n (a - \lambda)^{n+1} = 0 \tag{22}$$

has positive eigenvalues  $\lambda_{1,2,\dots,n} = r$  and  $\lambda_{n+1,\dots,2n+1} = a$ . Therefore the infection free steady-state is always unstable.

(b) The characteristic equation of the hyperplane  $S_2^2$ ,

$$\lambda^n (a + \lambda) \prod_{i=1}^n \{\lambda - (r - K_0\bar{A}_0 - K\bar{A}_i)\} = 0 \tag{23}$$

has eigenvalues  $\lambda_{1,2,\dots,n} = 0$ ,  $\lambda_{n+1,\dots,2n} = r - K_0\bar{A}_0 - K\bar{A}_i$ ,  $\lambda_{2n+1} = -a$ . Therefore,  $S_2^2$  is unstable when  $r > K_0\bar{A}_0 + K\bar{A}_i$  for at least one  $i$ . The stability of any steady-state that belongs to the hyperplane  $S_2^2$  cannot be determined from linear analysis.

(c) If (18) holds for  $m=1$ , then it also holds for all  $m=2, 3, \dots, n$ . For each  $m$ , there will be steady-states with exactly  $\binom{n}{m}$  virus strains and corresponding antibodies present that satisfy equalities (19).

We investigate the local stability of the chronic steady-states for which  $m$  strains persist and  $n-m$  strains are cleared. The steady-states have the characteristic equation

$$\det(J - \lambda I_{2n+1}) = \left( \lambda - \frac{rK\lambda}{mK_0\lambda_0 + K\lambda} \right)^{n-m} \det \begin{pmatrix} x & y & \dots & y & z \\ y & x & \dots & y & z \\ \dots & \dots & \dots & \dots & \dots \\ y & x & \dots & x & z \\ w & w & \dots & w & v \end{pmatrix} = \left( \lambda - \frac{rK\lambda}{mK_0\lambda_0 + K\lambda} \right)^{n-m} (y-x)^{m-1} \{(x+(m-1)y)v + mzw\}, \tag{24}$$

where

$$x = \lambda^2 + (\beta\bar{A} + \beta\bar{A}_T - a)\lambda + K\bar{A}(\beta\bar{A}_T - a),$$

$$y = \beta\bar{A}\lambda,$$

$$z = \bar{A}(\beta\lambda + K_0(\beta\bar{A}_T - a)),$$

$$w = \bar{A}_0(\lambda - a + \beta\bar{A}_T),$$

$$v = n\bar{A}(\lambda - a + \beta\bar{A}_T), \tag{25}$$

which simplifies to

$$\det(J - \lambda I_{2n+1}) = \left( \lambda - \frac{rK\lambda}{mK_0\lambda_0 + K\lambda} \right)^{n-m} (\lambda + \beta\bar{A}_T - a) \times (\lambda^2 + (\beta\bar{A}_T - a)\lambda + K\bar{A}(\beta\bar{A}_T - a))^{m-1} \times (\bar{A}\lambda^2 + (\beta\bar{A}_T - a + m\beta\bar{A} + \beta\bar{A}_0)\lambda + r(\beta\bar{A}_T - a)). \tag{26}$$

The first  $n-m$  eigenvalues  $\lambda_{1,\dots,n-m} = rK\lambda / (mK_0\lambda_0 + K\lambda)$  are positive. Therefore the chronic steady-states  $S_3^2$  for which  $m$  strains persist and  $n-m$  strains are cleared are always unstable.

Finally, we will show that the unique steady-state with  $m=n$  virus strains and corresponding antibodies present is asymptotically stable.

$S_3^2$ , satisfying (19) for  $m=n$ , has the characteristic equation

$$\det(J - \lambda I_{2n+1}) = \det \begin{pmatrix} x & y & \dots & y & z \\ y & x & \dots & y & z \\ \dots & \dots & \dots & \dots & \dots \\ y & x & \dots & x & z \\ w & w & \dots & w & v \end{pmatrix} = (y-x)^{n-1} \{ (x+(n-1)y)v + nzw \}, \tag{27}$$

where

$$\begin{aligned} x &= \lambda^2 + (\beta\bar{A} + \beta\bar{A}_T - a)\lambda + K\bar{A}(\beta\bar{A}_T - a), \\ y &= \beta\bar{A}\lambda, \\ z &= \bar{A}\{\beta\lambda + K_0(\beta\bar{A}_T - a)\}, \\ w &= \bar{A}_0(\lambda - a + \beta\bar{A}_T), \\ v &= n\bar{A}(\lambda - a + \beta\bar{A}_T), \end{aligned} \tag{28}$$

which simplifies to

$$\det(J - \lambda I_{2n+1}) = (\lambda + \beta\bar{A}_T - a)(\lambda^2 + (\beta\bar{A}_T - a)\lambda + K\bar{A}(\beta\bar{A}_T - a))^{n-1} \times (\bar{A}\lambda^2 + (\beta\bar{A}_T - a + n\beta\bar{A} + \beta\bar{A}_0)\lambda + r(\beta\bar{A}_T - a)). \tag{29}$$

One can show that all eigenvalues have negative real parts provided that  $\beta\bar{A}_T > a$ . Therefore, if the chronic steady-state exists then it is stable. In other words, when the viral production exceeds the combined removal by antibodies the viruses will persist.  $\square$

### 3. Model of antibody responses following natural infection

Model (1) assumes that the viruses are introduced into the host at random times through, for example, a continuous immunization. We are interested in how these results change in an individual chronic HIV infection, where the virus mutates over time. Assuming that a primary infection with  $V_1$  leads to production of strain-specific and poly-specific neutralizing antibodies  $A_1$  and  $A_0$  (for example, the poly-specific production may be caused by previous vaccination), and that  $V_1$  mutates over time into strains  $V_i$  ( $i=2, \dots, n$ ) at rates  $\mu_{ij} > 0$ , which stimulate strain-specific immune cells to produce antibodies,  $A_i$ , model (1) becomes

$$\frac{dV_i}{dt} = r_i \sum_{j=1}^n \mu_{ij} V_j - V_i(KA_i + K_0A_0),$$

$$\frac{dA_i}{dt} = \lambda V_i + A_i(a - \beta A_T),$$

$$\Omega = \frac{\left(\frac{K_0}{K} + \frac{\lambda}{\lambda_0}\right) \left(2\frac{K_0}{K} + \frac{\lambda}{\lambda_0}\right)}{\frac{K_0}{K} \left(1 + \frac{\lambda}{\lambda_0}\right) \left(4\frac{K_0}{K} + 3\frac{\lambda}{\lambda_0} - 2\mu \left(2\frac{K_0}{K} + \frac{\lambda}{\lambda_0}\right) + \sqrt{\left(4\frac{K_0}{K} + 3\frac{\lambda}{\lambda_0} - 2\mu \left(2\frac{K_0}{K} + \frac{\lambda}{\lambda_0}\right)\right)^2 - 8(1-\mu)^2 \left(2\frac{K_0}{K} + \frac{\lambda}{\lambda_0}\right) \left(\frac{K_0}{K} + \frac{\lambda}{\lambda_0}\right)}\right)}, \tag{32}$$

$$\frac{dA_0}{dt} = \lambda_0 T + A_0(a - \beta A_T), \tag{30}$$

with  $V_1(0) = V_{1,0}$ ,  $V_i(0) = A_i(0) = A_0(0) = 0$  for  $i > 2$ .  $Q = \{\mu_{ij}\}_{1 \leq i, j \leq n}$  is a mutation matrix with non-negative off-diagonal entries and columns entries that add up to one. We consider two situations describing HIV evolution over time:

(A) The initial virus strain  $V_1$  mutates to produce virus strain  $V_2$  at rate  $\mu_{12} > 0$ , which mutates to produce virus  $V_3$  at

rate  $\mu_{23} > 0$  and so forth. The mutation is irreversible, and the mutation matrix describing this situation has the form:

$$Q = \begin{pmatrix} 1 - \mu_{12} & 0 & 0 & \dots & 0 \\ \mu_{12} & 1 - \mu_{23} & 0 & \dots & 0 \\ \vdots & \ddots & \ddots & \dots & \vdots \\ 0 & 0 & \dots & \mu_{n-1n} & 1 \end{pmatrix},$$

with  $\mu_{ii+1} < 1$ .

(B) Viruses mutate forward and backward randomly with the additional assumption that the mutation matrix  $Q = \{\mu_{ij}\}_{1 \leq i, j \leq n}$  is irreducible.

Note that  $Q$  has a simple dominant eigenvalue 1 with a corresponding non-negative eigenvector  $z \geq 0$  such that  $Qz = z$ . In case (1)  $z$  is an entry-wise positive vector (by the Perron-Frobenius theorem) and in case (2)  $z = (0, 0, \dots, 0, 1)^T$ .

As before we assume that all viruses replicate at the same rate  $r_i = r$ . We perform stability analysis of model (30) for the mutation matrix  $Q$  satisfying condition (A). When the antibody response is poly-specific all viruses are cleared when  $r < K_0a/\beta$  and persist otherwise. This relation is independent on the mutation matrix  $Q$  or the number of viruses present  $n$  (see Appendix A).

When the antibody responses are poly-specific and strain-specific we study viruses' long term behavior for the case  $n=2$  and mutation matrix satisfying condition (A), i.e. virus  $V_1$  mutates to produce virus  $V_2$  at rate  $\mu$  and the mutation is irreversible. System (30) becomes

$$\frac{dV_1}{dt} = r(1 - \mu)V_1 - V_1(KA_1 + K_0A_0),$$

$$\frac{dV_2}{dt} = r\mu V_1 + rV_2 - V_2(KA_2 + K_0A_0),$$

$$\frac{dA_1}{dt} = \lambda V_1 + A_1(a - \beta A_T),$$

$$\frac{dA_2}{dt} = \lambda V_2 + A_2(a - \beta A_T),$$

$$\frac{dA_0}{dt} = \lambda_0(V_1 + V_2) + A_0(a - \beta A_T), \tag{31}$$

with  $V_1(0) = V_{1,0}$ ,  $V_2(0) = A_1(0) = A_2(0) = A_0(0) = 0$ .

We show that for  $r < \min\{(K_0\lambda_0 + K\lambda)/(\lambda + \lambda_0), K_0\Omega\}a/\beta$  both viruses are cleared. Conversely, when  $\mu > K\lambda/(K\lambda + K_0\lambda_0)$  and  $r > ((K_0\lambda_0 + K\lambda)/(\lambda_0 + \lambda))a/\beta$  at least one virus strain persists. Similarly for  $\mu < K\lambda/(K\lambda + K_0\lambda_0)$  and  $r > \Omega K_0a/\beta$ , both viruses persist, where

as shown in Appendix B. Note that  $\Omega$  depends on the relative ratio of the poly-specific and strain-specific antibody production and viral removal rates.

### 4. Numerical results

Previous studies (Ciupe et al., 2006; Stafford et al., 2000) have considered an initial HIV load of  $10^{-9}$  virions per  $\mu\text{l}$ , corresponding to the presence of a small number of virions in the inoculum. We increase this estimate to  $10^{-1}$  virions per  $\mu\text{l}$  to account for a

stronger continuous immunization. The viral dynamics is not sensitive to this value, as we can show numerically. When we vary the initial inoculum five orders of magnitude, the peak of the virus shifts to the right by only one day.

Viruses replicate at an effective rate of  $r=25$  virions per day (Ciupe et al., 2006; Stafford et al., 2000). In response, B cells become activated and differentiate into antibody producing plasma cells. Typical antibody affinities for the elicited antigen are  $10^5 \text{ M}^{-1}$  (Hollinger and Liang, 2001). Since each HIV virion has many potential binding sites and affinity maturation may occur, we assume the avidity of specific and poly-specific antibodies to be as high as  $6 \times 10^9 \text{ M}^{-1}$  per day for strain-specific antibody and  $3 \times 10^9 \text{ M}^{-1}$  per day for the poly-specific antibody. Using the Avogadro's number we can convert the avidity rates measured in inverse molar into removal rates measured in  $\mu\text{l}$  per molecule as follows:

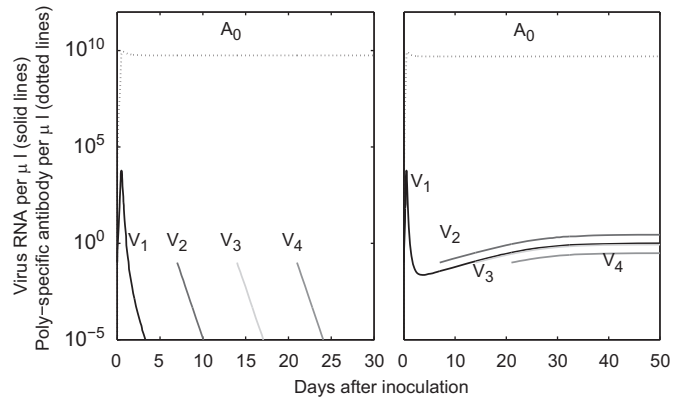
$$1 \text{ M}^{-1} = 1 \frac{\text{Liter}}{\text{mole}} = \frac{10^6 \mu\text{l}}{\text{mole}} = \frac{10^6 \mu\text{l}}{6 \times 10^{23} \text{ molecules}} = \frac{\mu\text{l}}{6 \times 10^{17} \text{ molecules}}. \quad (33)$$

Using this conversion we obtain removal rates of  $K = 10^{-8} \mu\text{l}$  per antibody molecule per day and  $5 \times 10^{-9} \mu\text{l}$  per antibody molecule per day by the strain-specific and poly-specific antibody respectively.

Initially, at the time of immunization, there are neither strain-specific nor poly-specific neutralizing antibodies present, i.e.  $A_i(0)=A_0(0)=0$  molecules per  $\mu\text{l}$ . One B cell secretes between  $10$  and  $10^4$  antibody molecules per second, corresponding to  $8 \times 10^5$  and  $8 \times 10^8$  antibody molecules per day (Bachmann et al., 1994). Assuming that one B cell is activated by one viral epitope, we consider an average antibody production rate of  $\lambda = \lambda_0 = 10^7$  molecules per day per virion (regardless of antibody type). Finally, we assume that the difference between antibody (B cell) proliferation rate and death rate is  $a=1.4$  per day (Hodgkin et al., 1996; Janeway et al., 2001) and that the source B cells compete with each other at a rate  $\beta$  varying between  $2.5 \times 10^{-11}$  and  $2.5 \times 10^{-9} \mu\text{l}$  per antibody molecule per day.

For the continuous immunization model (1), numerical results for the interaction between four virus strains, introduced in the body at times  $t_1=0$ ,  $t_2=5$ ,  $t_3=10$  and  $t_4=15$ , in the sole presence of poly-specific antibody are presented in Fig. 1. Poly-specific neutralizing antibody is produced immediately after infection with virus  $V_1$ , expands at a fast rate, and reaches its peak at the same time as the virus. A slight decrease to its steady-state value occurs three days later. When  $r < K_0 a / \beta$ ,  $V_1$  and all subsequent viral infections decay exponentially (left panel). When  $r > K_0 a / \beta$  viruses persists and reach different steady-state values. While we know the steady-state position of the total virus load  $V_T$ , we cannot determine the position of individual viral steady-states which is highly dependent on initial conditions and inoculation times. If two or all viruses are introduced at time zero and replicate at the same rate,  $r$  then they have identical dynamics (not shown). When, however, viruses  $V_2$ ,  $V_3$  and  $V_4$  are introduced later than virus  $V_1$  and antibody  $A_0$  they reach steady-states values that may be different than the steady-state value of virus  $V_1$ .

When both poly-specific and strain-specific neutralizing antibodies are presented then both strain-specific and poly-specific neutralizing antibodies are produced immediately after infection with virus  $V_1$ . They expand at a fast rate, and reach high steady-state values. When  $r < ((4K_0\lambda_0 + K\lambda) / (4(\lambda + \lambda_0))) a / \beta$ ,  $V_1$  and all subsequent virus strains decay exponentially (Fig. 2, left upper panel). The introduction of new virus strains leads to production of corresponding strain-specific antibodies which expand to lower steady-state values due to competition with existent antibody. While we know the total antibody value,  $A_T$ , we cannot predict individual antibody values at steady-state which are



**Fig. 1.** Virus dynamics (solid lines) in the presence of poly-specific broadly neutralizing antibodies (dotted line): (left panel) for the clearance condition  $r < K_0 a / \beta$ ; (right panel) for the chronic condition  $r > K_0 a / \beta$ . Viruses are introduced as independent immunizations every five days. Parameter used in the simulations are  $r=25$ ,  $a=1.4$ ,  $K_0=5 \times 10^{-9}$ ,  $\lambda_0=10^7$ , and  $\beta=2.5 \times 10^{-10}$  (left panel);  $\beta=2.82 \times 10^{-10}$  (right panel).

highly dependent of initial conditions and inoculation times. If one or all strain-specific antibody are introduced at the same time as the poly-specific antibody then their steady-state levels are identical. The other strain-specific antibodies are prevented from expanding due to their competition with high  $A_0$  and  $A_1$  antibody loads at the time of their appearance (Fig. 2, left, lower panel). When  $r > ((4K_0\lambda_0 + K\lambda) / (4(\lambda + \lambda_0))) a / \beta$ , all viruses persist and undergo damped oscillations. This is due to the existence of complex eigenvalues with negative real parts in (29) (Fig. 2, right, upper panel). Strain-specific antibodies reach the same steady-state which is lower than that of poly-specific antibody (Fig. 2, left, lower panel). The combined antibody response is inefficient in controlling the infection.

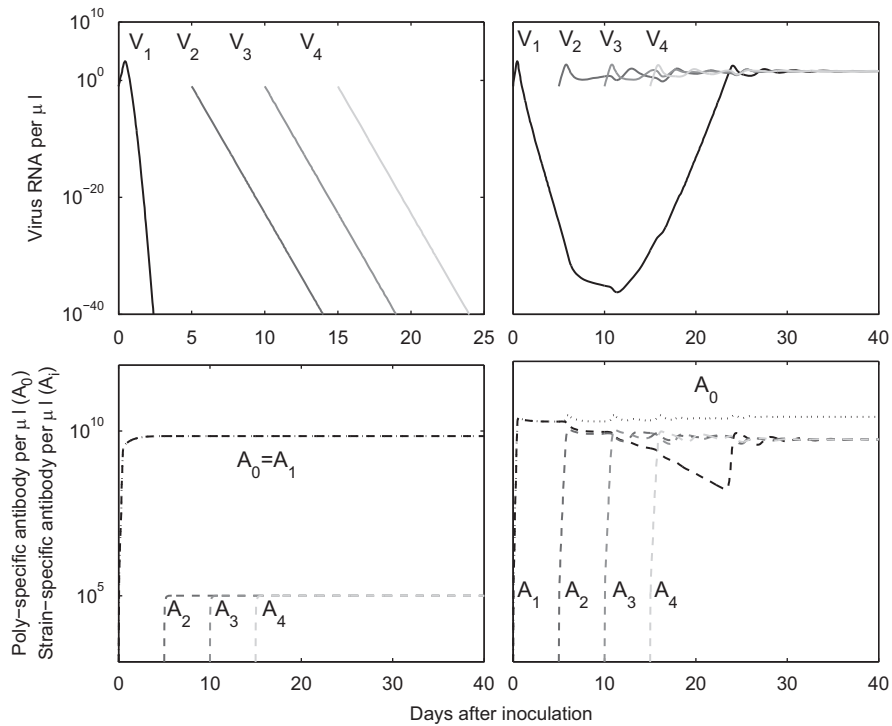
Putting together the analytical results regarding virus dynamics in the presence of poly-specific neutralizing antibodies alone and in the presence of competing poly-specific and strain-specific neutralizing antibodies, we find that for any  $m \geq 2$  for which,

$$\frac{a}{\beta} K_0 > r > \frac{a}{\beta} \left( \frac{m\lambda_0 K_0 + \lambda K}{m(\lambda_0 + \lambda)} \right) \quad (34)$$

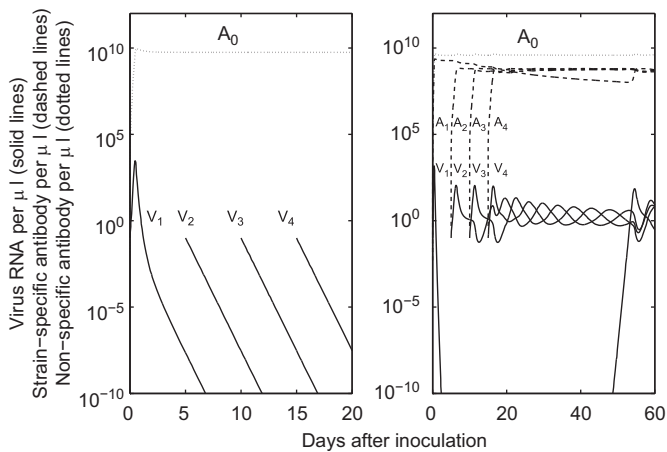
viruses are cleared in the presence of poly-specific neutralizing antibodies but persist in the presence of additional immune responses, in the form of strain-specific neutralizing antibodies (see Fig. 3).

For the natural infection model (30), we consider an initial viral load of  $10^{-1}$  virions per  $\mu\text{l}$ , which mutates over time at rate  $\mu$ , varying between 1% and 80% to produce a second virus. The virus is eliminated at rate  $10^{-8} \mu\text{l}$  per antibody molecule per day by the strain-specific neutralizing antibodies and  $5 \times 10^{-9} \mu\text{l}$  per antibody molecule per day by the poly-specific neutralizing antibodies (Hollinger and Liang, 2001). There are no strain-specific and poly-specific neutralizing antibodies in the body at the time of infection, i.e.  $A_i(0)=A_0(0)=0$  molecules per  $\mu\text{l}$ . Antibodies are produced at rate  $\lambda = \lambda_0 = 10^7$  molecules per day per virion regardless of the antibody type (Bachmann et al., 1994), and compete with each other at rate  $\beta$  varying between  $10^{-10}$  and  $5 \times 10^{-10} \mu\text{l}$  per antibody molecule per day. Rates  $r$  and  $a$  are as in the immunization model.

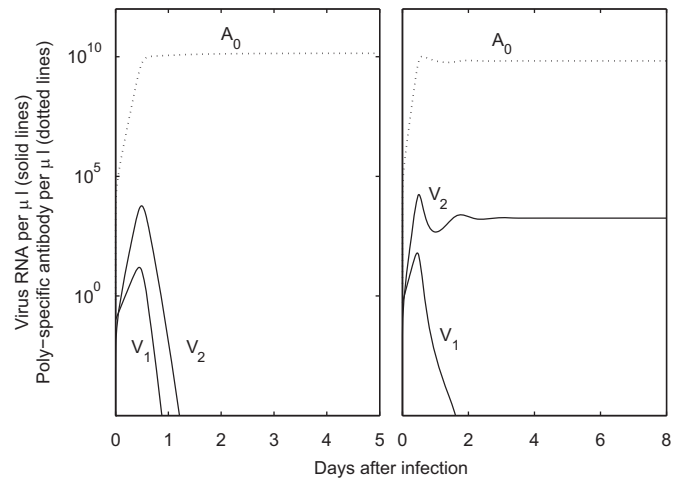
Numerical results for the interaction between two virus strains in the sole presence of poly-specific neutralizing antibodies and stepwise mutation matrix,  $Q$ , are presented in Fig. 4. Infection with  $V_1$  and mutant strain  $V_2$  leads to immediate production of



**Fig. 2.** Virus dynamics (solid lines) in the presence of both poly-specific neutralizing antibodies (dotted line) and strain-specific neutralizing antibodies (dashed lines): (left panel) for the clearance condition  $r < a/\beta((4\lambda_0K_0 + \lambda K)/4(\lambda_0 + \lambda))$ ; (right panel) for the chronic condition  $r > a/\beta((4\lambda_0K_0 + \lambda K)/4(\lambda_0 + \lambda))$ . Viruses are introduced as independent immunizations every five days. Parameters  $a, r, K_0, \lambda_0$  are as in Fig. 1 and  $K=10^{-8}, \lambda=10^7$  and  $\beta=10^{-10}$  (left panel) and  $\beta=2.5 \times 10^{-10}$  (right panel).



**Fig. 3.** Paradoxical results showing: (left panel) viral clearance (solid lines) in the sole presence of poly-specific neutralizing antibody responses (dotted line), (right panel): viral persistence (solid lines) in the presence of stronger (yet competing) poly-specific (dashed lines) and strain-specific neutralizing antibody responses (dotted line) for parameters satisfying  $(a/\beta)((4\lambda_0K_0 + \lambda K)/4(\lambda_0 + \lambda)) < r < K_0a/\beta$ .  $a, r, K, K_0, \lambda, \lambda_0$  are as in Fig. 2 and  $\beta=2.5 \times 10^{-10}$ .

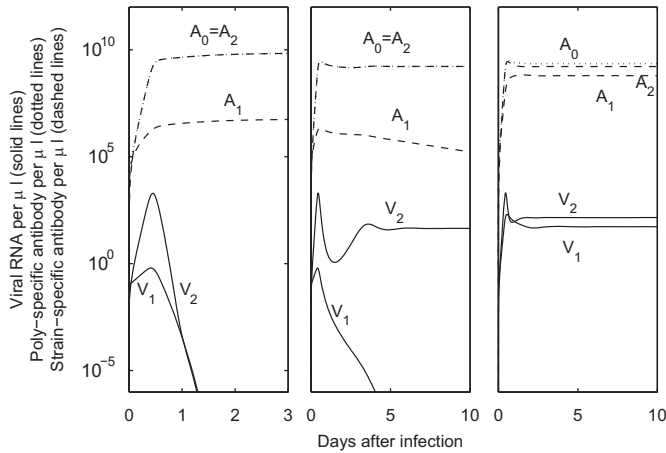


**Fig. 4.** Virus dynamics (solid lines) following natural infection in the presence of broadly neutralizing poly-specific antibodies (dotted line) when virus's mutation is described by condition (A): (left panel) for the clearance condition  $r < K_0a/\beta$ ; (right panel) for the chronic condition  $r > K_0a/\beta$ . Parameter used in the simulations are  $r=25, a=1.4, K_0=5 \times 10^{-9}, \lambda_0=10^7, \mu=0.5$  and  $\beta=10^{-10}$  (left panel);  $\beta=5 \times 10^{-10}$  (right panel).

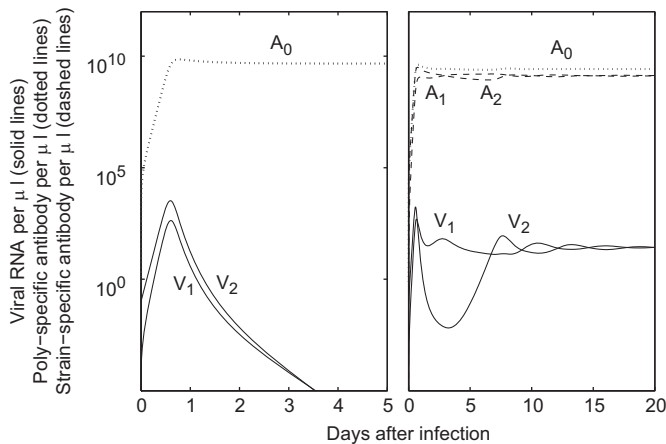
poly-specific antibody who clears both viruses when  $r < K_0a/\beta$  (left panel). When  $r > K_0a/\beta$ , only the dominant virus load  $V_2$  persists (right panel). The clearance conditions are independent of the mutation rate  $\mu$ , which only controls the rate at which the dominant virus gets established.

When both strain-specific and poly-specific neutralizing antibodies are present and for mutation matrix,  $Q$ , satisfying condition (A), infection with  $V_1$  and mutant strain  $V_2$  leads to immediate production of both strain-specific and poly-specific antibody who clear both viruses when  $r < \min\{(K_0\lambda_0 + K\lambda)/(\lambda + \lambda_0), K_0\Omega\}a/\beta$  (Fig. 5, left panel). Poly-specific and strain specific antibodies are produced

immediately after infection and our model predicts the total antibody value needed for clearance,  $A_T$ , but not the individual antibody values at steady-state. When  $r > ((K_0\lambda_0 + K\lambda)/(\lambda + \lambda_0))a/\beta$ , and the mutation rate satisfies  $\mu > K\lambda/(K_0\lambda_0 + K\lambda)$  then a single chronic infection establishes where the dominant virus persists and the suboptimal virus is cleared. The poly-specific and dominant virus-specific antibodies have the same dynamic when  $\lambda = \lambda_0$ , while the other strain-specific antibody is degraded and leaves the body (Fig. 5, middle panel). When  $r > K_0\Omega a/\beta$  and the mutation rate satisfies  $\mu < K\lambda/(K_0\lambda_0 + K\lambda)$  then both virus strains persist. The strain-specific antibody reach steady-state levels smaller than the



**Fig. 5.** Virus dynamics (solid lines) following natural infection in the presence of both poly-specific neutralizing antibodies (dotted line) and strain-specific neutralizing antibodies (dashed lines) when virus's mutation is described by condition (A): (left panel) for condition  $r < \min\{(K_0\lambda_0 + K\lambda)/(\lambda + \lambda_0), K_0\Omega\}a/\beta$ ; (middle panel) for the single-infection chronic conditions  $r > ((K_0\lambda_0 + K\lambda)/(\lambda + \lambda_0))(a/\beta)$  and  $\mu > K\lambda/(K_0\lambda_0 + K\lambda)$ ; (right panel) for the multiple-infection chronic conditions  $r > K_0\Omega a/\beta$  and  $\mu < K\lambda/(K_0\lambda_0 + K\lambda)$ . Parameter  $r$ ,  $a$ ,  $K_0$ ,  $\lambda_0$  are as in Fig. 4,  $K = 10^{-8}$ ,  $\lambda = 10^7$ , and  $\beta = 10^{-10}$ ,  $\mu = 0.5$  (left panel);  $\beta = 5 \times 10^{-10}$ ,  $\mu = 0.8$  (middle panel);  $\beta = 5 \times 10^{-10}$ ,  $\mu = 0.5$  (right panel).



**Fig. 6.** Paradoxical results showing: (left panel) viral clearance (solid lines) in the sole presence of broadly neutralizing poly-specific antibody responses (dotted line), and (right panel) when virus's mutation is described by condition (A): viral persistence (solid lines) in the presence of stronger (yet competing) poly-specific (dashed lines) and strain-specific neutralizing antibody responses (dotted line) for natural infection and parameters satisfying  $K_0\Omega a/\beta < r < K_0a/\beta$ . We consider natural infection with virus strain  $V_1$ , which mutates over time at rate  $\mu < K\lambda/(K\lambda + K_0\lambda_0)$ . Parameters used in simulations are  $r=20$ ,  $a=1.4$ ,  $K_0=K=5 \times 10^{-9}$ ,  $\lambda = \lambda_0 = 10^7$ ,  $\beta = 3 \times 10^{-10}$  and  $\mu = 0.01$ .

poly-specific antibody and their combined avidity is inefficient in controlling the virus (Fig. 5, right panel).

That parameter region,

$$\frac{a}{\beta}K_0 > r > \frac{a}{\beta}K_0\Omega,$$

$$\mu < \frac{K\lambda}{K_0\lambda_0 + K\lambda} \quad (35)$$

describes the interesting situation where viruses are cleared in the presence of poly-specific immune responses and persist in the presence of additional (yet competing) immune responses, in the form of strain-specific neutralizing antibodies (see Fig. 6).

## 5. Discussion

We developed mathematical models of HIV viral dynamics that account for the counterintuitive hypothesis that additional immune responses (in the form of strain-specific antibody responses) may be detrimental to the host and lead to viral persistence. We show that this phenomenon may occur even when successful previous vaccination leads to production of poly-specific broadly neutralizing antibodies. For parameter regimes for which the poly-specific broadly neutralizing antibody response (when operating alone, that is, unaccompanied by strain-specific B cells) are sufficient for clearance of the virus, the presence of additional strain-specific antibodies leads to viral rebound and in the end viral chronicity.

In the first model, we described host–virus interaction during immunization with several virus strains and found that for parameters satisfying

$$\frac{a}{\beta}K_0 > r > \frac{a}{\beta} \left( \frac{m\lambda_0 K_0 + \lambda K}{m(\lambda_0 + \lambda)} \right) \quad (36)$$

viruses go extinct in the presence of only poly-specific broadly neutralizing antibodies, and persist when both strain-specific and poly-specific neutralizing antibodies are present (see Fig. 3). The results are based on the assumption that viruses replicate at the same rate  $r$ . This assumption is justified by recent findings by Arnott et al. (2010) that have shown that viruses obtained shortly after initial infection from individuals who were not taking antiretroviral therapy (ART) have a higher fitness level than was previously believed and therefore justifying our assumption that closely induced viral strains can have the same replication rates. However, since it is known that in the long-run fitness changes and viruses become more (less) fit in the absence (presence) of ART we have run simulations to see how this change affects our results. We have found the existence of parameter regimes for which four viruses replicating at different rates go extinct in the presence of only poly-specific broadly neutralizing antibodies, and persist when both strain-specific and poly-specific neutralizing antibodies are present (see Fig. 8). Analytical results that sustain this observation will be presented elsewhere.

For a natural infection with a virus that mutates over time at a rate  $\mu < K\lambda/(K_0\lambda_0 + K\lambda)$ , when

$$\frac{a}{\beta}K_0 > r > \frac{a}{\beta}K_0\Omega \quad (37)$$

viruses go extinct in the presence of only poly-specific broadly neutralizing antibodies, and persist when both strain-specific and poly-specific neutralizing antibodies are present (see Fig. 6). The results are maintained when viruses have different fitness rates (not shown).

These results allow us to advance the idea that one of the reasons for the absence (or inefficiency) of poly-specific broadly neutralizing antibodies, *in vivo*, is the competition between plasma lymphocytes that produces them with the plasma lymphocytes producing strain-specific neutralizing antibodies. Particularly, even if such poly-specific antibodies are being induced (say through successful vaccines), they may be kept at low enough levels by the more fit strain-specific antibodies. Paradoxically, the presence of additional, specific, immune response is detrimental to the host and allows for the establishment of chronic infections. The suppression of poly-specific immune cells by the more fit immune cells has been documented both in HIV and HCV infections (Heyman, 2003; Zhang et al., 2004), but has never been implied as the reason for viral chronicity. Our study implies that competition between immune cells leading to suppression of B cells capable of inducing broadly neutralizing responses may be sufficient for HIV to become chronic. The



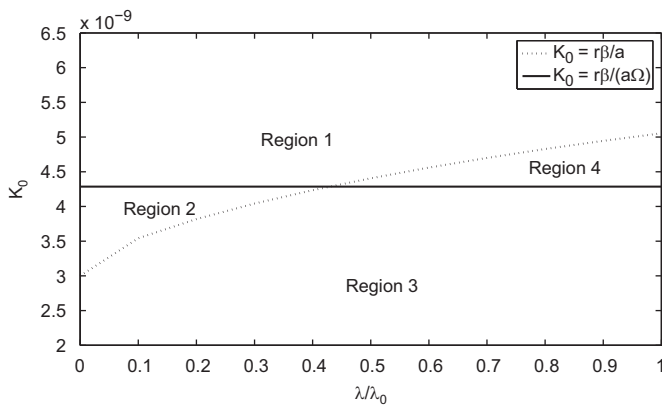
implication is even more worrisome if we consider that the contemporary strain-specific antibodies usually recognize and inhibit preceding but not current viral strains (Burton et al., 2004; Richman et al., 2003; Wei et al., 2003). Our model assumes that neutralizing antibodies to the current dominant viral strain are produced immediately after virus infection, or mutation. A delay in their production by two weeks results in a chronic infection with an increased viral set point by one order of magnitude (results not shown).

The analytical results for systems (1) and (30) when both antibody types are present are based on local analysis. We hypothesized that the conditions for long-term viral clearance and persistence are independent of initial conditions. Our

conclusions are bolstered by numerical results; future work is needed to prove global stability analytically.

In the model of natural infection where the virus mutates, the analytical results are presented for the particular case of two virus–two strain-specific antibody populations. Numerically, we can show that viral clearance in the presence of broadly neutralizing poly-specific antibodies and viral persistence in the presence of both strain-specific and poly-specific neutralizing antibodies in the same parameter regime occurs for any number of new viral strains. Moreover, the analytical results for the mutation matrix satisfying condition (A) can be obtained for a mutation matrix satisfying condition (B), as long as  $Q_c$  is irreducible (results not shown).

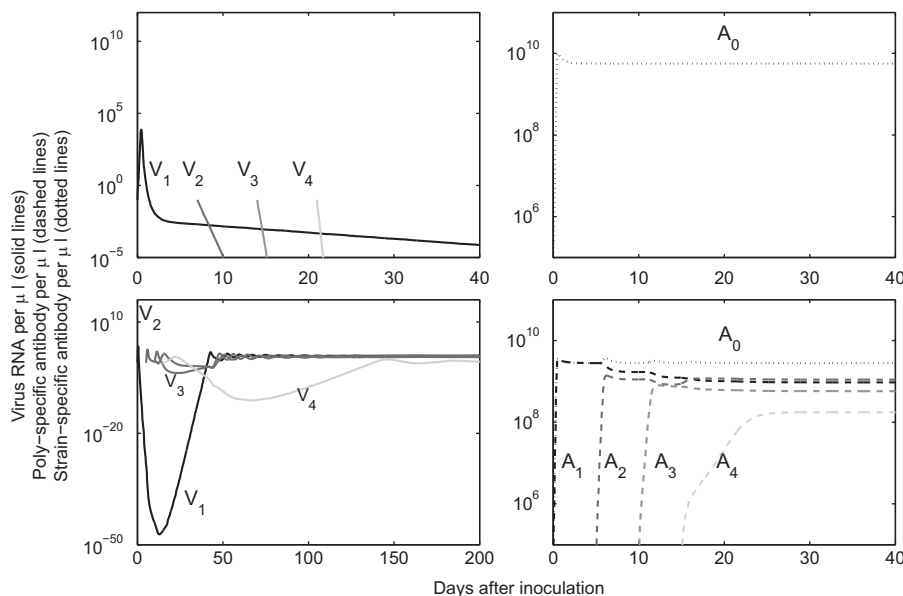
The condition of viral clearance in the sole presence of the poly-specific antibody is given by  $r < K_0 a / \beta$ . Since  $K_0 a / \beta < (K_0 \lambda_0 + K \lambda) / (\lambda + \lambda_0) a / \beta$ , viral chronicity in the presence of competing strain-specific and poly-specific neutralizing antibodies happens when the double chronic infection steady-state (but not the single infection one) exists (parameters described in case 3). If we can induce a poly-specific neutralizing antibody of equal avidity to that of strain-specific antibody, then for known virus average production and antibody life span we can determine the correlation between the poly-specific antibody levels and the minimum avidity rates needed for this condition to fail. As seen in Fig. 7, clearance in the presence of poly-specific broadly neutralizing antibody alone (regions 1 and 4) is maintained for competing poly-specific and strain-specific antibodies when poly-specific antibody levels  $\lambda_0$  are much higher than strain-specific antibody levels  $\lambda$  (region 2). When their levels are similar then we can insure clearance in the competition model by increasing the avidity of the poly-specific broadly neutralizing antibody  $K_0$  (region 4).



**Fig. 7.** Minimal values of poly-specific antibody avidity rate  $K_0$  for which viruses are cleared by poly-specific (solid line) and competing poly-specific and strain-specific broadly neutralizing antibodies for mutation rates  $\mu = 0.3$  as functions of  $\lambda/\lambda_0$ . For high poly-specific/strain-specific antibody ratio clearance by poly-specific antibodies alone is sufficient for clearance by competing poly-specific and strain-specific neutralizing antibodies regardless of mutation rates. For similar values of poly-specific than strain-specific antibody, clearance by poly-specific antibody alone does not insure clearance by competing poly-specific and strain-specific broadly neutralizing antibodies for which we need an increase in the avidity rates of poly-specific antibody to control the infection. Parameters  $a, r, \beta$  are as in Fig. 6 and  $K = K_0$ .

### 6. Conclusions

In this study, we investigated the hypothesis that poly-specific broadly neutralizing antibodies develop alongside strain-specific neutralizing antibodies. Using a mathematical modeling approach, we have determined the parameter regions where competition between poly-specific and strain-specific antibodies



**Fig. 8.** Paradoxical results showing: (left panel) viral clearance (solid lines) in the sole presence of poly-specific neutralizing antibody responses (dotted line), and (right panel): viral persistence (solid lines) in the presence of stronger (yet competing) poly-specific (dashed lines) and strain-specific neutralizing antibody responses (dotted line) for viruses with different replication rates. Parameters  $a, K, K_0, \lambda, \lambda_0, \beta$  are as in Fig. 3 and  $r_1 = 27, r_2 = 25, r_3 = 20, r_4 = 12$ .

can help the virus escape and predicted ways of preventing it, providing insight into the ultimate roles of antibody responses in controlling HIV infection. We predict that in a preventive vaccination design, one can prevent/delay viral chronicity by inducing poly-specific antibodies of high avidity, increasing the overall poly-specific antibody levels and by speeding the rate at which viruses mutate.

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## Appendix A

*Virus evolution during poly-specific antibody response:* We assume that primary inoculation leads to infection by a single virus strain  $V_1$ . This virus mutates over time under pressure from poly-specific immune response,  $A_0$ , giving rise to  $n$  genetically distinct virus strains  $V=(V_1, V_2, \dots, V_n)^T$  at rates given by the mutation matrix  $Q$ , satisfying condition (A) or (B). As before, we consider the replication rate  $r_i=r$  to be independent of the virus strain  $i$ . The model describing the virus-host interaction becomes

$$\begin{aligned} \frac{dV}{dt} &= (rQ - K_0 A_0 I_n) V, \\ \frac{dA_0}{dt} &= \lambda_0 T + A_0(a - \beta A_0), \end{aligned} \quad (38)$$

with  $V_1(0) > 0$  and  $V_i(0) = A(0) = 0$ , for  $i=2, \dots, n$ .

Since  $T(0) > 0$ , we can define  $f(t) = (V/T)(t)$ , for  $i=1, \dots, n$ . Then the following result follows.

**Proposition A.1.** *The dynamics of (38) are equivalent to the dynamics of*

$$\begin{aligned} \frac{df}{dt} &= r(Q - I_n)f, \\ \frac{dT}{dt} &= (r - K_0 A_0)T, \\ \frac{dA_0}{dt} &= \lambda_0 T + A_0(a - \beta A_0). \end{aligned} \quad (39)$$

for mutation matrix  $Q$  satisfying condition (A) or (B).

**Proof.** Note that

$$\frac{df}{dt}(t) = (rQ - K_0 A_0 I_n)f - (r - K_0 A_0)f = r(Q - I_n)f, \quad (40)$$

with  $f(0) \geq 0$  and  $1^T f(0) = 1$ . We see that there is a bijective correspondence between solutions of (38) with  $V(0) \neq 0$ , and solutions of (39).  $\square$

*Steady-state analysis:* Notice that the last two equations of (39) are decoupled from the first  $n$ . We study the stability of steady-states of this planar subsystem next. System (38) has three steady-states:

1. The infection free steady-state  $S_1^3 = (0, 0)$ .
2. The viral clearance steady-state  $S_2^3 = (0, a/\beta)$ .
3. The chronic steady-state  $S_3^3 = ((r/K_0 \lambda_0)(\beta r/K_0 - a), r/K_0)$ , which exists for  $r > K_0 a/\beta$ .

**Proposition A.2.** (a) *The infection free steady-state  $S_1^3$  is always unstable.*

(b) *If  $r < K_0 a/\beta$ , then  $S_2^3$  is GAS with respect to initial conditions  $T(0) > 0$ .*

(c) *If  $r > K_0 a/\beta$ , then  $S_3^3$  is GAS with respect to initial conditions  $T(0) > 0$ .*

**Proof.** The proof is similar to that of Propositions 2 and 3.  $\square$

**Theorem A.3.** *If  $r > K_0 a/\beta$ , then every solution  $(f(t), T(t), A_0(t))$  of (39) with  $T(0) \neq 0$  satisfies*

$$\lim_{t \rightarrow +\infty} (f(t), T(t), A_0(t)) = \left( (1/1^T z)z, \frac{r}{K_0 \lambda_0} \left( \beta \frac{r}{K_0} - a \right), \frac{r}{K_0} \right), \quad (41)$$

where  $z \geq 0$  is the dominant eigenvector of the simple eigenvalue 1 of the matrix  $Q$  ( $Qz = z$ ).

**Proof.** The proof follows from Proposition 6 if we show that  $f(t) \rightarrow (1/1^T z)z$ . From the eigenvector expansion we have that

$$f(t) = c_1 z + \sum_{j>2} c_j e^{r_j t} z_j, \quad (42)$$

where the real part of all  $r_j$ 's is negative and  $c_1 > 0$ .<sup>1</sup> Then

$$\lim_{t \rightarrow +\infty} f(t) = c_1 z \quad (43)$$

and since  $1^T f(t) = 1$  for all  $t$ , it follows that  $c_1 = 1/1^T z$ .  $\square$

**Corollary A.4.** *Under the conditions of Theorem 1 every solution  $(V(t), A_0(t))$  of (38) satisfies*

$$\lim_{t \rightarrow +\infty} (V(t), A_0(t)) = \left( \left( \frac{r}{K_0 \lambda_0} \left( \beta \frac{r}{K_0} - a \right) / 1^T z \right) z, \frac{r}{K_0} \right). \quad (44)$$

**Proof.** This is immediate from Theorem 1 since  $f(t) = V(t)/T(t)$ .  $\square$

**Proposition A.5.** *If  $r < K_0 a/\beta$ , then every solution  $(V(t), A_0(t))$  of (38) satisfies*

$$\lim_{t \rightarrow +\infty} V(t) = 0. \quad (45)$$

**Proof.** This is immediate from Proposition 6 since  $0 \leq V(t)$ .  $\square$

## Appendix B

*Virus evolution during both strain-specific and poly-specific antibody responses:* Let us consider the general case given by system (30), where virus strain  $V_1$  mutates over time under the pressure of both specific and poly-specific immune responses  $A_1$  and  $A_0$  to produce  $n-1$  genetically distinct virus strains  $V_i$  ( $i=2, \dots, n$ ) and their corresponding strain-specific neutralizing antibodies,  $A_i$ . Moreover, the mutation matrix,  $Q = \{\mu_{ij}\}_{1 \leq i, j \leq n}$ , satisfies condition (A). Similar results follow for condition (B) and will not be shown here.

*Steady-state analysis:* We study viruses' long term behavior for the case  $n=2$  and mutation matrix satisfying condition (A), i.e. virus  $V_1$  mutates to produce virus  $V_2$  at rate  $\mu$  and the mutation is irreversible. System (30) becomes

$$\begin{aligned} \frac{dV_1}{dt} &= r(1-\mu)V_1 - V_1(KA_1 + K_0 A_0), \\ \frac{dV_2}{dt} &= r\mu V_1 + rV_2 - V_2(KA_2 + K_0 A_0), \\ \frac{dA_1}{dt} &= \lambda V_1 + A_1(a - \beta A_T), \\ \frac{dA_2}{dt} &= \lambda V_2 + A_2(a - \beta A_T), \\ \frac{dA_0}{dt} &= \lambda_0(V_1 + V_2) + A_0(a - \beta A_T), \end{aligned} \quad (46)$$

with  $V_1(0) = V_{1,0}$ ,  $V_2(0) = A_1(0) = A_2(0) = A_0(0) = 0$ .

<sup>1</sup> Indeed, for  $j \geq 2$ , we have that  $0 = 1^T(Q - I_n)z_j = (r_j - 1)1^T z_j$ , and thus  $1^T z_j = 0$ . This implies that  $0 < 1^T f(0) = c_1 1^T z$  and thus that  $c_1 > 0$ .

System (46) has at most four types of non-negative steady-states:

1. The infection free steady-state  $S_1^4 = (0,0,0,0)$ .
2. The viral clearance hyperplane  $S_2^4 = (0,0,\bar{A}_1,\bar{A}_2,\bar{A}_0)$ , such that  $\bar{A}_T = a/\beta$ .
3. The chronic single infection steady-state

$$S_3^4 = \left(0, \frac{r}{K_0\lambda_0 + K\lambda} \left(\beta \frac{r(\lambda_0 + \lambda)}{K_0\lambda_0 + K\lambda} - a\right), 0, \frac{r\lambda}{K_0\lambda_0 + K\lambda}, \frac{r\lambda_0}{K_0\lambda_0 + K\lambda}\right), \tag{47}$$

which exists when  $r > ((K_0\lambda_0 + K\lambda)/(\lambda_0 + \lambda))a/\beta$ .

4. The chronic co-infection steady-state  $S_4^4 = (\bar{V}_1, \bar{V}_2, \bar{A}_1, \bar{A}_2, \bar{A}_0)$ ,

where

$$x = \frac{K_0}{K} + \frac{\lambda}{\lambda_0},$$

$$y = 2\frac{K_0}{K} + \frac{\lambda}{\lambda_0},$$

$$\bar{A}_0 = \frac{r}{2xyK} \left(2x + y - 2\mu y + \sqrt{(2x + y - 2\mu y)^2 - 8(1 - \mu)^2 xy}\right),$$

$$\bar{A}_1 = \frac{r(1 - \mu)}{K} - \frac{K_0}{K} \bar{A}_0,$$

$$\bar{A}_2 = \left(\frac{K_0}{K} + \frac{\lambda}{\lambda_0}\right) \bar{A}_0 - \frac{r(1 - \mu)}{K},$$

$$\bar{V}_1 = \frac{1}{\lambda} \left(\beta \left(1 + \frac{\lambda}{\lambda_0}\right) \bar{A}_0 - a\right) \left(\frac{r(1 - \mu)}{K} - \frac{K_0}{K} \bar{A}_0\right),$$

$$\bar{V}_2 = \frac{1}{\lambda} \left(\beta \left(1 + \frac{\lambda}{\lambda_0}\right) \bar{A}_0 - a\right) \left(\left(\frac{K_0}{K} + \frac{\lambda}{\lambda_0}\right) \bar{A}_0 - \frac{r(1 - \mu)}{K}\right). \tag{48}$$

$S_4^4$  exists when  $\mu < K\lambda/(K\lambda + K_0\lambda_0) = (2x - y)/x$  and  $r > K_0\Omega a/\beta$ , where

$$\Omega = \frac{2xy}{(y - x)(1 + 2x - y)(2x + y - 2\mu y + \sqrt{(2x + y - 2\mu y)^2 - 8(1 - \mu)^2 xy})}. \tag{49}$$

Case 1: When

- 1a:  $\mu > K\lambda/(K\lambda + K_0\lambda_0)$  and  $r < ((K_0\lambda_0 + K\lambda)/(\lambda_0 + \lambda))a/\beta$  or
- 1b:  $\mu < K\lambda/(K\lambda + K_0\lambda_0)$  and  $r < \min\{((K_0\lambda_0 + K\lambda)/(\lambda_0 + \lambda))a/\beta, K_0\Omega a/\beta\}$

then  $S_1^4$  and  $S_2^4$  exist.

Case 2: When

- 2a:  $\mu > K\lambda/(K\lambda + K_0\lambda_0)$  and  $r > ((K_0\lambda_0 + K\lambda)/(\lambda_0 + \lambda))a/\beta$  or
- 2b:  $\mu < K\lambda/(K\lambda + K_0\lambda_0)$  and  $K_0\Omega a/\beta > r > ((K_0\lambda_0 + K\lambda)/(\lambda_0 + \lambda))a/\beta$

then  $S_1^4, S_2^4$  and  $S_3^4$  exist.

Case 3: When  $\mu < K\lambda/(K\lambda + K_0\lambda_0)$  and  $K_0\Omega a/\beta < r < ((K_0\lambda_0 + K\lambda)/(\lambda_0 + \lambda))a/\beta$  then  $S_1^4, S_2^4$  and  $S_4^4$  exist.

Case 4: When  $\mu < K\lambda/(K\lambda + K_0\lambda_0)$  and  $r > \max\{((K_0\lambda_0 + K\lambda)/(\lambda_0 + \lambda))a/\beta, K_0\Omega a/\beta\}$  then all four steady-states exist.

**Proposition B.1.** (a) The infection free steady-state  $S_1^4$  is always unstable.

(b) The viral clearance hyperplane  $S_2^4$  has zero eigenvalues.

(c) The chronic single infection steady-state  $S_3^4$  is asymptotically stable for parameters satisfying condition 2a and unstable for parameters satisfying condition 2b.

(d) The chronic co-infection steady-state  $S_4^4$  is asymptotically stable whenever it exists (for parameters satisfying conditions 3 and 4).

**Proof.** The Jacobian matrix corresponding to the linearized system is

$$J = \begin{pmatrix} Y_1 & 0 & -k\bar{V}_1 & 0 & -K_0\bar{V}_1 \\ r\mu & Y_2 & 0 & -K\bar{V}_2 & -K_0\bar{V}_2 \\ \lambda & 0 & a - \beta\bar{A}_T - \beta\bar{A}_1 & -\beta\bar{A}_1 & -\beta\bar{A}_1 \\ 0 & \lambda & -\beta\bar{A}_2 & a - \beta\bar{A}_T - \beta\bar{A}_2 & -\beta\bar{A}_2 \\ \lambda_0 & \lambda_0 & -\beta\bar{A}_0 & -\beta\bar{A}_0 & a - \beta\bar{A}_T - \beta\bar{A}_0 \end{pmatrix}, \tag{50}$$

with

$$Y_1 = r(1 - \mu) - K_0\bar{A}_0 - K\bar{A}_1,$$

$$Y_2 = r - K_0\bar{A}_0 - K\bar{A}_2. \tag{51}$$

(a) The characteristic equation of  $S_1^4$ ,

$$(r(1 - \mu) - \lambda)(r - \lambda)(a - \lambda)^3 = 0 \tag{52}$$

has positive eigenvalues  $\lambda_1 = r(1 - \mu)$ ,  $\lambda_2 = r$  and  $\lambda_{3,4,5} = a$ . Therefore, the infection free steady-state is always unstable.

(b) The characteristic equation of hyperplane  $S_2^4$ ,

$$\lambda^2(a + \lambda)(\lambda - (r - K_0\bar{A}_0 - K\bar{A}_2))(\lambda - (r(1 - \mu) - K_0\bar{A}_0 - K\bar{A}_1)) = 0 \tag{53}$$

has eigenvalues  $\lambda_{1,2} = 0$ ,  $\lambda_3 = -a$ ,  $\lambda_4 = r - K_0\bar{A}_0 - K\bar{A}_2$  and  $\lambda_5 = r(1 - \mu) - K_0\bar{A}_0 - K\bar{A}_1$ . Therefore,  $S_2^4$  is unstable for  $r > \min\{K_0\bar{A}_0 + K\bar{A}_2, 1/(1 - \mu)(K_0\bar{A}_0 + K\bar{A}_1)\}$ . Since some eigenvalues are zero, the stability cannot be determined from linear analysis. We will show numerically the hyperplane is asymptotically stable for parameters satisfying condition (A).

(c) The chronic single infection steady-state  $S_3^4$  has the characteristic equation

$$\left(r(1 - \mu) - \frac{rK_0\lambda_0}{K_0\lambda_0 + K\lambda} - \lambda\right)(a - \beta\eta - \lambda)^2(\lambda^2 + \lambda(2\beta\eta - a) + (\beta\eta - a)K\eta) = 0, \tag{54}$$

where  $\eta = r(\lambda_0 + \lambda)/(K_0\lambda_0 + K\lambda)$ . The eigenvalue

$$\lambda_1 = r(1 - \mu) - \frac{rK_0\lambda_0}{K_0\lambda_0 + K\lambda} \tag{55}$$

is negative when  $\mu > K\lambda/(K\lambda + K_0\lambda_0)$  and positive otherwise. The rest of the eigenvalues

$$\lambda_{2,3} = a - \beta \frac{r(\lambda_0 + \lambda)}{K_0\lambda_0 + K\lambda},$$

$$\lambda_{4,5} = \frac{1}{2} \left(a - 2\beta\eta \pm \sqrt{(a - 2\beta\eta)^2 - 4K\eta(\beta\eta - a)}\right) \tag{56}$$

are negative when  $r > (a/\beta)(K_0\lambda_0 + K\lambda)/(\lambda_0 + \lambda)$ . This happens every time steady-state  $S_3^4$  exists.

(d) Let  $\omega = \beta\bar{A}_T - a = \beta r/K_0\Omega - a$ . We will show that when the chronic steady-state  $S_4^4$  exists (respectively, when  $\omega$  is positive) it is asymptotically stable. The characteristic equation corresponding to the chronic steady-state is

$$(\lambda + \beta\bar{A}_T - a)(\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4) = 0, \tag{57}$$

where

$$a_1 = 2\omega + \beta\bar{A}_T + r\mu \frac{\bar{V}_1}{\bar{V}_2},$$

$$a_2 = (K_0\lambda_0 + K\lambda)(\bar{V}_1 + \bar{V}_2) + \omega(\omega + \beta\bar{A}_T) + r\mu \frac{\bar{V}_1}{\bar{V}_2} (2\omega + \beta\bar{A}_T),$$

$$a_3 = (K_0\lambda_0 + K\lambda) \left( \omega(\bar{V}_1 + \bar{V}_2) + r\mu \frac{\bar{V}_1^2}{\bar{V}_2} \right) + \frac{\bar{V}_1}{\bar{V}_2} (r\mu\omega(\omega + \beta\bar{A}_T) + (r\mu K_0\lambda_0 + 2(\lambda + \lambda_0)k\beta\bar{A}_2)\bar{V}_2),$$

$$a_4 = K\lambda\bar{V}_1\bar{V}_2(2K_0\lambda_0 + K\lambda) + r\mu\omega \left( (K_0\lambda_0 + K\lambda) \frac{\bar{V}_1^2}{\bar{V}_2} + K_0\lambda_0\bar{V}_1 \right). \quad (58)$$

The eigenvalue  $\lambda_1 = -\omega$  is negative for positive  $\omega$ . By the Ruth–Hurwitz condition, the remaining eigenvalues solving Eq. (57) have negative real parts if and only if

$$a_1 > 0, \quad a_4 > 0, \quad B_1 \equiv a_1 a_2 - a_3 > 0, \quad \text{and} \quad B_2 \equiv B_1 a_3 - a_1 a_4 > 0. \quad (59)$$

Variables  $a_1$ ,  $a_4$  and

$$B_1 = \omega(\omega + \beta\bar{A}_T)(2\omega + \beta\bar{A}_T) + \omega(\bar{V}_1 + \bar{V}_2)(K_0\lambda_0 + K\lambda) + r\mu K\lambda\bar{V}_1 + K\lambda\beta\bar{A}_2 \frac{\bar{V}_1^2 + \bar{V}_2^2}{\bar{V}_1 + \bar{V}_2} + K_0\lambda_0\beta\bar{A}_T(\bar{V}_1 + \bar{V}_2) \quad (60)$$

are polynomials in  $\omega$  with positive coefficients. The proof of the last relation,  $B_2 > 0$ , is tedious and can be verified using maple for parameters where  $S_4^*$  exists.  $\square$

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