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# Model for competition from self during passive immunization, with application to broadly neutralizing antibodies for HIV

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ABSTRACT

We propose a mathematical model to interpret observations concerning the behavior of broadly neutralizing antibodies for chronic HIV *in vivo*. The model enables us to identify a threshold antibody level that must be achieved to decrease the viral load effectively. Although this threshold has not been reached in existing passive immunization studies, it is within range of humoral immune responses, suggesting that therapeutic vaccines are feasible. In an appendix, we develop a model of passive immunization against influenza, and acute infection.



## 1. Introduction

With the recent failure of vaccines to elicit T-cell-mediated immunity to HIV [1], there has been renewed interest in eliciting broadly neutralizing antibodies to the virus [2]. Of the three most well-characterized such antibodies, one, 2G12, binds to gp120 [3]; the others, 2F5 and 4E10, react with conserved membrane-proximal amino acids in gp41 [4]. Understanding how these molecules function *in vivo* is important for designing vaccines and treatments based on broadly neutralizing antibodies. For example, quantitative analysis of data on passive immunization of macaques with 2G12 and 2F5 prior to viral challenge [5–7] suggested that the administration of antibodies could decrease the numbers of cells initially infected and modulate the long-term progress of the disease by limiting the depletion of CD4+ T cells [7].

However, Trkola et al. [3] subsequently studied whether passive immunization with these antibodies reduced the viral load in humans infected with HIV-1, after cessation of antiretroviral treatment (ART). They found that high doses of the three antibodies in combination delayed viral rebound but did not change the ultimate viral load. Later studies showed fast viral escape from 2G12 by mutation of the gp120 epitope; no such escape from 2F5 and 4E10 was observed [3,8]. These results are in striking contrast to those for passive immunization against other viral infections. For example, Sui et al. [9] recently discovered a broadly neutralizing antibody that blocks a broad spectrum of avian and human influenza A infections in mice. What makes passive immunization against HIV different from that against influenza? The answer to this question bears directly on assessing the degree to which a therapeutic vaccine that elicited broadly neutralizing antibodies to HIV would decrease the viral load and, in turn, the transmission of infection.

Here, we quantitatively investigate one factor that could limit the impact of these broadly neutralizing antibodies on the viral load *in vivo*. Our study is motivated by the observation that 2F5 and 4E10 also bind a variety of self epitopes such as cardiolipin [1], a normal component of human plasma lipoproteins [10]. The measured concentration of cardiolipin in human plasma is about 300 nM. The viral load of an HIV-infected patient in the chronic phase is about $10^6$ copies/ml, which is roughly $10^{-5}$ nM. The concentration of cardiolipin is thus much higher than the concentration of HIV viruses *in vivo*. Based on the relative concentration of these self epitopes and their reaction rates with the antibodies, our hypothesis is that these self eptiopes can out compete the viral gp41 epitopes for the

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antibodies when they are administered passively. In this note, we build on earlier theoretical work [11–14] to develop a simple mathematical model to delineate this hypothesis and to estimate how much the various contributing factors influence the viral load. We identify three regimes of behavior based on the relative concentrations of antibodies and competing self epitopes; in particular, high concentrations of antibodies are required for the viral load to decrease proportionally with dose. Whether these concentrations could be achieved in a humoral response elicited by a therapeutic vaccine is discussed. In an appendix, we contrast the response to passive immunization of a chronic infection like HIV with that of an acute infection like influenza.

## 2. Methods

### 2.1. Model

Models of HIV and CD4+ T cell dynamics are reviewed in [11–15]. These models generally account explicitly for the virus and its target cells; the various factors that contribute to removal of the virus are treated in aggregate. Callaway and Perelson [11] compared several such models with ART and found that the behaviors of most were very sensitive to the parameters used to describe the action of the drugs. We build directly on a simple model that they found to be robust in this respect:

$$\frac{d[T]}{dt} = \lambda_T - d[T] - (1-\varepsilon_{drug})\beta[T][v] \tag{1}$$

$$\frac{d[I]}{dt} = (1-\varepsilon_{drug})\beta[T][v] - \delta_I'[I]^{\omega+1} \tag{2}$$

$$\frac{d[v]}{dt} = p[I] - c_v[v] \tag{3}$$

where $[T]$ and $[I]$ are the concentrations of susceptible and infected CD4+ T cells; $\lambda_T$ is the rate at which new susceptible cells are produced, and $d$ is their death rate; $\beta$ is the rate constant for infection; viruses are produced and cleared with rate constants $p$ and $c_v$. The parameter $\varepsilon_{drug}$ describes the efficacy of the ART: $\varepsilon_{drug} = 1$ means that the drug completely blocks infection, and $\varepsilon_{drug} = 0$ means that it has no impact. The non-linear term $\delta_I'[I]^{\omega+1}$ is important for making the model robust to the choice of $\varepsilon_{drug}$. The mechanistic picture giving rise to this term is that infected cells elicit a cytotoxic response which then results in their death. This response depends on the concentration of the infected cells: a higher population of infected cells elicits a higher population of cytotoxic cells. As discussed in [11], a way to model this effect without adding additional species to the model is to consider the death rate to be a function of the infected cell density, and a reasonable nonlinear function is a power law.

We modify and extend this model to include competition between viral and self epitopes for binding passively administered antibodies. To this end, we introduce explicit antibody terms to Eq. (3):

$$\frac{d[v]}{dt} = p[I] - (c_v + k_v^a[Ab])[v] + k_v^d[vAb] \tag{3'}$$

and an equation for the formation of complexes between antibodies and viral epitopes:

$$\frac{d[vAb]}{dt} = k_v^a[v][Ab] - k_v^d[vAb] - c_{vAb}[vAb]. \tag{4}$$

Above, $[v]$, $[Ab]$, $[vAb]$ denote the concentrations of viral epitopes, broadly neutralizing antibodies, and their complexes. The antibodies associate with the self and viral epitopes to produce complexes with rates $k_s^a$ and $k_v^a$, respectively; the complexes can dissociate with rates $k_s^d$ and $k_v^d$ or be cleared with rate constant $c_{vAB}$. For simplicity, we neglect differences between viral strains, which is reasonable because our interest is in broadly neutralizing antibodies. To Eqs. (1), (2) and (3′), we add the self epitope dynamics and the consequent equation for free antibodies:

$$\frac{d[S]}{dt} = -k_s^a[S][Ab] + k_s^d[SAb] - c_s[S] + \lambda_s \tag{5}$$

$$\frac{d[SAb]}{dt} = k_s^a[S][Ab] - k_s^d[SAb] - c_{sAb}[SAb] \tag{6}$$

$$\frac{d[Ab]}{dt} = -k_s^a[S][Ab] - k_v^a[v][Ab] + k_s^d[SAb] + k_v^d[vAb] - c_{Ab}[Ab] + \lambda_{Ab}. \tag{7}$$

Here, $[S]$ and $[SAb]$ denote the concentrations of self epitopes and their complexes with broadly neutralizing antibodies. The production of self epitopes with rate $\lambda_s$ is balanced by their clearance with rate constant $c_s$, such that the system remains at a stationary state in the absence of the antibodies. Analogous source and sink terms are included for the antibodies; when the antibodies are injected ($\lambda_{Ab} > 0$), they perturb the system from this stationary state. Here, $c_{Ab}$ and $c_{sAb}$ are the clearance rates of the antibody and its complex with self epitopes. In summary, the full model comprises Eqs. (1)–(7) with (3′) replacing (3).

### 2.2. Fitting patient data

In Ref. [3], patients diagnosed with chronic HIV-1 infection and treated with ART were studied. The data for viral rebound in the absence and presence of passively administered antibodies was obtained in two separate intervals in which ART was discontinued. We fit the model to the data of viral rebound in Ref. [3] in two stages that reflect the structure of the experiment. In the first stage, we fit the data for the viral rebound in the absence of passively administered antibodies using only the subset of parameters governing the viral and T cell dynamics. In the second stage, we fit the remaining data and include the parameters describing the antibodies, their competition with self, and the clearance of the resulting complexes. In other words, we restrict the number of parameters that we fit in each stage to the minimum necessary because the data are limited.

In the first stage of the fitting, our model reduces to that of Callaway and Perelson [11] (Eqs. (1)–(3)). The initial amount of uninfected ($T$) and infected ($I$) T-cells is not individually reported in Ref. [3], but the total amount of patient T-cells ≈ 532,000 cells/ml, is given in the supplement of Ref. [3]. We take the ratio of these two types of cells ($T_0/I_0$) to be a fitting parameter in the model. The value of $\varepsilon_{\mathrm{drug}}$ is set to zero because drug therapy was discontinued. During the fitting, the parameter values were allowed to range from 0.1 to 10 times the values in Ref. [11].

We used a Metropolis Monte Carlo approach to minimize the mean squared error between the logarithm (base 10) of the simulated and measured trajectories for viral rebound. The effective temperature was 0.01 (in units of the squared deviation of the viral load). At each simulation step, we selected whether to vary one or all parameters with equal probability, and selected trial values for parameters that differed from their present values by up to 10%. The acceptance rate was 16%. Because both free virus and antibody-bound virus contribute to measured viral RNA levels, we take the viral load to be the sum of $[v]$ and $[vAb]$.

We use the values $\lambda_T$, $d$, $\beta$, $\delta_I'$, $p$, $c_v$, $\omega$ and $T_0/I_0$ that are obtained from the first phase of the fitting to limit the number of free parameters in the second phase of the fitting, in which we incorporate the effects of the broadly neutralizing antibodies through the full model in Section 2.1. We assume that the antibodies are injected at 13 equally spaced times over 11 weeks by setting $\lambda_{Ab} = 0$ in Eq. (7), and, at each time interval, resetting the $[Ab]$ level to the experimental dose.

**Table 1**
Fits of the three-equation model for T cell dynamics.

| Patient | $\lambda_T$ (cells ml$^{-1}$ day$^{-1}$) | $d$ (day$^{-1}$) | $\beta$ (cells$^{-1}$ ml day$^{-1}$) | $\delta'_I$ (day$^{-1}$(ml cell$^{-1}$)$^{\omega}$) |
|---|---|---|---|---|
| NAB02 | 1690 | 8.02$e$−2 | 4.89$e$−6 | 4.74$e$−3 |
| NAB04 | 760 | 1.48$e$−3 | 4.83$e$−6 | 3.58$e$−2 |
| NAB05 | 4290 | 3.40$e$−2 | 2.22$e$−6 | 3.96$e$−2 |
| NAB06 | 812 | 2.99$e$−2 | 2.21$e$−7 | 2.49$e$−2 |
| NAB07 | 2280 | 6.45$e$−2 | 2.14$e$−6 | 1.46$e$−2 |

| Patient | $p$ (day$^{-1}$) | $c_v$ (day$^{-1}$) | $\omega$ | $T_0/I_0$ | $E$[a] | $\sqrt{E/n}$[b] |
|---|---|---|---|---|---|---|
| NAB02 | 12.1 | 55.6 | 1.79$e$−2 | 1.09$e$5 | 1.32 | 0.28 |
| NAB04 | 12.7 | 48.2 | 6.41$e$−3 | 7.87$e$5 | 2.53 | 0.37 |
| NAB05 | 28.1 | 55.5 | 1.19$e$−2 | 1.12$e$5 | 1.31 | 0.27 |
| NAB06 | 62.0 | 18.6 | 9.61$e$−3 | 2.97$e$4 | 4.05 | 0.58 |
| NAB07 | 7.62 | 23.3 | 7.89$e$−3 | 5.02$e$4 | 3.24 | 0.52 |

[a] $E$ is the squared difference of the logarithms (base 10) of simulated and observed viral loads.
[b] $n$ is the number of data points.

The units of the experimental antibody levels have to be converted to nM to be consistent with the units of the model. Because we do not know the ratio of IgG to IgM antibodies, we consider the conversion factor between these two units as a fitting parameter. The result that we obtain for this parameter should fall in the range 3–20 nM/(μg Ab/ml blood) depending on the ratio of IgG (∼150 kDa) to IgM (∼900 kDa); we obtain values between 5.7 and 8.0 nM/(μg Ab/ml blood). To maintain a constant level of self epitopes, we fixed $\lambda_s/c_s = 300$ nM, where $c_s$ is the value that we obtain from the fitting procedure for the clearance rate of the self epitopes. This is consistent with Ref. [10], in which a constant level of 300 nM cardiolipin was measured in blood.

## 3. Results

Here, we explore the behavior of the model introduced in Section 2. We first consider a reduced set of equations that permits analytical solution to show the accessible steady-state regimes; simplifying assumptions are evaluated by comparing with long-time results of numerical integration without these assumptions. Then, we compute with the full model and fit data from patients to estimate parameters. These values determine which of the possible regimes are actually applicable, which, in turn, can inform the design of vaccines and treatments.

### 3.1. Steady-state behaviors of the model

In this section, we establish the general behavior of the model analytically. To this end, we assume that the system is in a chronic HIV-infected phase such that the viral load is constant in the absence of the treatment, and we replace Eqs. (1)–(3′) with a single one:

$$\frac{d[v]}{dt} = -k_v^a[v][Ab] + k_v^d[vAb] - c_v[v] + \lambda_v. \tag{8}$$

In so doing, we neglect variations in the number of infected cells and take the viral production rate to be constant ($\lambda_v$). Furthermore, in this section, we model the antibodies as coming continuously from a constant source even though Trkola et al. [3] administered the antibodies in a series of injections (i.e., punctuated events) to enable solution of the equations. Specifically, we define $t = 0$ as the start of passive immunization and denote concentrations at this time by a subscript "0". For $t \le 0$, $[S] = \lambda_s/c_s$ and $[v] = \lambda_v/c_v$; there are no complexes. At $t = 0$, we switch $[Ab]$ to a finite value and set $\lambda_{Ab} = c_{Ab}[Ab]_0$.

With these initial conditions, we determine the equilibrium reached following injection by setting the left hand sides of Eqs. (4)–(8) to zero (i.e., by taking the concentrations to be unchanging). Then,

$$[v] = \frac{[v]_0}{1 + r_v[Ab]} \tag{9}$$

$$[S] = \frac{[S]_0}{1 + r_s[Ab]} \tag{10}$$

$$[Ab] = \frac{[Ab]_0}{1 + r_a[S] + r_v c_v[v]/c_{Ab}}, \tag{11}$$

where $r_s = k_s^a c_{SAb}/c_s(k_s^d + c_{SAb})$, $r_v = k_v^a c_{vAb}/c_v(k_v^d + c_{vAb})$, and $r_a = r_s c_s/s_{Ab}$. We can safely neglect the last term in the denominator of Eq. (11) for typical viral loads (<$10^6$ copies/ml), and even somewhat higher concentrations that allow accounting for the stoichiometry of the epitopes on the viral particles. In this case,

$$[Ab] \approx \frac{[Ab]_0}{1 + r_a[S]} = \frac{[Ab]_0}{1 + r_a[S]_0/(1 + r_s[Ab])}.$$

This quadratic equation in $[Ab]$ can be solved and substituted into Eq. (9) to obtain the ultimate viral load. Doing so (not shown) reveals three possible situations, the choice of which depends on the initial concentrations $[Ab]_0$ and $[S]_0$:

I. When the level of antibodies is low in comparison to the level of self epitopes such that $r_a[S]_0 \gg r_s[Ab] \gg 1$, the final viral load is $[v] \approx [v]_0/(1 + r_v[Ab]_0/r_a[S]_0) \approx [v]_0$ and the impact of the broadly neutralizing antibodies is negligible.
II. When $r_a[S]_0 \approx r_s[Ab] \gg 1$, the final viral load is $[v] \approx ([v]_0/r_v)\sqrt{r_s/[Ab]_0}$. In this case, the viral load depends inversely on the square root of the concentration of the broadly neutralizing antibodies.
III. When the level of antibodies is much higher than the level of self epitopes such that $r_s[Ab] \gg r_a[S]_0 \gg 1$, $[v] \approx [v]_0/r_v[Ab]_0$ and the viral load depends inversely on the concentration of the antibodies. This is the best-case scenario.

The analysis immediately above shows that the efficacy of broadly neutralizing antibodies is determined by their level relative to relevant self epitopes. To determine which situations are pertinent to passive immunization and humoral responses elicited by vaccination, as well as to evaluate the simplifying assumptions made above, we examine the time-dependent behavior of the model, by numerically integrating Eqs. (4)–(8) with the parameter values of Table 1. These parameters are estimated by fitting the full model in Section 2 to the experimental viral load rebound of Ref. [3], as discussed in Section 3.2.

As expected, the initial drop in viral load depends on the value of $[Ab]_0$, as does the new equilibrium point reached (Fig. 1). Moreover, the time required for the viral load to rebound increases with

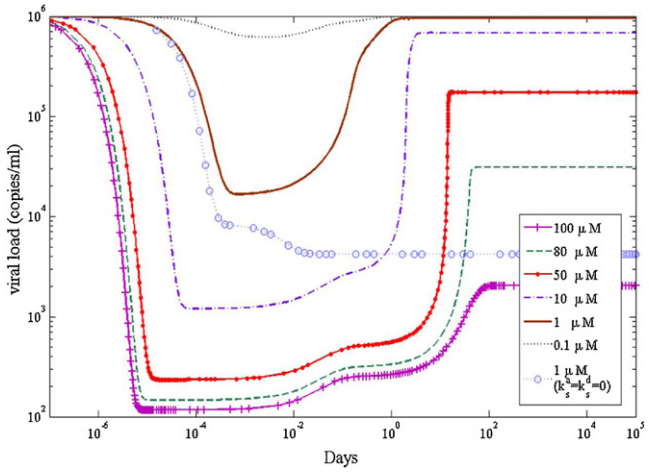


**Fig. 1.** Evolution of viral load as a function of time and antibody dose. We define $t = 0$ as the time of starting the continuous injection and set the initial concentrations to be $[S]_0 = \lambda_s/c_s$, $[v]_0 = \lambda_v/c_v$ and $[Ab]_0 = \lambda_{Ab}/c_{Ab}$; there are no complexes at $t = 0$. The response of the viral load in the absence of self-reactivity is indicated by blue circles (i.e., $k_s^a = k_s^d = 0$) and $[Ab]_0 = 1$ μM. Results shown are for numerical integration of the model in Section 3.1 comprised of Eqs. (4)–(8), with parameters obtained for patient NAB05 (Tables 1 and 2).

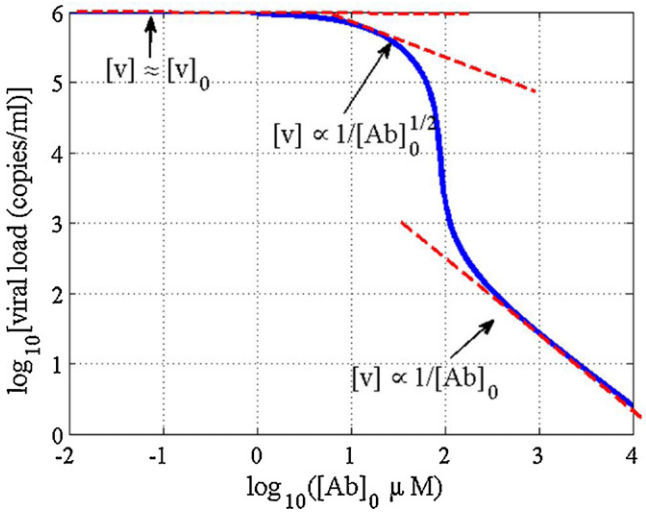


**Fig. 2.** Dependence of the stationary viral load on the dose of continuously injected *Ab* (model in Section 3.1 comprised of Eqs. (4)–(8)). We define $t = 0$ as the time of starting the passive immunization and set the initial concentrations to be $[v]_0 = \lambda_v/c_v = 10^6$ copies/ml, $[S]_0 = \lambda_s/c_s = 300$ nM, and $[Ab]_0 = \lambda_{Ab}/c_{Ab}$; there are no complexes at $t = 0$. The dashed lines indicate the $[v] \approx [v]_0$ plateau for low doses, the $[v] \propto [Ab]_0^{-1/2}$ scaling at intermediate doses, and the $[v] \propto [Ab]_0^{-1}$ scaling when the injection dose is very high. Parameters are those for patient NAB05 (Tables 1 and 2).

$[Ab]_0$. However, $[Ab]_0$ must be much higher than $[S]_0$ (300 nM) to get a significant decrease in the final viral load. The molecular weight of IgG antibodies is ~150 kDa and that of IgM antibodies is ~900 kDa. This means that the dose of antibody which was used in passive immunization is between ~0.5 μM and ~3 μM. This dose is quite high, but when it is compared to the pertinent concentration scale, $r_a[S]_0/r_s$ (see Section 3.1 for discussion), we see that $[Ab]_0 < r_a[S]_0/r_s \sim 88.59$ μM. In other words, the model indicates that the dose is not sufficient to reduce the viral load, consistent with the experimental results [3]. It should be noted that we estimated the value of $r_a[S]_0/r_s$ by fitting the model to experimental time series. Measured stoichiometries would better constrain this threshold ratio.

The stationary viral load is plotted as a function of the dose of continuously injected antibodies in Fig. 2. The different scaling behaviors that we identified above are indicated. Also, for comparison, in the absence of self-reactivity (i.e., $k_s^a = k_s^d = 0$), the viral load rapidly decreases more than a hundred fold and remains at a low level (Fig. 1).

### 3.2. Parameter estimation from patient data

In Section 3.1, we assumed that viruses are produced at a constant rate, which is appropriate for a chronic infection in which the number of infected cells remains roughly constant. We now consider the full model in Section 2.1, which explicitly treats the dynamics of CD4+ T cells and ART. We fit this model to the data in Ref. [3] as described in Section 2.2. Each patient that we consider was diagnosed with chronic HIV-1 infection and treated with ART; data for viral rebound in the absence and presence of passively administered antibodies was obtained in two separate intervals in which ART was discontinued. We consider five patients: NAB02, NAB04, NAB05, NAB06, and NAB07 (Tables 1 and 2) because there are sufficient data for both cases (with and without passive immunization). We exclude NAB03 despite a comparable number of measurements since the dynamics were very different from other patients.

Results for all five patients are given in Tables 1 and 2. We additionally graph the results for patient NAB05, which permitted the best fits (Figs. 3 and 4). The estimated parameter values can be compared with independent data for broadly neutralizing antibodies. Alam et al. [16] studied the kinetics of 2F5 and 4E10 binding to cardiolipin and gp41. Based on their measurements, the binding and unbinding of antibodies to viral epitopes are of the order of $k_v^a \approx 10\,\text{nM}^{-1}\,\text{day}^{-1}$ and $k_v^d \approx 100\,\text{day}^{-1}$, which is consistent with the estimated values. Armbruster et al. [17] measured the elimination half-lives of 4E10, 2F5 and 2G12 as 6.6, 3.2 and 14.1 days in a

**Table 2**
Fits of the extended model combining T cell dynamics and virus-self competition.

| Patient | $k_v^a$ (nM$^{-1}$day) | $k_v^d$ (day$^{-1}$) | $k_s^a$ (nM$^{-1}$ day$^{-1}$) | $k_s^d$ (day$^{-1}$) | $c_s$ (day$^{-1}$) |
|---|---|---|---|---|---|
| NAB02 | 5.815 | 80.95 | 34.93 | 138.7 | 95.63 |
| NAB04 | 4.072 | 144.5 | 25.84 | 57.28 | 45.32 |
| NAB05 | 18.11 | 155.9 | 14.25 | 252.4 | 17.54 |
| NAB06 | 4.688 | 187.9 | 71.88 | 103.0 | 66.86 |
| NAB07 | 12.27 | 834.71 | 48.23 | 58.82 | 88.17 |

| Patient | $c_{sAb}$ (day$^{-1}$) | $c_{sAb}$ (day$^{-1}$) | $c_{Ab}$ (day$^{-1}$) | Conversion factor (nM/(μg Ab/mL blood)) | $E$[a] | $\sqrt{E/n}$[b] |
|---|---|---|---|---|---|---|
| NAB02 | 2.007 | 0.1002 | 0.0915 | 5.700 | 12.27 | 0.7644 |
| NAB04 | 99.59 | 0.1014 | 0.1707 | 6.296 | 11.78 | 0.7490 |
| NAB05 | 21.83 | 3.419 | 0.0594 | 7.233 | 4.01 | 0.4370 |
| NAB06 | 0.1331 | 2.575 | 0.0500 | 6.279 | 13.87 | 0.8127 |
| NAB07 | 17.71 | 1.714 | 0.044 | 8.049 | 8.27 | 0.6275 |

[a] $E$ is the squared difference of the logarithms (base 10) of simulated and observed viral loads.
[b] $n$ is the number of data points.

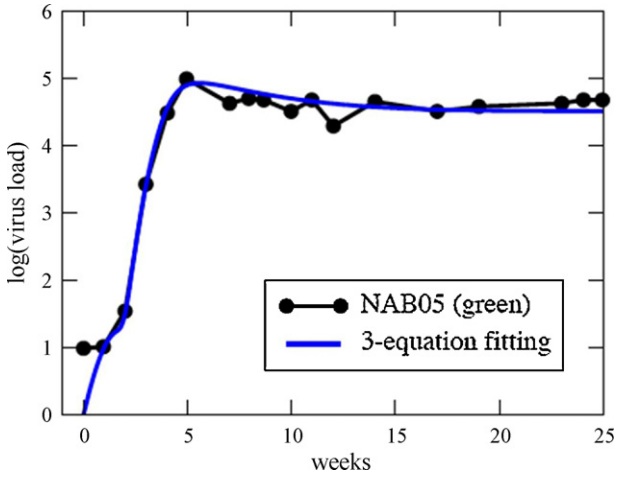


**Fig. 3.** The virus rebound of patient NAB05 of Ref. [3] (circles) and the fitted three-equation model (Eqs. (1)–(3)) after discontinuing the ART therapy in the absence of passive antibody administration.

passive immunization assay. Since 2G12 does not cross-react with self, we assume that the half-life of 2G12 can be used to estimate the natural clearance rate of HIV monoclonal antibodies. Therefore, our estimation of $\mu_{Ab} \approx 0.059\,\text{day}^{-1}$ obtained by varying the antibody clearance rate is quite reasonable. Our central hypothesis is that 4E10 and 2F5 have a shorter half-life than 2G12 because they cross-react with self. Our estimation of the clearance rate of self epitopes and antibody complexes gives us a half-life less than a day.

In Fig. 4A we see that if we use the fitted parameters and only increase the antibody level by 50-fold, the virus amount is effectively suppressed while passive antibody treatment is performed. Consistent with the analytical results in Section 3.1, to suppress the viral load with broadly neutralizing antibodies, a much higher level of antibody treatment is required. In Fig. 4B and C the evolution of uninfected and infected T-cells dynamics is predicted from the model. After the antibody treatment is discontinued the viral load rebounds again. For higher levels of antibody, the time required to rebound takes longer. In order to continuously suppress the viral load, a continuous source of antibody is required. This indicates the importance of having a natural source for these antibodies.

## 4. Discussion

The broadly neutralizing antibodies 2F5 and 4E10, which target the gp41 membrane proximal region, are cross-reactive with self, and we have shown that the competition from self can limit their efficacy in passive immunization studies [3]. Recently, another mathematical model [18] (which did not consider self epitopes) raised concerns that there could additionally be competition between broadly neutralizing and strain-specific antibodies. The competition with self can be overcome by sufficiently high levels of broadly neutralizing antibodies, so it is worth considering whether these levels could be accessed by the humoral response. Although there is evidence that tolerance mechanisms suppress production of 2F5 and 4E10 [19], such mechanisms could potentially be overcome if doing so would lead to therapeutic advantages. Perelson et al. [20] predict that, in a humoral response, one can achieve a maximum antigen-specific antibody level of 1300 μg/ml, which is equivalent to ~10 μM for IgG and ~1.5 μM for IgM. These concentrations would be in a range to have a potential impact on viral loads and, in turn, transmission. Alternatively, one could imagine overcoming the inhibitory effect of self-epitopes by raising

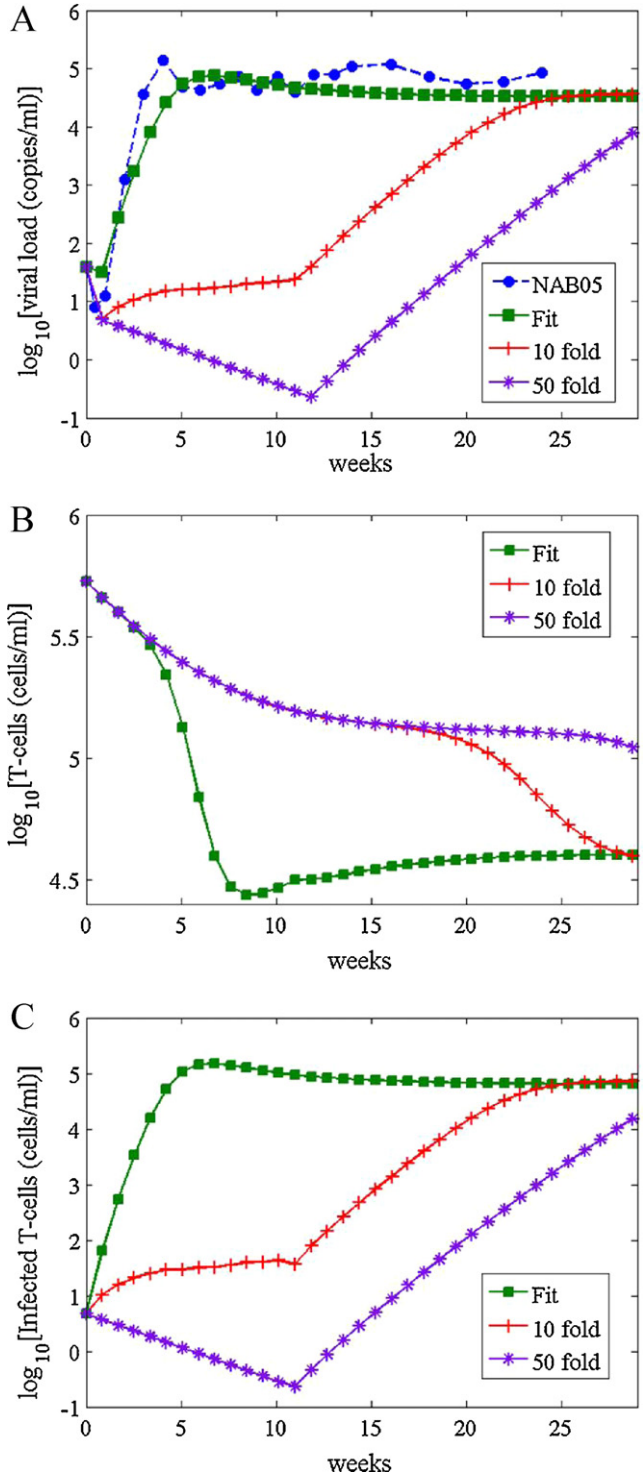


**Fig. 4.** Best-fit model for patient NAB05 of Ref. [3]. (A) Viral load, (B) un-infected T cells, and (C) infected T cells. The model is defined by Eqs. (1)–(8) as discussed in Section 2. The Ab treatment period is the first 11 weeks. The red + and purple * demonstrate the dynamics if the level of the injected antibody is increased 10- and 50-fold. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

(or administering) self-specific antibodies (e.g., anti-cardiolipin), although care would be required to limit autoimmunity.

More immediately, our study suggests that it would be useful to examine the effects of incorporating self epitopes into assays *in vitro*. Indeed, it has been demonstrated experimentally that the binding of poly-reactive anti-self antibodies toward a specific

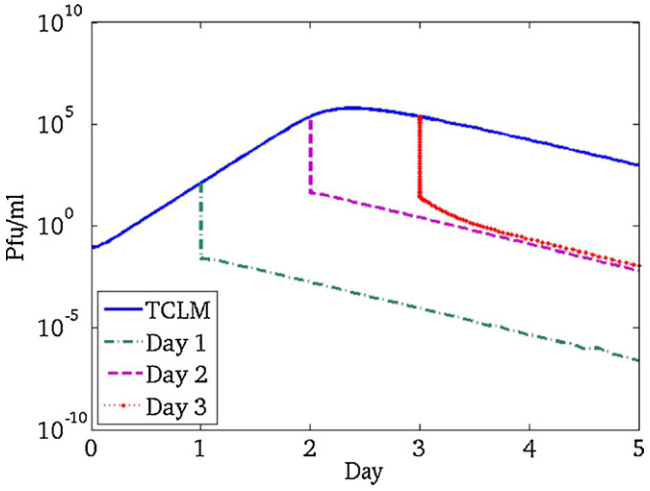


**Fig. 5.** The drop of the infectious viral concentration after passive immunization is implemented to the target cell-limited model (TCLM) after days 1–3.

foreign antigen can be masked by cross-reaction with self-antigens [21,22]. Past *in vitro* studies on broadly neutralizing antibodies for HIV did not consider competition from self. For instance, Manrique et al. [8] studied the *in vivo* and *in vitro* escape of HIV from 2F5, 4E10 and 2G12 antibodies. They report that in contrast to 2G12, which is not cross-reactive, they do not observe any viral mutation that can lead to resistance to 2F5 and 4E10 *in vivo*; furthermore, they observed that the virus mutates differently *in vivo* and *in vitro*. It would thus be worth revisiting *in vitro* escape studies and incorporating self epitopes as a step toward further understanding broadly neutralizing antibodies. Finally, since we initiated this work, some additional broadly neutralizing antibodies were identified [23,24]. Our study suggests that it could be worth carefully characterizing their self reactivity and revisiting passive administration with these antibodies.

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## Appendix A.

In the main text, we focused on chronic HIV infection. The competition between viral and self epitopes requires the dose of antibodies to be above a threshold to be effective. Because passive immunization has been shown to be effective against influenza A and there are reasonable quantitative data [9], it is worth developing a model of passive immunization in the context of an acute infection. To this end, we adapt a simple model for influenza A infection [25]. The infection is limited by the availability of susceptible target cells rather than the immune response in this model. Mathematically, it is equivalent to Eqs. (1)–(3) with $\lambda_T$, $d$, $\varepsilon_{drug}$, and $\omega$ set to zero. As above, we represent the injection of broadly neutralizing antibodies by Eq. (3′). The difference is that, because the system is no longer at steady-state at the time of injection, we initially simulate with Eq. (3) and then suddenly switch to Eq. (3′). We model the antibodies binding to the virus with Eqs. (4) and (7). Because only a single dose of the antibody is injected in Ref. [9], we set $\lambda_{Ab}$ to zero. Moreover, we assume the influenza A broadly neutralizing antibodies do not interact strongly with self epitopes and set $k_s^a$ and $k_s^d$ to zero.

We take the parameters for modeling the acute infection from Ref. [25]: infection rate constant $\beta = 1.89 \times 10^{-5}\,(\text{PFU/ml})^{-1}\,\text{day}^{-1}$, average rate of increase of viral titer per infected cell $p = 1.7 \times 10^{-2}\,(\text{PFU/ml day}^{-1})$, viral clearance rate $c_v = 3.0\,\text{day}^{-1}$, and infected cell death rate $\delta'_I = 4.0\,\text{day}^{-1}$. The initial value of $T$ is $4 \times 10^8$ cells. In Ref. [25], the viral infectious titer is expressed in 50% tissue culture infective doses ($\text{TCID}_{50}$). Here, we are interested in the number of infectious viruses per ml rather than the $\text{TCID}_{50}$. If $m$ is the mean number of infectious units per volume (PFU/ml) and $P_0$ is the proportion of negative test tubes, then by assuming a Poisson distribution, we have $P_0 \approx e^{-m}$. For any titer expressed as a $\text{TCID}_{50}$, $P_0 = 0.5$. Thus $e^{-m} = 0.5$ and $m = -\ln 0.5$ which is $\sim$0.7. Therefore, we multiply the $\text{TCID}_{50}$ titer by 0.7 to estimate the mean number of infectious viruses.

In Ref. [9], 15 mg/kg of broadly neutralizing antibodies were passively injected into mice at days one, two or three after they were infected with influenza. They observed a significant suppression of the viral load in the lungs. If we assume that the average blood volume for a laboratory mouse is 6–8% of the total body weight, then we obtain an initial antibody concentration $[Ab]_0 \approx 1500\,\text{nM}$ or $[Ab]_0 \approx 10^{15}$ molecules/ml. We use this as the initial level of the antibody in the model. The kinetic parameters for antibody-influenza binding are measured In Ref. [9]. In Eq. (3), we use $k_v^a = 10^{-10}\,(\text{particles/ml})^{-1}\,\text{day}^{-1}$ for the association rate and $k_v^d = 10\,\text{day}^{-1}$ for the dissociation rate.

In Fig. 5 we can see that the infectious viral concentration is significantly suppressed after injecting the antibody at days one, two and three. The result is consistent with the experimental results of Ref. [9], where they see a 1000-fold suppression in the level of infectious virus at day 4 in the lungs of mice after a passive administration of broadly neutralizing antibodies. This reflects the absence of self competition rather than differences between chronic and acute infection dynamics, as passive immunization is also predicted to be effective by the models in the main text with $k_s^a$ and $k_s^d$ set to zero (Fig. 1).

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