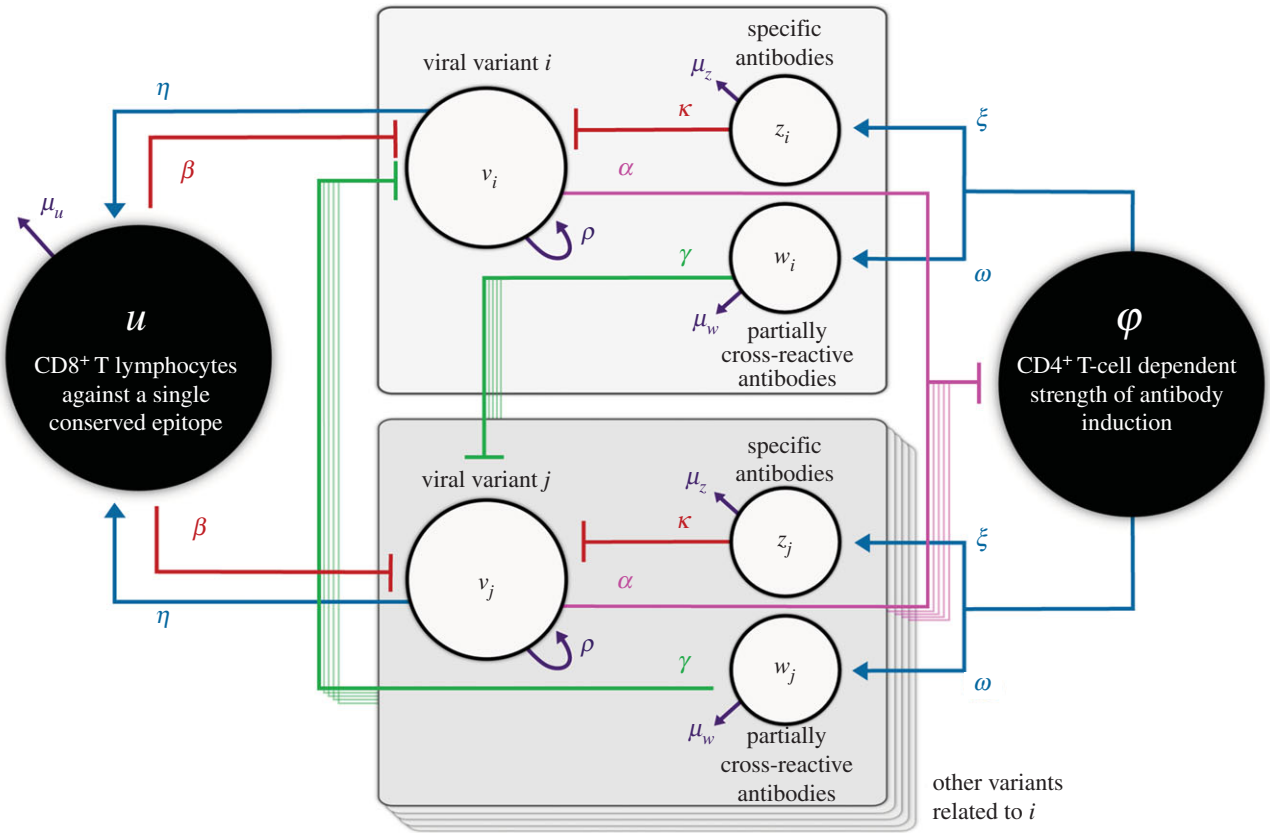

Figure 1. Model schematic. The population of viral variants of antigenic type i (v_i) stimulates (shown by blue arrows) specific and partially cross-reactive antibodies as well as non-specific effector CD8$^+$ T-cell responses. CD4$^+$ T-cell help is essential for the induction of the antibody responses. v_i can be attacked by all of these responses (shown by red bars) as well by partially cross-reactive antibodies (shown by green bars) raised against other variants j (stacked one behind the other) which share epitopes with i. CD4$^+$ T-cells are attacked by all viral variants (as shown by pink bars): this is captured in the model by a reduction in CD4$^+$ T-cell dependent strength of antibody induction, φ. All viral variants grow at a rate ρ; μ_u, μ_w and μ_z, respectively, represent the death rates of effector CD8$^+$ T cells, specific and partially cross-reactive antibodies. See §5 Material and methods for further details.

it has been demonstrated that NAbs can exert potent antiviral effects at low or even undetectable titres in both humans [25] and in non-human primate models [26].

Here, we reconcile these conflicting observations using a model in which virus control is achieved by a combination of short-lived responses against CD8$^+$ T-cell epitopes as well as long-lived antibodies to more diverse surface antigens. We use this framework to show antibody responses can also retard escape from CD8$^+$ T-cell responses and lead to strong fluctuations in the frequency of CD8$^+$ T-cell escape mutants during the course of infection. Escape from CD8$^+$ T-cell responses accelerates disease progression; however, the ultimate breakdown of virus control is linked to the loss of antibody induction due to depletion of CD4$^+$ T cells.

2. Model structure

We visualize the virus as containing (i) CD8$^+$ T-cell epitopes of limited variability that elicit cytotoxic responses [27] that decay rapidly in the absence of antigen [5,28], (ii) highly variable epitopes (specifically in the Env glycoprotein) that elicit both highly specific NAb responses maintained by long-lived plasma cells [29,30] and more broadly cross-reactive responses (CR-Ab) of shorter duration. Within our model, CD4$^+$ T cells are necessary for the induction of the antibody responses but do not influence the induction of effector CD8$^+$ T-cell responses (although they may have a role in the establishment of CD8$^+$ T-cell memory). Finally, we assume that CD4$^+$ cell counts decline at a rate proportional to viraemia. A schematic of the model structure is provided in figure 1 and the corresponding equations are shown in §5 Material and methods.

3. Results

(a) Viral dynamics

The observed dynamics of viraemia during the natural course of HIV-1 infection, with respect to three critical features, are readily generated under the minimal set of assumptions outlined above:

(i) The initial increase in viraemia triggers CD8$^+$ T-cell responses as well as short-lived non-neutralizing partially cross-reactive antibody responses; highly specific NAb responses are induced at a slower rate as they have to undergo affinity maturation and therefore do not reach detectable levels until several months after infection [14,15]. Through a combination of these processes, a dynamic equilibrium is established in which viraemia fluctuates around a steady set-point, while CD4$^+$ T-cell counts continue to decline (figure 2*a*).

(ii) When CD4$^+$ T-cell counts drop to very low levels, antibody induction is compromised and a rapid transition occurs to a different dynamical state with a significantly higher viraemia corresponding to the clinical condition of AIDS (figure 2*a*). The difference in lifespan of effector

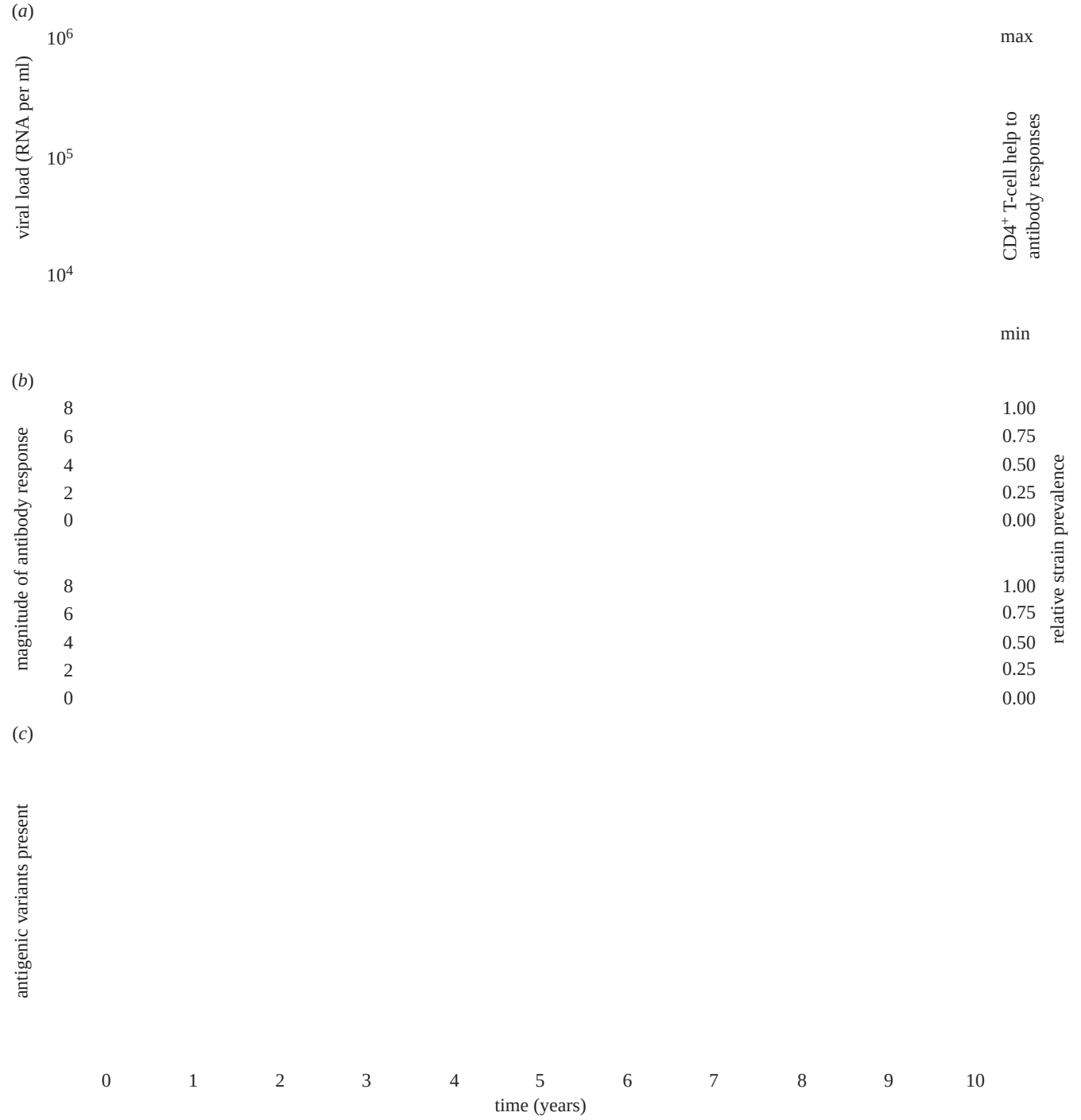

Figure 2. Viral dynamics. (a) Changes in viraemia (solid multicoloured line) and $CD4^þ$ T-cell help to antibody responses (dashed grey line) during the course of an infection, with the colour of the line illustrating which of the 81 possible antigenic variants is most prevalent at each time point. The black line shows a rolling average of viraemia over the three months preceding the timepoint or, when peak viraemia occurred less than three months earlier, the average over the period from peak viraemia to that timepoint. (b) Changes with time in specific (black line) and cross-reactive (grey line) antibody responses (given in arbitrary units) against two particular antigenic variants whose relative prevalence is shown by green and red lines, respectively. (c) Each line tracks the prevalence of an antigenic variant with dots indicating a prevalence in excess of 10%. Re-emergence is indicated by a dashed line connecting periods of prevalence in excess of 10%. The two variants presented in (b) are shown by the dashed arrows. (Parameters: r ... 8; $1/m_u$ ... 10 days; $1/m_w$ ... 100 days; $1/m_z$ ... 1000 days; b ... g ... k ... 1; $w(0)$ ... 1; h ... j ... v ... 3.2 10^{25}; $1/a$ ... 1.6 10^7 days; antigenic variants are defined by combinations of four epitopes, each with three possible states, i.e. a {3,3,3,3} system.)

$CD8^þ$ T cells as compared with NAb responses is the principal cause of the sharp increase in viraemia when the $CD4^þ$ T-cell count drops below a certain threshold (electronic supplementary material, figure S1a); this increase may be augmented by the loss of partially cross-reactive antibodies which also rely on $CD4^þ$ T-cell help for induction (electronic supplementary material, figure S1b,c). However, long-lived antibody responses tend to induce wider fluctuations around set-point (electronic supplementary material, figure S1d–f). At present, there is insufficient empirical data concerning variation in viral load during chronic infection to suggest which combination of $CD8^þ$ T cell and antibody lifespans most closely reproduces the dynamics of HIV-1, but empirical estimates (less than 50 days) for effector $CD8^þ$ T-cell responses