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Agent based modeling of viral infections: an investigation across several spatio-temporal scales

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Publication date

2014

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Citation for published version (APA):

Mancini, E. (2014). *Agent based modeling of viral infections: an investigation across several spatio-temporal scales*. [Thesis, fully internal, Universiteit van Amsterdam].

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5. *In silico* studies reveal two phases of sustained response of a patient's immune system to treatment during primary HIV infection

5.1 Introduction

The question when to initiate combination antiretroviral therapy (cART) is still a core controversy within the medical community [1-3]. The controversy revolves around two main issues: the first is fighting the HIV pandemic at global level and the second is choosing the treatment strategy that increases the life expectancy and the quality of life of individual patients. Regarding the first issue the general opinion has shifted toward the Test & Treat strategy that recommends continuous treatment as soon as they are identified [4]. The rationale behind this choice is that suppressing HIV viral load lowers the risk of new infections, possibly reducing the size of the epidemic [5-7]. Despite the most recent US guidelines recommend adopting the Test & Treat strategy many researchers are strongly advocating further evaluation of the consequences of such strategy and its real chances of defeating the pandemics [8-10]. However, identifying the best treatment strategy for an individual patient is still an unsolved problem and is the topic of this paper.

Since 1998 the National Institute of Health has updated guidelines in which, over the years, the best time to start cART for an individual patient has slowly shifted toward earlier treatment [4]. Recently, several studies reported benefits of temporary cART during the primary infection including lowering of the viral setpoint [11, 12] and limitation of viral reservoirs [13], which re-opened the discussion of starting treatment early. On the other hand, various studies have not observed changes in the viral setpoint [14, 15] or have reported a worsening in the disease progression [16, 17]. Because of such conflicting results the optimal conditions to start cART are still controversial.

The currently available clinical data is insufficient to identify the most opportune time for the patient to start treatment. Although new clinical trials are being performed, the potential risk to patients' health slows down the clinical investigations. Our aim is to predict quantitatively the sustained response of the immune system to HIV infection with respect to treatment, during the first 4 years post infection. To this end we define a Sustained Response Score (SRS) for the adaptive immune response to a perturbation at a given time post-infection, under the assumption that cART perturbs the progression of the untreated HIV infection in the infected patients. We validate our predictions numerically and by use of available clinical data from the Primo-SHM study [18]. Obtaining statistical significance requires a large dataset on the concentration of T helper lymphocytes and viral particles over time. Data from hospitals and clinical trials is too sparse, providing only up to a few data points per patient. Therefore we generate datasets by simulating the HIV infection in 500 virtual patients for a period of 6 years post infection in time steps of 8 hours. We perform the simulations using an established agent-based model that has been validated using clinical data [19-23].

5.1.1 Model

We model the adaptive immune response to HIV infection in each virtual patient by simulating individual immune cells, viral particles, and cytokines, which interact in a volume of four microliters of a lymph node (Figure 1a). For this purpose we use C-ImmSim, a validated agent-based model of HIV infection [19-23]. The free parameters of this model have been tuned and validated against clinical data over the past 10 years. The first reason for choosing C-ImmSim is that it can be used to interpolate existing clinical data. The second reason is that it simulates the underlying virology of the adaptive immune response more closely than mathematical models [24-27]. The study of HIV through cellular automata and agent-based models is quite common [19-23,28-30] due to the discrete nature of the biological entities involved as well as the complexity of their collective dynamics. The main advantage of C-ImmSim over mathematical

models for HIV infection lies in its ability to simulate different populations of each cell type, distinguished by their specificity to the HIV virus. We assume that mechanisms like cross-reactivity, affinity maturation and the complex interplay of the HIV virus with the different subsets of immune cells play a fundamental role in the HIV dynamics. C-ImmSim has been used to investigate the differences in early versus deferred treatment [21] and phenomena associated with the HIV infection [19,20,22,30].

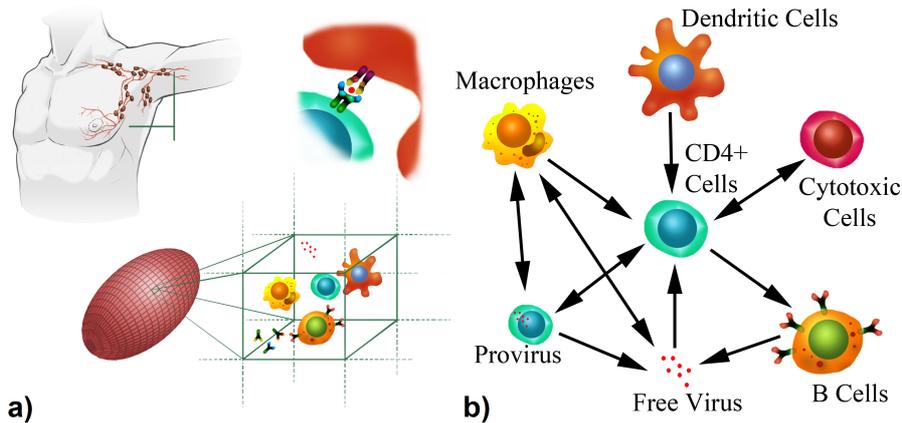


Figure 1. a): The in silico experiments are performed in a 3-dimensional ellipsoidal lattice. The lattice represents a lymph node with a volume of 4 microliters. Each lattice point represents a microscopic volume in which stochastic interactions occur between the modeled entities. Some of the entities in the model are shown in the sketch: $CD4^+$ T-lymphocytes, B-lymphocytes, antibodies (Ab), macrophages (MA), dendritic cells (DC) and interferon γ ; b): The interactions between the main cellular compartments in the adaptive immune response. This network describes the adaptive immune response to HIV, that in our model is simulated by a three dimensional agent-based model of a lymph node. The virus can be in two forms: free virus (infectious virions) and viral genome copies contained in both silently and actively infected cells (provirus). The complexity of this network does not lie in its topological complexity but is hidden in the complex spatio-temporal interactions (arrows) between the nodes.

The network of interactions between the main cellular compartments involved in the adaptive immune response and the virus is

summarized in Figure 1b. The complexity of this network lies in the edges (the interactions) and not in the connectivity of the nodes.

5.1.2 Virtual clinical data

We vary three parameters to generate 500 different virtual patients: the first two parameters represent the two major histocompatibility complexes (MHC-I and MHC-II) of the virtual patients' immune cells. The third parameter distributes up to 4096 different MHC-I and MHC-II cell receptors over the population of cells for the specific patient. The virtual clinical data used for this analysis consists of cell counts per microliter for each of the main cellular entities involved in the adaptive immune response: T helper lymphocytes ($CD4^+$ cells), cytotoxic lymphocytes, macrophages, B cells and dendritic cells. In addition, the data includes viral particle counts per milliliter (viral load) and the amount of virus inside the infected cells per microliter (provirus). The model stores both cellular and viral data for every 8 hours of simulated time from a single lymph node of 4 microliters for each of the 500 different virtual patients. A minor limitation of the model is that it simulates the immune response to the HIV virus only in a lymph node and not in other types of lymphatic tissues that have different cellular densities. This limitation has been addressed during the validation of the model, when we used clinical data on viral load, $CD4^+$ cell counts and time to AIDS. In this sense our model of the HIV response in a lymph node replicates the dynamics of the HIV infection in an infected patient.

5.1.3 Sustained response score

Let X and Y be two stochastic dynamical processes for a given initial state, i.e., each element $X(t)$ is a random variable of the state of process X at time t . We define the point-to-point sustained response score $S_{X \rightarrow Y}(t, t + \Delta)$ of the state of a stochastic process $Y(t + \Delta)$ on the

previous state of another stochastic process $X(t)$ by their mutual information [31], defined as

$$S_{X \rightarrow Y}(t, t + \Delta) = I(X(t), Y(t + \Delta)) = \sum_{x \in X(t)} \sum_{y \in Y(t + \Delta)} p(x, y) \log \left(\frac{p(x, y)}{p(x)p(y)} \right). \quad (1)$$

Where, $p(x, y)$ is defined as the joint probability that $X(t)=x$ and $Y(t)=y$; $p(x)$ and $p(y)$ are the corresponding marginal probabilities.

For combinations of the stochastic processes of the provirus and CD4⁺ cells Equation 1.1 describes a causality relation because there is no third process that influences both provirus and CD4⁺ cells simultaneously. This would create a non-zero mutual information due to correlation [32,33]. The only exception here is in the macrophages processes, but their dynamics is considerably noisier than that of CD4⁺ cells and provirus. The main contribution of the macrophages is to act as reservoirs but such characteristic is already contained in the provirus process.

We use this point-to-point sustained response score $S_{X \rightarrow Y}(t, t + \Delta)$ to define a point-wise sustained response score $S_{X \rightarrow Y}(t)$ as the characteristic time at which $S_{X \rightarrow Y}(t, t + \Delta)$ decays to a constant as function of Δ . Intuitively, this is how long a state of process X at time t has an effect on the subsequent behavior of process Y . We observe that $S_{X \rightarrow Y}(t, t + \Delta)$ typically first grows to a peak and then decays roughly exponentially, as function of Δ (see Methods). Therefore, in words, we define the sustained response score $S_{X \rightarrow Y}(t)$ as the time of the peak μ plus the half-time of the decay τ , and multiply this quantity by the height of the peak ι in order to correct for the magnitude of the impact. SRS is a measure of the response of the immune system of a patient to a temporary treatment. A high SRS at time t means the

beneficial effect of treatment started at time t will last longer. In formula,

$$\begin{aligned}
S_{X \rightarrow Y}(t) &= \iota \cdot (\mu + \tau), \text{ where} \\
\iota &= S_{X \rightarrow Y}(t, t + \mu), \\
\mu &= \arg \max_{\Delta} S_{X \rightarrow Y}(t, t + \Delta), \\
\tau &= \left\{ \Delta > \mu : S_{X \rightarrow Y}(t, t + \Delta) = \frac{1}{2} \cdot \iota \right\}.
\end{aligned} \tag{2}$$

5.2 Results

We focus our analysis on the three most important indicators of the HIV infection: CD4⁺ cells (T helper lymphocytes), Provirus (the amount of virus hidden in infected cells) and viral load (\log_{10} viral RNA copies/ml). The key elements to evaluate the progression of HIV in a patient are its CD4⁺ cell count and the amount of viral genome copies in the infected cells (provirus) whose role in the survivability of virtual HIV infected patients has been already shown [30]. The role of provirus in the HIV infection has been recently reassessed experimentally, indicating that the size of replication-competent latent HIV reservoirs can be up to 60-fold greater than previously estimated [34]. Since early treatment has been reported to affect the size of HIV reservoirs [13] and the viral set point [11, 12], both directly related to the provirus, the SRS of the provirus with respect to other indicators (Figure 2c and 2d) is a relevant quantity for the most opportune timing of a treatment.

Our results confirm that the immune system has the longest sustained response to treatment during the acute phase of the HIV infection, as indicated by a very high SRS during the first two months after infection. In addition to this phase the results indicate a secondary phase during which the SRS plateaus are still at a relatively high value. The duration of this phase is roughly ten months. In Figure 2 we show the SRS of all the possible pairs with provirus and CD4⁺ cells counts. Each point of the SRS curve is the product of the mutual information at the peak (green marker in Figure 2e) and the sum of the

delay in the mutual information peak plus the information dissipation time. In Figure 2e each graph shows the change in mutual information in the $CD4^+$ cells over time generated by a perturbation of the provirus level at the initial time point (respectively at about 2, 6 and 22 months post infection as indicated by the red markers in Figure 2d).

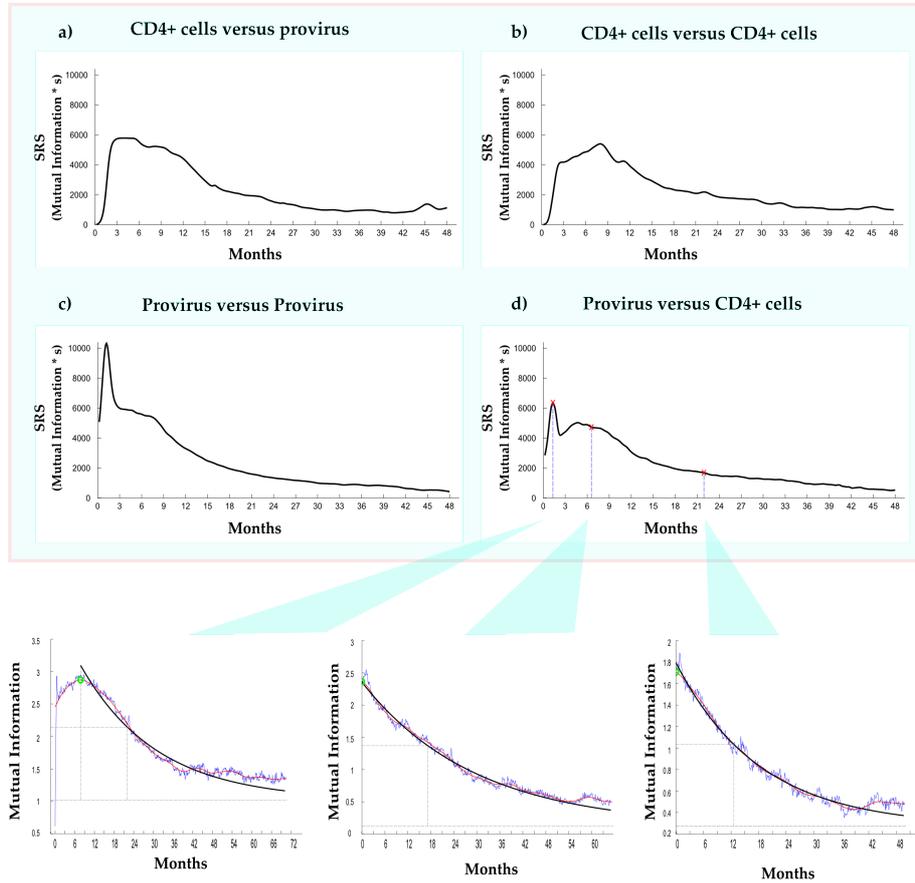


Figure 2: Panels a,b,c,d: Sustained Response Score over time of all the possible pairs with $CD4^+$ cells counts and provirus. SRS is proportional to the duration of the response of the immune system to a temporary treatment. A high SRS at time t means the beneficial effect of treatment started at time t will last longer. Each panel shows the SRS of the second entity to changes in the first entity. For example panel d shows the effect on the $CD4^+$ cell count due to a change in the provirus. Panels a and b show a plateau in the SRS of $CD4^+$ cells

in the first 12 months post infection. The SRS for the plateau is 5 times higher than the SRS relative to the chronic phase of the infection. Panels c and d show as expected a peak in the SRS of the provirus during the acute phase of the HIV infection. After this peak we observe a plateau (until 10 months post infection) with a SRS about 5 times higher than the SRS of the chronic phase on the infection. The plateaus in the four panels show the increased beneficial effects of cART during the first 10 months post infection. The red markers in panel d represent the SRS calculated from the Mutual information graphs shown in panel e. Panel e (lower set of 3 graphs): Mutual information for provirus at time t versus $CD4^+$ cells over time. Mutual information is a measure of the correlation of the $CD4^+$ cell count over time to changes in the Provirus at various times (90 days, 180 days and 500 days respectively). From a medical perspective it measures the impact on the $CD4^+$ cells recovery if the size of HIV reservoir is affected by treatment with cART at a given time. The curve fitting was performed over all the data points after the peak of mutual information. We used an exponential curve fitting to calculate the information dissipation time as the time at which 50% of the information over the baseline was lost.

5.2.1 $CD4^+$ cells Sustained Response Score

The sustained response score for $CD4^+$ cells in the first 10 – 12 months post infection, shown in Figure 2a and 2b, is significantly higher than the baseline, where the baseline is defined as the SRS at the chronic phase of the infection. For the $CD4^+$ cell count we find that there is only one phase of sustained response due to treatment that lasts up to 12 months post infection. Interestingly during the acute phase the SRS of $CD4^+$ cells is low. The phase of high SRS could mark the period during which a fluctuation in the total amount of T lymphocytes might have a long lasting effect on the disease progression.

5.2.2 Provirus Sustained Response Score

The sustained response score of the provirus is characterized by two phases: an initial intense but short phase and a longer but milder secondary phase. The initial phase of sustained response closely follows the acute phase of the HIV infection and has a SRS about 5 times higher than the baseline score pertaining the chronic phase of

the infection. This first phase lasts only a few weeks but starting cART during this phase, as expected, ensures the long-term benefits documented in literature [21, 35]. The secondary phase starts at about 3 months post infection and lasts about 6 months. During this secondary phase of sustained response, although clearly lower than during the acute phase of the infection, the HIV infection still has a SRS significantly higher than the baseline level for the next four years of infection. This higher score implies that a perturbation in the system, such as temporary cART, will have a longer lasting effect than a similar treatment applied anytime after this period. In other words, reducing the growth of provirus (a measure of HIV reservoirs) during this secondary phase of sustained response has a long lasting effect both on the size of HIV reservoirs (Figure 2 panel c) and on the CD4⁺ cells counts (Figure 2 panel d) at later times.

5.2.3 Validation

Our interpretation of the SRS is validated numerically and by a clinical study published in 2012 by the PRIMO-SHM study group [18]. The clinical study assessed the benefits of temporary cART during primary HIV infection. It shows that a period of 24 weeks of cART started within 6 months post infection lowers the viral set point and defers the restart of cART during chronic HIV infection. This is consistent with our prediction that a secondary phase of strong sustained response lasts up to about 10 months post infection.

In Figure 3 we compare the simulation results for 500 virtual patients with the clinical data from PRIMO-SHM study. In absolute terms the simulation results are shifted compared to the clinical data. A possible explanation is that in PRIMO-SHM all the enrolled patients had a symptomatic acute infection, which could indicate a bias to fast progressors. In our simulations we excluded such fast progressors. This explanation is supported by the lower CD4⁺ cell counts observed in the clinical trial in comparison to the simulated ones. A more aggressive infection might also explain the stronger effect of

temporary treatment on the viral set point observed in the PRIMO-SHM trial.

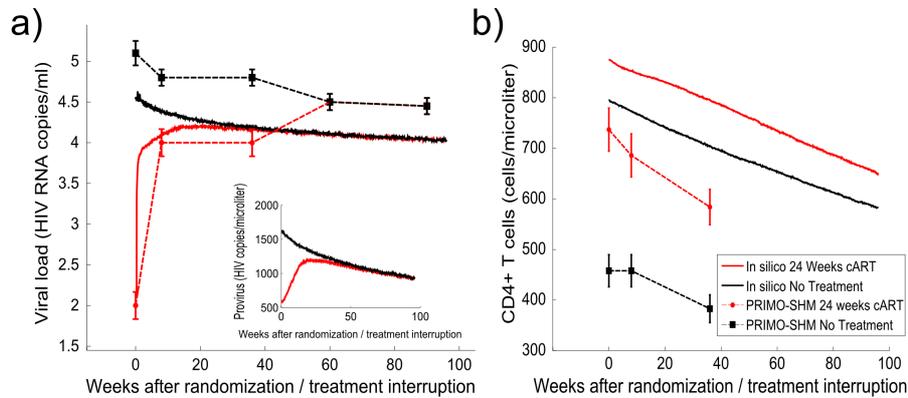


Figure 3: Validation. Comparison of the in silico experiments (continuous lines) with clinical data of the PRIMO-SHM study group (circle and square markers) on viral load and CD4⁺ cell count after randomization/treatment interruption in the no treatment and treatment arms. Although in both panels the clinical data appears to be rescaled by a constant factor, the dynamics is qualitatively comparable. In the inset of panel a) we show the prediction of the effect of temporary cART on the size of HIV reservoirs after treatment interruption.

Qualitatively in both in silico experiments and clinical data the temporary treatment has a long lasting effect on both CD4⁺ cell counts and viral load. In our experiments the viral load converges to the untreated level after roughly one year, faster than observed in the Primo-SHM study. Conversely the CD4⁺ cell counts in our experiments show the same dynamics of the clinical study.

5.3 Discussion

The PRIMO-SHM clinical study shows that starting a temporary cART within 6 months post infection lowers the viral set point. However, it is unknown to what extent this effect is due to patients in the acute phase. It is known that temporary cART administered during the

acute phase has a life long effect, but it is unclear how this effectiveness decreases over time. We predict a phase of long-lasting sustained response during the acute phase followed by a plateau of roughly ten months during which the sustained response of the immune system is still more intense than the one relative to the chronic phase. Our study provides an explanation to the temporary beneficial effect of cART observed in the PRIMO-SHM study.

It is well known that cART is associated to an increase in the CD4⁺ cells count at any time during the HIV infection. Less is known about the effects of cART on HIV reservoirs at different stages of the infection. In our analysis the size of HIV reservoirs evaluated by the provirus is reduced by the use of temporary cART for a period of about 1 year after treatment interruption. The correlation between the survivability of patients and the size of the population of infected cells has been observed in in silico experiments [30], highlighting the importance of controlling HIV reservoirs to reduce the number of deaths in the long term. The temporary reduction of the size of HIV reservoirs confirms the previously observed lack of long-term effects of treatment started after the acute infection. The inability of the immune system to identify and eliminate silently infected cells of the HIV reservoirs is a possible explanation of the slow decrease of Provirus under cART.

5.4 Methods

5.4.1 Estimating mutual information from discrete data

The mutual information $I(X_t, Y_u)$ between the random variables X_t and Y_u is estimated by constructing an equidistant contingency table [33] of the two corresponding vectors x_t^1, \dots, x_t^{500} and y_u^1, \dots, y_u^{500} , which are the 500 cell counts of all virtual patients at time t . To construct this table we divide the range of values of each vector into h bins of equal size. Here we use a variable h proportional to the resolution at which we discretize the data. We set the resolution parameter at 0.05. This allows us to use more bins when the variance

in the data becomes bigger. Two observed pairs of cell counts are considered equal if they fall into the same bin.

In general, mutual information measures both causation and correlation simultaneously. However, here we use mutual information as a measure of causation due to the particular underlying dynamics of the HIV immune response, shown in Figure 1b. For the pairs of cell types we analyze, there is only a directed path between the cell types; there is no third cell type that has a directed path to both analyzed cell types.

5.4.2 Estimating the time-delay τ of the peak mutual information

We calculate the mutual information using data from 500 virtual patients with different immune systems. The heterogeneity of the virtual patients is necessary to model the observed variability in the immune response to HIV and the stochastic properties of the model introduce noise in the data. In order to identify the presence of a peak in the mutual information averaged over the whole set of virtual patients we need to filter such noise. To do so we use a Gaussian kernel with a fixed bandwidth for a Nadaraya-Watson kernel regression [36]. After smoothing the average mutual information we observe two main types of curve: in the first type the mutual information has a peak at time 0 and decreases exponentially toward an asymptotic value. This means that the amount of information the first entity possesses about the second entity is highest at time 0 and decreases afterward. In the second type we observe a delay in the peak in the mutual information. This can be interpreted as the first entity having more information about the status of the second entity that is a number of time steps in the future.

5.4.3 Estimating the information dissipation time d_i

We calculate the information dissipation time for each mutual information curve by fitting an exponential function to the mutual information curve. For the curves with a time-delay in the peak of mutual information we fit only the data from the peak onward. The

information dissipation time d_i is defined as the number of days between the time of the peak of mutual information and time at which 50% of the intensity is lost.

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Supporting Information

In Figure S1 we show the three indicators that drive the SRS of all the possible pairs with CD4⁺ cells counts and provirus. In each panel the first graph displays the delay in the peak of mutual information. This delay indicates the time it takes to a perturbation in a variable to have its maximum impact on the other variable. Such delay is present only in the pairs with CD4⁺ as the susceptible variable and disappears after the acute phase. The second graph shows the information dissipation time. Its calculation is discussed in the methods section. For all the pairs the information dissipation time is between three and seven times higher than the baseline in the first ten months post infection. This result clearly shows how a perturbation in the system during the first nine months affects the system for a much longer period than any other time in the first four years of the infection. The intensity of the mutual information peak over time is shown in the third graph of each panel. We observe a peak in the intensity corresponding to the acute phase of the HIV infection only in the pair with provirus as the susceptible variable. As expected the main peak is close to the acute phase, since the first month is crucial to the dynamics of the provirus as it aggressively infects healthy CD4⁺ cells. The unexpected result is the presence of a second period of about 24 months in which the mutual information peak starts to slowly lose intensity only after 12 months post infection.

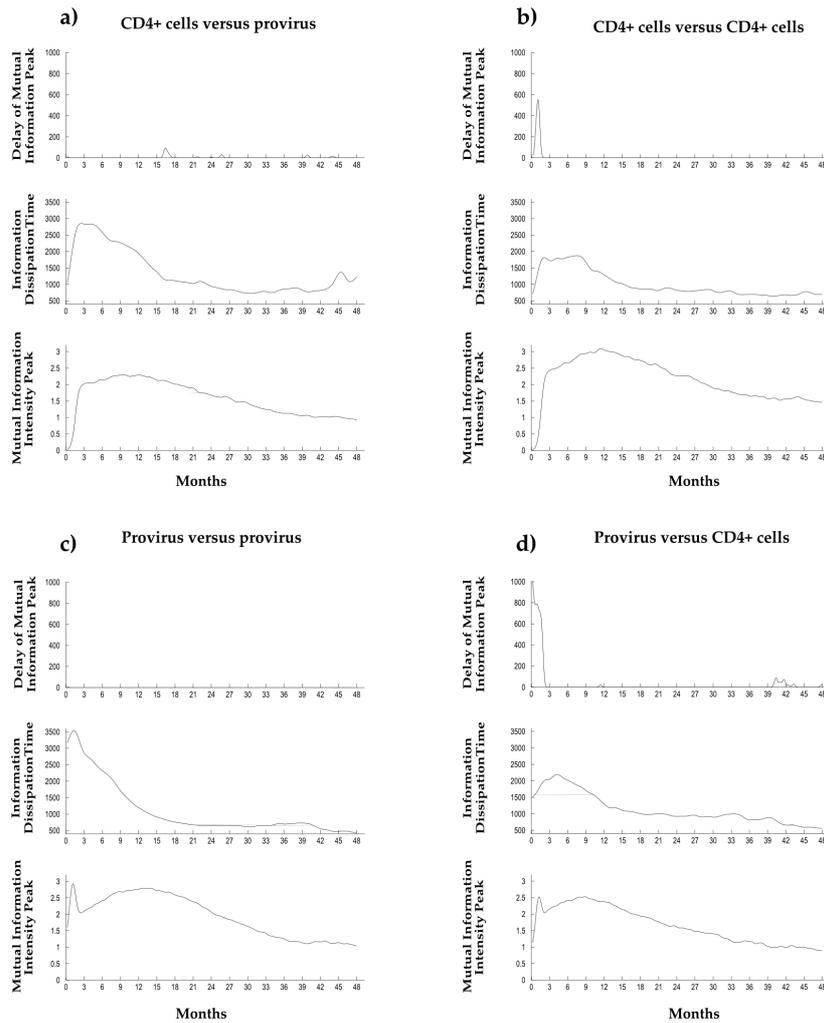


Figure S1: The three variables used to compute the SRS. Each panel a-d shows the value over time of the three variables for one of the possible pairs of $CD4^+$ cells counts and provirus. In each panel the first graph displays the delay in the peak of mutual information. This delay indicates the time it takes to a perturbation in a variable to have its maximum correlation on the other variable. The second graph shows the information dissipation time discussed in the methods section. The intensity of the mutual information peak over time is shown in the third graph of each panel.