Estimation of the initial viral growth rate and the basic reproductive number during acute HIV-1 infection

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Abstract

During primary infection, the number of HIV-1 virus particles in plasma increases rapidly, reaches a peak and then declines until it reaches a set-point level. Understanding the kinetics of primary infection, and its effect on the establishment of chronic infection, is important in defining the early pathogenesis of HIV. We studied the viral dynamics of very early HIV-1 infection in 47 subjects identified through plasma donation screening. We calculate how fast the viral load increases and how variable this parameter is among individuals. We also estimate the basic reproductive ratio, the number of new infected cells generated by an infectious cell at the start of infection when target cells are not limiting. The initial viral doubling time has a median of 0.65 days with interquartile range 0.56 – 0.91 days. The median basic reproductive ratio was 8.0 with interquartile range 4.9 – 11. In 15 patients, we also observed the decay of plasma virus post-peak and found that the virus decay occurred at a median rate of 0.60 day^{-1}, corresponding to a half-life of 1.2 days. The median peak viral load was 5.8 log_{10} HIV-1 RNA copies/ml and it was reached 14 days after virus was quantifiable with an assay with a lower limit of detection of 50 copies/ml. These results characterize the early plasma viral dynamics in acute HIV infection better than it has been possible thus far. They also define better the challenge that the immune response (or therapeutic intervention) has to overcome to defeat HIV at this early stage.
Introduction

During primary infection, the number of HIV-1 virus particles in plasma increases rapidly, reaches a peak and then declines until it reaches a set-point level (i.e. a quasi-steady state) (3, 26). Often, the peak in viral load coincides with the first appearance of an acquired immune response. Thus, early HIV infection can be seen as a race between the immune system and the virus (4). It has been suggested, based on the macaque model with SIV infection, that the early viral expansion is somewhat homogeneous across subjects, but the set-point viral load varies by orders of magnitude (14). However, studies with SIV also suggest that the early events during viral expansion, i.e., before the peak, are important in defining the set-point viral load later in infection (14).

Thus, improved knowledge of the very early expansion of HIV-1 will be beneficial for our understanding of primary infection, and its effect in the establishment of chronic infection. Moreover, if the immune system primed by a vaccine could respond quickly enough to HIV, perhaps it would be possible to prevent infection. However, all but the recombinant canary pox plus gp120 vaccine, used in the RV144 trial in Thailand (23), have failed to provide protection and the immune response generated by T-cell based vaccines has been described as too little, too late (1, 5, 24). Here we characterize the early events in infection and the pre-peak expansion of HIV-1 to better understand the biology of infection.

We examine longitudinal viral load data from 47 frequent plasma donors who became HIV+ during the course of their plasma donations. Thus, this data set includes samples in which virus was absent or below the limit of detection of the assay used, as well as viral loads at very early times post exposure with HIV. From this data, we
quantify the rate of viral expansion during primary HIV infection. Previously, Fiebig et al. (8, 9) analyzed some aspects of early viral load expansion, the existence of viral blips, and the timing of HIV-1 marker expression, defining the stages for early infection (9). Here we extend these analyses to characterize in detail the expansion of the virus and its basic reproductive ratio, $R_0$. In the context of within host viral dynamics, $R_0$ is a measure of whether a virus can establish infection (12). It specifically measures how many cells a single infected cell will infect when there is no target cell limitation. If $R_0$ is less than one, on average an infected cell infects less than one susceptible cell, and the infection will die out. If $R_0$ is greater than one, on average an infected cell infects more than one susceptible cell, and generally the infection will spread (25).

$R_0$ for HIV infection in humans has been estimated previously in smaller datasets. Little et al. (15) used both viral load and CD4+ T-cell count data to find $R_0$ in four individuals, whose infection was identified within a couple of weeks of exposure. Stafford et al. (27) estimated $R_0$ from viral load data obtained from 10 primary infection patients, again identified within a few weeks of infection. Our work differs from these previous studies in that we analyze a much larger number of patients and the viral load data that we analyze encompasses the earliest stages of infection, in fact in most cases before the viral load is even detectable. By contrast both Little et al. (15) and Stafford et al. (27) analyzed data primarily obtained near or after the peak in viral load.

Methods

Patient Data: Plasma Donor Panels
Two sets of archived plasma donor samples (n=51) were obtained from Zeptometrix (Buffalo, NY) and Seracare (Milford, MA). The Zeptometrix plasma dataset was originally collected by Alpha Therapeutic Corporation (Los Angeles, CA) from August 1996 through December 1998, and the Seracare plasma dataset was collected from Boston Biomedica (West Bridgewater, MA) from June 1984 through October 1994. At both collection sites, each patient donated 600-800 ml of plasma, which was frozen within eight hours to -20°C or less. The plasma samples were stored up to two months then sent in pools of 512 to be serologically screened for HIV. Donors who were HIV positive were notified and deferred from subsequent donation. HIV positive samples were aliquoted, and refrozen at -20°C. Aliquoted samples of plasma donors were reanalyzed with the Roche Amplicore HIV-1 RT PCR Ultra assay by Quest Diagnostics (Lyndhurst, NY), with a lower limit of quantification of 50 HIV-1 RNA copies/mL. The data is fully anonymous, without any possibility to link it back to the original donors.

**Definition and calculation of $R_0$**

We use a target-cell-limited model of HIV infection, which has been shown to capture the dynamics of primary infection (19, 21, 27) to analyze the plasma donor samples. In a target-cell-limited model, viral growth depends on the availability of target cells, and the death of infected cells occurs at a constant rate, $\delta$, consistent with death due to viral cytopathic effects. While an immune response may also contribute to infected cell death, we assume that any innate response is approximately constant and included in the net death rate ($\delta$), whereas an acquired response is most likely absent during the early
stages of infection pre-viral load peak (10, 13), alternatively an innate response might .

This model can be summarized by the following equations:

\[
\frac{dT}{dt} = \lambda - dT - kVT \tag{1}
\]

\[
\frac{dI}{dt} = kV(t - \tau)(t - \tau)e^{-d\tau} - \delta I \tag{2}
\]

\[
\frac{dV}{dt} = pI - cV \tag{3}
\]

where \( T \) is the target cell density; \( I \) is the productively infected cell density; \( V \) is the HIV-1 RNA concentration; \( \lambda \) is the rate of target cell generation; \( d \) is the target cell death rate; \( k \) is the rate constant for infection; \( \delta \) is the death rate of infected cells; \( p \) is the rate of virus production from one infected cell; and \( c \) is the virion clearance rate constant. Here we also assume that, after a virion infects a cell, there is a time delay, \( \tau \), before that cell produces virus, i.e. \( \tau \) represents the length of the eclipse phase of the viral lifecycle (7, 20). The term \( e^{-d\tau} \) is the probability that a cell does not die during the eclipse phase of length \( \tau \) (11, 17, 18). Here, for simplicity we have assumed that a cell that is infected but not yet producing virus dies at a rate \( d \), equal to that of an uninfected cell (see Eq. (1)). In this way, productively infected cells are the result of infection events that occurred \( \tau \) time units ago, assuming the infected cells survive to the present time (\( e^{-d\tau} \)).

While \( R_0 \) can be formally calculated from the model equations (25), the following is an intuitive derivation. Each infected cell produces virus at rate \( p \). While producing virus, infected cells live, on average, a time \((1/\delta)\). Thus, on average each infected cell produces a total of \( p/\delta \) virions. Because virus is cleared with rate \( c \) per virion, each virion survives on average for a time \( 1/c \). During this time, before targets cells become limiting,
each virion on average infects $kT_0e^{-d\tau}/c$ cells, where $T_0$ is the pre-infection target cell density, and $e^{-d\tau}$ is the probability that the cell will not die before becoming productively infected and producing any virus. Thus, the total number of cells productively infected by the $p/\delta$ virions released from one infected cell is $R_0 = p k T_0 e^{-d\tau}/c$. From Eq. (1), the pre-infection steady-state target cell density is $T_0 = \lambda/d$. This gives the following expression for $R_0$

$$R_0 = \frac{kp\lambda}{c\delta d} e^{-d\tau}.$$  

Viral load expansion rate and $R_0$

Estimating $R_0$ from Eq. (4) requires having enough data to estimate all seven parameters in this equation. Stafford et al. (27), who analyzed data collected over the first 80 to 100 days of infection, used this approach. Since plasma donation was stopped once individuals were identified as HIV positive, our data sets tend to have frequent early samples but limited data post-peak viral load. We can use this data to find $R_0$ by an alternative approach that first estimates the viral expansion rate, $r$, which can be found from consecutive measurements of the viral load. In early HIV infection, before the peak in viral load, we assume the total number of uninfected target cells is approximately constant and equal to $T_0 = \lambda/d$. Thus, in early infection, the target-cell limited model is reduced to equations (2) and (3) with $T = T_0$. In this case, one finds that to a good approximation the viral load initially increases as $V(t) = V_0 \exp(rt)$, where $r$, the initial viral load expansion rate, is the dominant (i.e. largest) solution of the equation,
\[ r^2 + (c + \delta) r + (\delta c - k p T_0 e^{-\tau}) = 0 \] (17). Using the definition of \( R_0 \) from equation (4) and \( T_0 = \lambda / d \), this becomes \[ r^2 + (c + \delta) r + \delta c (1 - e^{-\tau} R_0) = 0. \] Solving for \( R_0 \), one finds

\[
R_0 = \left( 1 + \frac{r}{\delta} \right) \left( 1 + \frac{r}{c} \right) e^{\tau}
\] (5)

If \( c \) is large compared to \( r \), then

\[
R_0 \approx \left( 1 + \frac{r}{\delta} \right) e^{\tau}
\] (6)

Estimates of \( c \) made during chronic infection suggest that \( c \sim 23 \text{ d}^{-1} \) (22). Below, we shall show that \( r \sim 1.1 \text{ d}^{-1} \) and thus if virion clearance is also rapid in acute infection, as has been shown in rhesus macaques (30), \( c \gg r \) is a good assumption and Eq. (6) can be used to estimate \( R_0 \), from the observed initial viral expansion rate, \( r \). Equation (6) tells us that for the same observed initial expansion rate, \( r \), the larger the delay, \( \tau \), the larger the estimated \( R_0 \). One way to understand this result is the larger the delay before viral production begins the slower the virus would be expected to expand. Thus, to match a given observed expansion rate, \( r \), the larger \( R_0 \) needs to be to offset the larger delay. A reasonable estimate for the value of \( \tau \) in vivo is \( \tau = 24 \text{ h} \) (7), which is also in agreement with in vitro data (2), and we will use this value to calculate \( R_0 \).

Estimates of \( r, \delta \) and \( R_0 \)

The value of \( R_0 \) depends on the values of \( r, \delta \), and \( \tau \). For all patients, we calculated \( r \) by two methods: in the first, the two viral load measurements defining the fastest expansion rate are used. We refer to this value of \( r \) as \( r_{\text{max}} \). In the second, all available viral loads for each patient, from the minimum or the last point at the lower limit of detection, to the peak viral load are used, and the data set is analyzed using a linear mixed effects model, in which the individual expansion rates vary around a group expansion rate (see below for details). We call this group expansion rate \( r_g \). The first
method of finding \( r \) gives the fastest observed viral expansion rate for each patient, \( r_{\text{max}} \).

The second method includes more data points for statistical accuracy and also models the expansion rate in the context of a group, which given the sparse data allows one to make better estimates for the whole population.

In the target-cell-limited model with \( c \gg \delta \) the virus concentration, \( V(t) \), and the density of productively infected cells, \( I(t) \) quickly become equilibrated, i.e. they become proportional to each other. Thus, after the peak, viral load and infected cells should decay at the same rate and the observed rate of viral decay from the peak, \( \alpha \), can be used as an estimate of the net loss rate of infected cells. This net rate of infected cell loss, \( \alpha \), will underestimate the true infected cell death rate, \( \delta \), since continuing viral infection will create new infected cells (6, 15, 19). As one can see from Eq. (6), using \( \alpha \) as an estimate of \( \delta \) when calculating \( R_0 \) will result in a higher \( R_0 \) than would be found by using the true value of \( \delta \). The parameters \( r \) and \( \alpha \), and how they relate to the viral load profile, are shown in Figure 1.

**Mixed effects models**

To analyze the kinetics of primary infection, the natural definition of \( t=0 \) is the time of infection. However, the time of infection is not available for the current data set involving plasma donors. Thus, we arbitrarily define the time origin as the time that the subject’s viral load first reached the limit of detection, 50 cp/ml, and call it \( T_{50} \). This definition allows us to align the viral load data of all the patients to a common reference time point. This parameter is estimated by the best fit of a model defining the exponential growth of the early viral load. Because many subjects have sparse measurements during
the initial increase in viral load, we fit a linear mixed effects model, which borrows
information across subjects while estimating both the population-average and subject-
specific parameters (29). To account for censoring at the assay detection limit, a full
likelihood based algorithm is used to estimate the mixed effects model (28).

The mixed-effects model estimation was performed after two pre-processing
steps: 1) removal of subjects who did not have enough viral load data in the early phase
of infection. Five subjects were removed: P9019, P9028, P9075, and P12007 had more
than two weeks between the last negative and first positive HIV-1 measurement, resulting
in great uncertainty about their early viral kinetics; and PRB940 who had only one data
point before the viral load peak, which is not enough for reliable estimation of the viral
kinetic parameters; 2) for the 42 subjects with data during the eclipse phase of infection,
viral loads within the upswing (exponential expansion) phase were selected to estimate
the time origin. Let $T_{50,i}$ denote the time origin and $\{\tilde{y}_{ij}, \tilde{t}_{ij}, j \in U_{i}\}$ denote a collection of
observations that are within the upswing window $U_{i}$ for each subject $i$. The upswing
window is determined such that (i) the enclosed viral loads have a significant exponential
increase and (ii) the maximum viral load and the last value at the limit of detection are
included. That is, for each subject, we fitted a series of linear regressions to the viral load
data in between the last censored value and the observed maximum value. The data
points corresponding to the largest window that permitted a significant expansion were
used for each subject. We then fitted a mixed-effects model to the log$_{10}$-transformed data;

$$\log_{10} \tilde{y}_{ij} = \alpha + (\beta + b_{i})(\tilde{t}_{ij} - T_{50,i}) + e_{ij}, (b_{i}, T_{50,i})^T \sim N(0, \Sigma), \text{ and } e_{ij} \sim N(0, \sigma_{e}^2),$$

where $\Sigma$ denotes the variance-covariance matrix of $(b_{i}, T_{50,i})^T$ and $e_{ij}$ are independent and
identically distributed random errors.
Statistics

Results are presented mostly as median and inter-quartile ranges (IQR), to better reflect the unknown distribution of the underlying measurements. However, for completeness, we have also presented means and standard deviations as specified in the text.

Results

Early Infection Data Sets

We obtained HIV viral load data from the plasma of 51 donors. The viral loads were measured by an RT-PCR assay with a lower limit of detection (LOD) of 50 copies/ml. Two donors (P6242 and P9078) were discarded from our analysis because they had only HIV-1 negative samples, and two more were also discarded because they were caught too late in this early phase, showing only viral load decline (P9014 and P9017). In addition, five other patients who did not have enough pre-peak viral load data were not included in the mixed-effect model analysis (see Methods).

There were a median of 10 data points for each analyzed donor, with infection estimated to occur a median of 21 days after the first collection date. There was a median interval of 5 days between the last sample below the lower limit of quantification and the first measurement above detection. A median of 4 data points were available after HIV-1 was detectable.

A better idea of the variation in the viral load profiles at these early times post-infection can be seen in Figure 2, where we plot the viral loads of all the patients with a...
common time origin, $T_{50}$ (see Methods). Many of the viral load expansion profiles exhibit a similar growth rate and seem to peak at about $10^6$ copies/ml, approximately 10 to 15 days post $T_{50}$.

Expansion rate/Doubling time

This dataset includes a large collection of plasma samples obtained before and soon after HIV-1 RNA is detectable, and thus presents a unique opportunity to directly estimate very early viral expansion rates. In order to obtain an estimate of the viral load expansion rate, we used two methods. In the first, we found the maximum slope between any two data points before the viral load peak. Using this method, we found the median $r_{\text{max}} = 1.06 \text{ day}^{-1}$ (IQR: 0.76 – 1.2 day$^{-1}$) and the corresponding doubling time was 0.65 days (IQR: 0.56 – 0.91 days) (Table 1). The second method involved using a linear mixed-effects model in which all the patient data obtained during the viral load increase was analyzed at once as a group (28) (see Methods). We found the group average ± standard deviation expansion rate $r_g = 1.09 \pm 0.18 \text{ day}^{-1}$, and the average doubling time was 0.66 ± 0.14 days (see Table 1). Thus, the two methods gave very consistent estimates for the expansion rate of HIV in early infection.

Time to viral load peak and profile shape

In fifteen patients (P1026, P1055, P6240, P6243, P6246, P9010, P9032, P9077, P9079, P12008, P63521, P63753, PRB940, PRB943 and PRB952) we can observe the viral load peaking and then starting to decline, since they have at least two data points post-peak (Figure 3). For these patients, the median time between the last measurement
below the lower limit of detection, 50 HIV RNA copies/ml, to the maximum measured viral load is 14 (IQR: 10.5 – 14) days. The median peak viral load for these patients is 5.8 log (RNA copies/ml) with IQR 4.7–6.0 log (RNA copies/ml). Estimates of the \( r_{\text{max}} \), \( \alpha \), \( R_0 \) and the half-life of the virus during its post-peak decline in these patients are listed in Table 1.

Viral decay/half-life

Since we have no data on the rate of decline of infected cells, we estimated the productively infected cell death rate, \( \delta \), by the viral load decay rate post peak, \( \alpha \) (Figure 1). Most patients do not have data for a period of time long enough to show viral decay. However, for the 15 patients who show a viral load peak, the median viral load decay rate is \( \alpha = 0.60 \, \text{day}^{-1} \), with IQR 0.40 – 0.83 day\(^{-1}\) (Table 1). The corresponding median viral load half-life is 1.2 days.

Estimates of \( R_0 \)

For all patients, we calculated \( R_0 \) using the estimated median viral decay rate of 0.60 day\(^{-1}\) from the previous section. For those patients who have enough data to estimate the viral decay rate (Figure 3), we also calculated \( R_0 \) using their individually determined value of \( \alpha \).

The median \( R_0 \) found with the fastest expansion rate for each individual patient, \( r_{\text{max}} \), along with the median individual decay rate of 0.60 day\(^{-1}\), with an eclipse time of one day is 8.0 (IQR: 4.9 – 11) (Table 1). A histogram of the distribution of \( R_0 \) values is shown in Figure 4. Using the average expansion rate from the group analysis, \( r_{g} \), the
decay rate of 0.60 day$^{-1}$, and an eclipse time of one day gives an average ± standard deviation of $R_{0g} = 8.8 \pm 2.5$.

In the subset of patients who show a viral load peak and subsequent decay, the individual maximal expansion and decay rates result in higher $R_0$ values, with median $R_0 = 13$ (IQR: 8.5 – 18).

**Discussion**

Here, we analyzed the viral load profiles of 47 patients in very early HIV-1 infection. This is a unique dataset that allows the observation and measurements of viral load during primary infection, even before the initial peak in viral load. Our main objective was to determine $R_0$, the basic reproductive ratio. For the whole population, based on a mixed-effects model, we obtain an estimate of $R_{0g} = 8.8$, if we assume that the eclipse phase of viral infection is 24 h (7). In addition, our results also give an idea of how variable $R_0$ is in the human population. Seventy-five percent of the individuals in our sample have $R_0 < 11$, but a few individuals can have a basic reproductive ratio larger than 20. Whether this is just a random distribution, or it represents individuals with specific susceptibility to infection can not be ascertained from this dataset. In any case, these results seem to indicate that a reduction in $R_0$ of 10 to 20-fold, say by vaccine induced immunity, could drive $R_0$ below one and lead to prevention of HIV infection in a majority of HIV-exposed individuals. Moreover, our estimate for the net loss rate of infected cells ($\alpha = 0.60 \text{ day}^{-1}$) is significantly smaller than that obtained by drug treatment during chronic infection, i.e., $\delta = 1.0 \text{ day}^{-1}$ (16). This could be because later in infection, an acquired immune response develops contributing to this loss. If this is the case, then this
effect mimicked by a vaccine could reduce $R_0$ to about 5. Alternatively, this difference could be due to ongoing viral infection, which would affect our estimate of $\alpha$ but not $\delta$. If we use $\delta=1.0\ day^{-1}$, the median $R_0$ would be $R_0=6$ even in early infection, before the development of acquired immunity, consistent with the prior analysis of Stafford et al. (27).

A question that remains is: what is occurring in patients prior to the time at which their viral load exceeds the lower limit of detection and hence prior to the time the virus starts to grow exponentially. In Fiebig et al. (8), viral blips occurring before this time were reported, and it may be that the viral load fluctuates before full viral infection sets in, as suggested by stochastic models of infection (J. E. Pearson, P. Krapivsky and A. S. Perelson, submitted for publication). If this is the case, there may be a window of opportunity, before the virus starts to grow uncontrollably, where an intervention (e.g., vaccine) could be effective even if it can not lower $R_0$ by 10 to 20-fold. Indeed, our estimates of $R_0$ are only valid once the virus starts to grow exponentially, before that, viral blips may indicate localized small bursts of viral production with $R_0$ below or near one. More experimental data using more sensitive assays at these extremely early times would be needed to understand these aspects of the viral dynamics.

Two other studies have analyzed the value of $R_0$ in the setting of HIV-1 infection. Stafford et al. (27) analyzed 10 patients with early infection, but identified only close to the peak in viral load, and fitted a model similar to that given by equations (1)-(3). In this way, they obtained estimates for the parameters of the model and were able to calculate $R_0$ using expression (4). They found a median $R_0=5.7$, with a range between 2.8 and 11.0. These values are lower than those found in the current study. This is most likely due to...
late identification of the subjects, when viral load growth decelerates as virus nears the peak. Indeed, using their data to calculate the maximum expansion rates, $r_{\text{max}}$, as here, we found a mean $r_{\text{max}} = 0.13 \text{ day}^{-1}$, much smaller than ours. On the other hand, calculating the decay rate from the peak for their subjects, we found $\alpha = 0.48 \text{ day}^{-1}$, just slightly smaller than ours.

The other study, by Little et al. (15), calculated $R_0$ in only four patients, and used a method analogous to the one in the current paper, i.e., calculating $R_0$ based on the initial expansion rate of the virus. However, for three patients, viral load measurements were collected only within days of the peak, potentially reflecting a reduced rate of expansion as the viral load growth slows before the peak. Thus, the authors attempted to infer the initial expansion rate by correcting the observed expansion rate taking into account the slowed expansion due to target cell loss (15). With this correction, the average expansion rate found was $2.0 \text{ day}^{-1}$, which is much higher than the expansion rate found here. Without the correction their expansion rate was $0.85 \text{ day}^{-1}$, slightly slower than our median of $1.06 \text{ day}^{-1}$. The $R_0$ value calculated also depended on the correction for target cells; it was calculated by multiplying the $R_0$ value obtained from the observed expansion rate by the fold decrease in CD4+ T-cells from an assumed pre-infection value of 1000/µl (the true value being unknown in that study) to the first measurement at presentation. Altogether, they found $R_0$ values of 23, 34, 7, and 12, averaging to 19.3. Our data, including many more patients with much better early sampling, allowed us to calculate an $R_0$ that is smaller than that found in Little et al. (15). The discrepancy could be either due to the correction factors introduced by Little et al. (15), or perhaps some bias in patient selection. The latter could arise since in Little et al. patients were identified because they...
were symptomatic (15). Interestingly, in that study they estimated the viral decline from peak (α) in eight subjects and found α=0.3 day$^{-1}$, slower than in the present study. It is interesting to compare our results to those found in macaques, which often are used as a prototypic model of HIV infection for vaccines studies. Nowak et al. (19) found the expansion rate r for 12 macaques infected with SIVsmE660. The average r for the group was 2.20 day$^{-1}$, similar to that found in Little et al., with a doubling time of 0.32 days. In Nowak et al. (19), the post-peak viral load decay occurred with a mean rate of 0.52 day$^{-1}$, with a range from 0.18-0.86 day$^{-1}$ (half-life of 1.33 days). These values are very similar to the values we found here. Due to the large estimated value of r, they estimated a mean $R_0$=36.5, ranging from 5.4-68, using an eclipse phase with length one day. This value, like the expansion rate r, is much greater than our highest $R_0$ values. The specific strain of SIV or the macaque model may account for the difference. And these differences may indicate that a vaccine that works in macaques has to pass a more stringent test, from the point of view of reducing viral growth, than that needed in humans.

Overall we were able to provide an estimate for $R_0$ and for its variation across infected individuals, based on very early viral load data post infection. According to our analysis, HIV has an $R_0$ with an inter-quartile range between 5 and 11, with most patients having an $R_0$ close to 8 (see histogram of $R_0$ in Figure 4). Thus, in order to prevent chronic infection in a majority of patients, an early infection intervention, such as a vaccine, must be about 90% effective in reducing viral growth.

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Figure captions

Figure 1. Schematic of the calculation of the expansion rate, \( r \), and the decay post-peak, \( \alpha \).

Figure 2. Profile of the initial viral load for all patients aligned at the beginning of the viral expansion.

Figure 3. Early viral load profiles for the fifteen patients who showed a viral peak and decay post-peak. The data in these patients were used to estimate the decay rate of the virus post-peak.

Figure 4. The histogram of \( R_0 \) calculated from the fastest expansion rate in each of the 47 patients studied.
Table 1. Estimates of the expansion rate and $R_0$ by the two methods used.

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ID patient ID, $r_{\text{max}}$ the maximal individual expansion rate; $T_2$ the doubling time; $\alpha$ decay rate for patients with data post peak; $T_{1/2}$ half life post peak; $R_0$ found with $r_{\text{max}}$, the median decay rate of 0.60 day$^{-1}$, and $T_{1/2}$ = 1 day; $R_0^*$ for those patients with individually estimated $\alpha$; $r_g$ is the expansion rate by the group analysis; $R_{0g}$ the expansion rate found with the group rate using a median decay of 0.60 day$^{-1}$; NA – not available.