

Variability in early HIV-1 population dynamics

Many quantitative models have recently been proposed and analysed for the evolution of HIV-1 populations in infected hosts, often with a view to ascertaining the effects of various regimes and combinations of drug treatments [1-4]. Stochastic effects, however, have been neglected. Such effects are observed in data on HIV-1 concentrations in plasma obtained by polymerase chain reaction methods in patients with acute HIV-1 infection in both the value of the peak HIV-1 RNA level (5.55-7.34 \log_{10} copies/ml) and the time at which this maximum value is reached (8-23 days after the onset of symptoms) [5,6]. Furthermore, after initiation of treatment, observations on the time course of plasma viral load usually reveal variability in relation to the predictions of the deterministic models that have so far been employed [3,7-9].

It is clear that variability in response to HIV-1 infection arises from both intrinsic sources and differences in immunophysiological parameters between patients. Intrinsic variability is due, for example, to the random nature of the interactions between free virions and uninfected CD4 cells, fluctuations in the rates of production of CD4 cells and their immigration into the blood, and variability in the numbers of virions produced by infected cells. The variability between patients arises from differences in immunophysiological characteristics. For example, the rate of infected cell loss, estimated by Perelson *et al.* [3] for eight patients on the basis of a deterministic model, ranged from 0.36 to 1.20 per day for productively infected CD4+ T cells, and from 0.055 to 0.181 per day for latently infected CD4+ T cells. The initial inoculum of virus and the initial number of uninfected CD4+ T cells also vary between patients.

We have attempted to understand these sources of variability by the development and analysis of a mathematical model for early HIV-1 dynamics. To this end, we have constructed a stochastic version of a slightly modified form of a deterministic model originally proposed by McLean *et al.* [10] and subsequently elaborated upon by Phillips [4]. Solutions for Phillips's model exhibit a pattern of changes in virus concentration similar to that observed in patients, without incorporating an HIV-specific immune response.

The stochastic model has four components: activated uninfected CD4+ T cells, latently and actively infected (virus-producing) CD4+ T cells, and free HIV-1 particles. Infection of CD4+ T lymphocytes includes mechanisms such as the binding of free virions to the cell receptors. The random nature of this process is taken into account in our model, considering that two events can occur in a small time interval: infection of a CD4+ T cell, or no infection. Other processes, such as the production and clearance of cells or virus, are consid-

ered in the first instance to be deterministic. The changes in cell and viral populations in a small time interval are random variables, the mean and variance of which can be evaluated. These calculations lead to stochastic differential equations [11] for a diffusion process, differing from the equations of Phillips [4] in that they contain additional noise terms. In addition to the chance mechanism in the infection of uninfected cells, we have included the stochastic nature of transitions of uninfected cells to the latent or active class of infected cells: infection results in a latently infected cell with probability P , or in an actively infected cell with probability $1 - P$. Further details will be published elsewhere.

We first address the intrinsic variability due to stochastic mechanisms in a given patient using simulations for the stochastic model with fixed parameter values. These results can provide insights into the variable nature of early HIV-1 dynamics in human hosts, which is of fundamental interest and is necessary as a starting point to studies of overall variability. We illustrate this by determining the probability distributions of the magnitude and time of occurrence of the peak viral load. Using the best available values (representing mean values) for the parameters [3,4,7-9], we have simulated the dynamics of the CD4+ T cell and HIV-1 populations over the first 60 days after initial infection, with a time step of 0.01 days. The volume considered was equal to the total blood volume, fixed at 5×10^3 ml. Histograms of the magnitude, V_{max} , and the time, T_{max} , of occurrence of the maximum viral density, based on 200 simulations, are shown in Fig. 1. We obtained peak

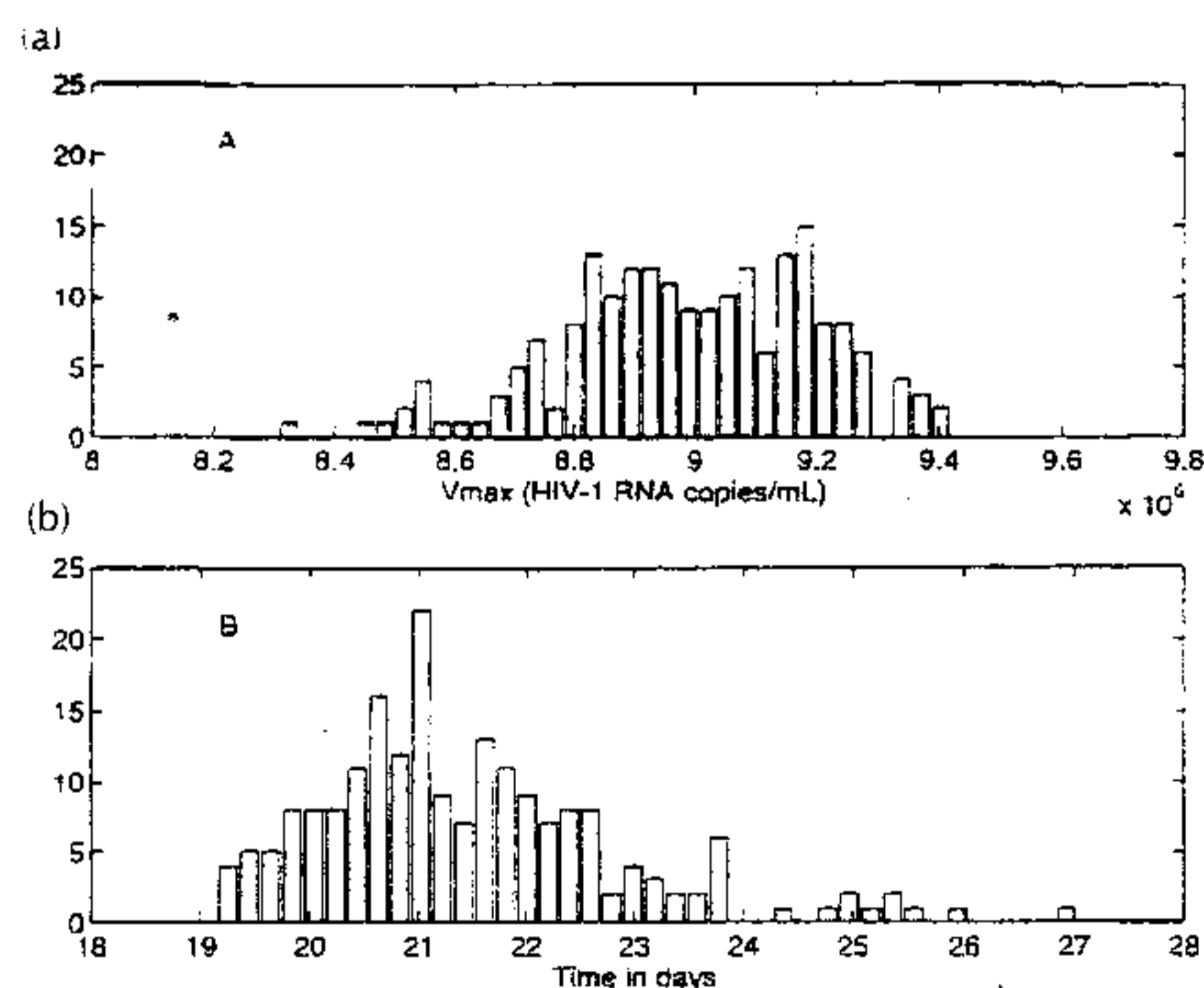


Fig. 1. Histograms of (a) the peak viral concentration (HIV-1 RNA copies/ml), and (b) the time of occurrence of the peak (days after infection), obtained from 200 simulations, with fixed parameters (equal to the values employed by Phillips [4]) in the stochastic model for early HIV-1 population dynamics.

viral loads of 6.91–6.97 \log_{10} HIV-1 RNA copies/ml occurring at times between 19 and 27 days. These results are in good agreement with the observed ranges [5,6]. It must be borne in mind that this relatively small variability did not include variation between patients.

In order to examine contributions to the variability from parameter variations among patients, we varied each parameter and the initial virion and uninfected CD4+ T-cell densities. The effects of changes of 25% in the parameter values on the mean peak viral load and on the mean and SD of the time of occurrence of the peak are shown in Table 1. The rate of activation of latently infected cells, and somewhat surprisingly, the initial virion density, were found to have little influence on the time course of infection. By contrast, results were sensitive to small changes in the death rate of uninfected CD4+ T cells, death rate of actively infected cells, and clearance rate of virus, increases in all of which led to a smaller and slower growth of the plasma virion concentration, whereas decreasing these quantities had the opposite effects. Similarly, increases in the rate of appearance of CD4+ T cells in plasma, fraction of infected cells that were latent, number of virions produced by infected cell, infection rate of CD4+ T cells, and initial total number of uninfected CD4+ T cells, all resulted in a faster and larger response relative to the standard values of these quantities. From the SD of T_{max} , it can also be observed that (for all parameters except clearance rate of free virus) when changes in parameters resulted in an earlier and greater

peak of viral concentration, they also led to a less variable response.

An important result is that the initial inoculum of virus has a low impact on the infection dynamics, at least in the early phases of infection: 100-fold increase of the initial number of virions results in a decrease of 2.3 days for T_{max} , no change for V_{max} , and a decrease of the SD of T_{max} from 0.9 to 0.5 days. This result can be compared with those of cohort studies that do not show any significant difference according to exposure group in the progression of infection [12].

From further studies, to be published elsewhere, the total variability obtained when uncertainties in all the parameters are combined is greater than that due to the intrinsic variability (Fig. 1) and can easily account for the observations described above.

Since the diagnosis of HIV-1 infection and consequent treatment in the early phases of infection can be based upon measures of viral load, stochastic models such as that for which we have reported results here, can be used to investigate questions relating to the statistics of early detection and testing. Furthermore, the use of a stochastic approach for HIV-1 population dynamics is particularly important in any situation where the viral concentration is small, in the early stages of infection, or after several months of strong antiretroviral therapy, where such a model may allow the prediction of the probability of eradicating the virus.

Table 1. Effects of changes (decrease and increase of 25%) in the parameter values on the mean peak viral concentration and the mean and SD of the time of occurrence of the peak, based on 20 simulations in each case.

Parameter (initial parameter*)	Decreased parameter (-25%)			Increased parameter (+25%)		
	Mean V_{max} (\log_{10} HIV-1 RNA copies/ml)	Mean T_{max} (days)	SD of T_{max} (days)	Mean V_{max} (\log_{10} HIV-1 RNA copies/ml)	Mean T_{max} (days)	SD of T_{max} (days)
Rate of activation of latently infected cells (0.036/day)	6.94	21.2	1.5	6.95	21.1	1.1
Initial virion density (2 virions)	6.95	21.7	1.4	6.95	21.4	0.5
Death rate of uninfected CD4+ T cells (0.00136/day)	7.12	17.6	0.9	6.81	26.0	1.4
Death rate of actively infected CD4+ T cells (0.33/day)	7.03	21.3	1.5	6.83	24.0	2.3
Clearance rate of virus (2/day)	7.10	19.1	0.9	6.83	24.0	0.8
Rate of production of CD4+ T cells/immigration in plasma (6.8×10^6 cells/day)	6.75	26.6	1.7	7.08	18.6	1.2
Fraction of latent uninfected CD4 cells (0.2)	6.76	27.1	1.7	7.09	18.0	0.8
No. virions produced by infected cell (100 virions/cell/day)	6.76	27.4	1.4	7.09	17.8	0.7
Infection rate of CD4+ T cells (5.4×10^{-11} /virion/day)	6.89	27.3	1.8	6.99	18.2	1.4
Initial total number of uninfected CD4+ T cells (5×10^9 cells)	6.76	26.6	1.9	7.09	18.0	0.8

With the initial parameter values, mean $V_{max} = 6.95 \log_{10}$ HIV RNA copies/ml; mean $T_{max} = 21.5$ days; SD of $T_{max} = 1.4$ days. *Value for total blood volume. V_{max} , Magnitude of maximum viral density; T_{max} , time of occurrence of maximum viral density.

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CD4+ lymphocyte count and plasma HIV RNA levels in a survey of 1602 HIV-infected patients in Bordeaux, France, 1996-1997

In 1996, it was shown that plasma HIV-1 RNA level could be a better prognostic marker of the evolution of HIV infection than CD4+ cell count [1] and HIV-1 RNA level assays began to be used routinely in France as well as in other western countries [2]. It is unlikely that plasma RNA level could replace CD4+ cell count in clinical practice or research [3,4]. Therefore, at least for clinicians, the degree of agreement between simultaneous measurements of CD4+ cell count and RNA level is important to know, especially for initiating anti-retroviral treatment. We present such a description in a large survey of HIV-infected patients.

The hospital-based surveillance system of the *Groupe d'Epidémiologie Clinique du SIDA en Aquitaine* includes all inpatients and outpatients of the participating hospital units (aged > 13 years) whose HIV-1 infection is confirmed by Western blot [5]. We analysed the relationship between the first RNA level measurement available with a threshold at 2.7 log₁₀ copies/ml for each patient between 1 July 1996 and 31 March 1997 and the CD4+ cell count measurement processed at the same time or in the preceding 3 months. All RNA measurements and CD4 cell counts were performed in a centralized laboratory with the same equipment. Five patients with acute HIV primary infection were excluded. Concordance between CD4+ cell count and

RNA level was studied cross-sectionally in two distinct populations: (i) patients who had never received anti-retroviral treatment, and (ii) patients treated with anti-retrovirals, generally by drug combinations, before and at the time of the first RNA level measurement. The cut-offs chosen for this description of the frequency distributions were based on previous publications on the prognostic role of CD4+ cell count [6] and RNA level [1].

During the study period, 1808 patients had at least one hospital stay or clinic visit reported; 1602 of them combined at least one RNA level measurement and a CD4 cell count. The median CD4+ cell count was 302 × 10⁶/l (interquartile range, 155-460 × 10⁶/l) and the median value of the first RNA level measurement was 3.91 log₁₀ copies/ml (SD, 0.94 log₁₀ copies/ml; interquartile range, 2.90-4.66 log₁₀ copies/ml); 803 patients (50%) were asymptomatic [Centers for Disease Control and Prevention (CDC) 1993 criteria, group A], 470 (29%) were non-AIDS symptomatic patients (CDC group B), and 329 (21%) had clinical AIDS.

Table 1 shows the relationship between RNA level and CD4+ cell count measurements in the non-treated group (n = 492) and the antiretroviral-treated group (n = 1044). In the non-treated group, median CD4+