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by

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Abstract

It is not well understood why the transmission of HIV may have a small probability of occurrence despite frequent high risk exposures or ongoing contact between members of a discordant couple. We explore the possible contributions made by distributions of system parameters beginning with the standard three-component differential equation model for the growth of an HIV virion population in an infected host in the absence of drug therapy. The overall dynamical behavior of the model is determined by the set of values of six parameters, some of which describe host immune system properties and others which describe virus properties. There may be one or two critical points whose natures play a key role in determining the outcome of infection and in particular whether the HIV population will persist or become extinct. There are two cases which may arise. In the first case, there is only one critical point P_1 at biological values and this is an asymptotically stable node. The system ends up with zero virions and so the host becomes HIV-free. In the second case, there are two critical points P_1 and P_2 at biological values. Here P_1 is an unstable saddle point and P_2 is an asymptotically stable spiral point with a non-zero virion level. In this case the HIV population persists unless parameters change. We let the parameter values take random values from distributions based on empirical data, but suitably truncated, and determine the probabilities of occurrence of the various combinations of critical points. From these simulations the probability that an HIV infection will persist, across a population, is estimated. It is found that with conservatively estimated distributions of parameters, within the framework of the standard 3-component model, the chances that a within host HIV population will become extinct is between 0.6% and 6.9%. With less conservative parameter estimates, the probability is estimated to be as high as 24%. The many complicating factors related to the transmission and possible spontaneous elimination of the virus and the need for experimental data to clarify whether transient infections may occur are discussed. More realistic yet complicated higher dimensional models are likely to yield smaller probabilities of extinction.

Short Title: HIV persistence in a new host
Keywords and Phrases: HIV infection; mathematical model; persistence; eradication.

1 Introduction and theory

A comprehensive understanding and analysis of the early stages of HIV infection, including the process of transmission, is important as it may lead to efficient methods of reducing the probability that the virus successfully establishes itself in a new host. In a previous article[1] we have addressed the problem of estimating the probability of a successful transmission of HIV infection to a new host.

There have been several mathematical models for the growth of within-host HIV populations, many of which are deterministic, for example[2–4] whereas others have incorporated chance mechanisms[5–7]. Such models have provided valuable insights into the time-course of viral dynamics and the effects of drug therapy. The simple 3-component differential equation model we examine in this article has been successfully employed to predict the temporal evolution of HIV populations in the primary stages of infection. As pointed out by Stafford[8], although some models have been hypothesized which describe the progression to acquired immunodeficiency syndrome (AIDS) (for example,[9]) useful information and possible prognoses can be obtained from a knowledge of the viral dynamics in the early stages. In untreated HIV infection, the risk of AIDS is known to be small until the CD4 cell count has reached low levels or the viral load has reached high levels[10] Indeed, our approach is to examine possible outcomes predicted by a model of primary infection for various parameter values to ascertain whether the virus will be likely to persist after the initial infection period or possibly spontaneously die out due simply to dynamical system properties. The term "die out" is somewhat ambiguous, as clinical tests for the presence of the virus generally have a threshold of 50 copies/ml of HIV-1 RNA,[11,12], although much lower levels, down to a few copies, have been demonstrated in laboratory studies[12–14]. It is known from clinical studies that if HIV persists into and beyond the primary stage then the baseline CD4 cell count is a major predictor of eventual outcome under highly active antiretroviral therapy (HAART)[15]. Our analysis is only applicable in the absence of HAART which can decrease the plasma viral load below the limit of detection[16]. Extensions to include the effects of such therapy will be considered elsewhere.

The matter of extinction of an HIV population in an individual new host also has been raised by some authors using stochastic differential equation or similar models[5,17,18]. In this article, however, we are concerned with estimat-

ing the probability that an HIV population does in fact become established in a host after a successful transmission on the assumption that the viral population evolves deterministically according to a well-known dynamical model. The probability of persistence is determined by the distributions of the parameters which describe the host's immune system, its interaction with the virus and the properties of the free virus. Thus, as in accordance with the standard deterministic model, extinction does not depend on the number of virus particles which become initially established in the new host. The veracity of such statements is contingent on the accuracy of the mathematical model, which due to its simplicity is only expected to give a very approximate prediction. Possible improvements in accuracy by means of more elaborate models are discussed in the last section.

2 Model description

Dynamical modeling of the growth of HIV populations within infected hosts is complicated by spatial inhomogeneities, due for example to the occurrence of various reservoirs, such as those particularly rapidly established in lymphatic tissues[19–22]. However, and perhaps surprisingly, it seems that the growth of HIV populations can be satisfactorily described even when such inhomogeneities are ignored, which is the usual approach[23] and the one adopted here. Some models had additional components representing resting and latently infected cells[2,4] but a relatively successful[8] now-accepted simple time-dependent three-component model for the evolution of within-host HIV virion numbers in human or simian hosts, without any spatial variables, has been employed for the last fifteen years or so. This model[3,24,25] has as component variables, at time t, $T(t)$, the number of target or activated $CD4^+$ T-cells, $T^*(t)$, the number of productively infected such cells and $V(t)$ the number of free virus. In the early stages of HIV infection, to about 100 days, and in the absence of drug therapy, these quantities satisfy approximately the following three deterministic ordinary differential equations

$$\frac{dT}{dt} = \lambda - \mu T - kTV \tag{1}$$

$$\frac{dT^*}{dt} = kTV - \delta T^* \tag{2}$$

$$\frac{dV}{dt} = pT^* - cV. \tag{3}$$

In Table 1 are shown the variables and parameters with their units.

In a recent article on simian immunodeficiency infection[27], an infection rate $k = k(t)$ which decreases exponentially in time to an asymptotic value has been found to give a better fit for the growth of the viral population. This aspect can be easily incorporated in the approach of this study by varying, for example, the mean of the distribution of the infection rate. We assume a single infection incident, alhough there may be theoretical ramifications of multiple such events[28].

Table 1: Variables and parameters

Symbol	Description	Units
T	Density of target CD4+ T cells	T-cells μl^{-1}
T*	Density of productively infected CD4+ T cells	T*-cells μl^{-1}
V	Density of virions	virions μl^{-1}
λ	Rate of arrival of target CD4+ T cells	T-cells μl^{-1} day^{-1}
μ	Per capita rate of decrease of target CD4+ T cells	day^{-1}
k	Rate of conversion of T to T* by virus	day^{-1} (virions μl^{-1})$^{-1}$
δ	Per capita rate of decrease of productively infected CD4+ T cells	day^{-1}
p	Rate at which T* cells produce virus	virions T*cells^{-1} day^{-1}
c	Per capita rate of decrease of virions	day^{-1}

2.1 Equilibrium analysis

Equilibrium point analysis of the system of differential equations (1)-(3) has been carried out by several authors (for example[8,24,29]). There are two equilibrium points, denoted by P_1 and P_2. These occur at (T, T^*, V)-values of

$$P_1 = \left(\frac{\lambda}{\mu}, 0, 0\right) \tag{4}$$

and

$$P_2 = \left(\frac{c\delta}{kp}, \frac{\lambda}{\delta} - \frac{c\mu}{kp}, \frac{\lambda p}{c\delta} - \frac{\mu}{k}\right). \tag{5}$$

To discuss the outcomes for an infection by HIV, one usually defines

$$R_0 = \frac{k\lambda p}{c\delta\mu}, \tag{6}$$

which leads to the following possibilities.

2.1.1 Case 1, $R_0 < 1$.

It is clear that in this case the equilibrium values of T^* and V are negative so that P_2 is outside the first octant at unbiological values. This might occur, for example, if the arrival rate of target CD4 + T cells from the thymus is sufficiently small to make

$$\lambda < \frac{c\mu\delta}{kp}. \tag{7}$$

Alternatively, large enough values of one or more of c, μ and δ and/or small enough values of one or both of k and p, will also tend to make this inequality hold. Effectively then there is just one critical point P_1 which is at zero virions ($V = 0$) and zero productively infected cells ($T^* = 0$) with the unperturbed equilibrium value of target CD4+ T cells at $T = \frac{\lambda}{\mu}$. Thus

$$R_0 < 1 \implies \lim_{t\to\infty} V(t) \to 0. \tag{8}$$

This means that, according to the model, the virus goes extinct and the infected host is, in principle, cleared of the HIV virus. If the host immune system parameters do not change as a consequence of the infection, then a second dose of virions would meet also with extinction and this process could, theoretically, be repeated indefinitely.

2.1.2 Case 2, $R_0 > 1$

In this case both critical points P_1 and P_2 are at biologically meaningful values in the first octant. The point P_1 is an unstable saddle point and the point P_2 is an asymptotically stable spiral point. Thus when case 2 conditions are fulfilled,

$$\lim_{t\to\infty} V(t) = V_f > 0, \tag{9}$$

where

$$V_f = \frac{\lambda p}{c\delta} - \frac{\mu}{k} \tag{10}$$

is the equilibrium value of the number density of virions.

Note that in[29] the possibility of an extra term $-kTV$ in (3) was considered leading to the replacement of p by $p - \delta$ in the expression for R_0. However, since $\delta << p$, the additional term, which was taken into account in the

calculations presented below, makes very little difference in determining the probabilities which we shall calculate. Note that at $R_0 = 1$, the bifurcation point, there is only one critical point P_1 so that $V \to 0$ as in Case 1[29].

It is apparent that factors which make R_0 larger, promote the persistence of the diseased state and factors which make R_0 smaller inhibit the host viral population. From the definition of R_0 it is clear that larger values of the following promote the persistence of HIV infection: k, leading to greater frequency of virus-T-cell interactions; λ, giving a larger density of target T-cells; and p, the number of virions produced per T*-cell. Similarly, larger values of the following tend to inhibit the HIV population: c, the viral clearance rate; δ, the rate of disappearance of T*-cells; and μ, the rate of disappearance of target T-cells. We use the term *promoters* for k, λ and p and we call c, δ and μ, *inhibitors*, these two groups being treated differently in the analysis below.

3 Methods

Let us denote the random variables representing the parameters by the symbols given in Table 2.

Table 2: Notation for random parameters

Parameter	Random
λ	Λ
μ	M
k	K
δ	Δ
p	P
c	C

Whether case 1 or case 2 applies depends on the values of the set of 6 random variables

$$U = \{\Lambda, M, K, \Delta, P, C\}. \tag{11}$$

The calculation which we address in this article is the determination of the probability of occurrence of the various values of U. In particular we will attempt to estimate

$$p_E = \text{Prob}\{U \in E\} \tag{12}$$

where E is the set of values of the 6 parameters which lead to P_1 being an asymptotically stable node. This will provide an estimate of the probability that the virus goes extinct, even in the absence of any drug treatment. Note that this is a population probability describing the chance that the virus does not persist in a randomly selected member of the population of hosts. It is not a probability that in a given individual the virus will go extinct as would be estimated with stochastic process models[5–7,17,18]. Thus, if the host population is of size N, and N_R is the number who recover from the viral infection without treatment, then

$$\mathrm{E}(N_R) = Np_E. \tag{13}$$

3.1 Estimation of p_E

All the parameters in U are non-negative and continuous and it is assumed that they may be ascribed probability density functions. Let us denote the densities of the six components by

$$f_\Lambda, f_M, f_K, f_\Delta, f_P, f_C. \tag{14}$$

It is feasible to determine p_E analytically by finding the distribution of R_0 if certain simplifying assumptions are made about the distributions of the various parameters. However, a better approach seems to be guided by empirical evidence to estimate the various densities f and then use simulation to estimate p_E.

Stafford, *et. al.*[8] gave estimates (their Table 2) for the values of the parameters μ, k, δ and p for 10 patients infected by HIV. In Table 3, we give the means, standard deviations, and upper and lower 95% confidence limits for the means as well as the maxima and minima for these four parameters. As in Stafford et al. it is assumed that $c = 3$, with no variance, for all patients and also that $\lambda = 10\mu$. The latter is consistent with Stafford et al.'s values for R_0. However, different values of λ are obtained using Stafford et al.'s equilibrium value for $T = T_{ss}$. Thus using $\lambda = 10\mu$, the mean is $\overline{\lambda} = 0.1089$ whereas using the values of T_{ss} one obtains $\overline{\lambda} = 0.193$. In the simulations below we use the values $\lambda = 10\mu$.

We note that based on the Stafford et al.[8] data, a 95% confidence interval for the mean of R_0 is (4.089, 7.310), so that the chance of $V_f = 0$ is practically

Table 3: Some statistics for 10 patients, from Stafford et al.[8]

	μ	k	δ	p
Mean	0.01089	1.179×10^{-3}	0.3660	1426.8
Standard deviation	0.005727	1.422×10^{-3}	0.193	2049.36
Minimum	0.0043	0.19×10^{-3}	0.13	98
Maximum	0.020	4.80×10^{-3}	0.80	7100
Upper 95% conf limit	0.00734	0.2976×10^{-3}	0.246377	156
Lower 95% conf limit	0.0144396	2.560×10^{-3}	0.4856	2697

zero, as would be expected from a group of patients who definitely have a sustained HIV infection. It is noted that in a later study of a larger group of patients[11], the mean value of R_0 was 8.63 with a range of values from 2.31 to 26.37.

3.2 Distributions of parameters

For the estimation of the probability that the virus goes extinct after infecting a new host, the distributions of the random variables $\Lambda, M, K, \Delta, P, C$ are required. These are not known with certainty so we assume as a first approximation that the parameters are normally distributed, although log-normal distributions have been previously employed[30]. For the density of C we take a delta-function concentrated at $c = 3$. If we take the remaining variables Λ, M, K, Δ, P to have normal distributions then there is always going to be a small probability mass for each variable at values less than zero, which is biologically unrealistic. Hence we have chosen truncated normal distributions. For a normal random variable X with mean m, standard deviation σ, truncated to be on the interval (α, β), the probability density function is[31]

$$f_X(x) = \frac{\phi\left(\frac{x-m}{\sigma}\right)}{\sigma\left[\Phi\left(\frac{\beta-m}{\sigma}\right) - \Phi\left(\frac{\alpha-m}{\sigma}\right)\right]}, \alpha < x < \beta, \tag{15}$$

where ϕ and Φ are the density and distribution function for a standard normal random variable. The mean of the truncated variable is

$$E[X] = m + \frac{\phi\left(\frac{\alpha-m}{\sigma}\right) - \phi\left(\frac{\beta-m}{\sigma}\right)}{\left[\Phi\left(\frac{\beta-m}{\sigma}\right) - \Phi\left(\frac{\alpha-m}{\sigma}\right)\right]}\sigma \tag{16}$$

which is useful for comparing with the mean of the parent distribution.

3.3 Sampling procedures

In order to estimate p_E we generate samples of size 10,000 for each of the parameters $\mu, \lambda, k, \delta, p$ using the truncated normal probability density functions. The distributions are specifed in terms of the four quantites: mean, standard deviation (both chosen before truncation), and the lower and upper truncation points. The following four approaches were used.

Method 1: Use the means and standard deviations of the Stafford et al.[8] data of Table 3 and use the minimum value of each parameter as α and the maximum value as β for the corresponding random variable.

Method 2: Take α to be half of the minimum value of the Stafford et al. data, and β as twice the maximum value of the Stafford et al. data. The motivation here is to extend the ranges of the parameter data of Stafford et al.[8], because those data are for patients who became infected and remained infected, whereas some members of the population may become infected with HIV and recover spontaneously if their immune system is able to eliminate the virus as in the case of $R_0 < 1$. Again we use the original standard deviations given in Table 3. However, instead of the actual mean, in order to examine outcomes with more extreme but possible parameter values, we have also used the estimated lower and upper confidence limits of the means.

Method 3: Here the means of the parameters which are promoters, k, λ, p are multiplied by 0.9, whereas the means of the parameters δ and μ which are inhibitors are multiplied by 1.1. The same standard deviations as in Method 1 are employed and the 95% confidence limits for the means are recalculated. We do this using the same sets of lower and upper bounds for the parameter densities as for Method 2.

Method 4: This method is also motivated by the shifting of the parameter distributions of the Stafford et al.[8] data to account for bias in the data due to the fact that they were taken from patients in whom HIV persisted. Here we multiply the means and the lower and upper bounds (taken to be the minimum and maximum values of the parameters in Table 3, as in Method 1) of the promoter parameters k, λ, p by values $s_p < 1$, and we multiply the means and the upper and lower bounds of the inhibitor parameters δ and μ by values $s_d > 1$. Such choices must lead to a greater chance of extinction of the virus.

In all cases the values of the random variable R_0, are computed, and hence the probability p_E that P_1 is an asymptotically stable node or equivalently that extinction of the host HIV population occurs, can be estimated.

4 Results

For Method 1, the use of the means and standard deviations of the data in Table 3 as well as the minima and maxima as the truncation limits resulted in the following means from formula (16) for the parameters: (with original means in brackets) $E[M] = 0.0114(0:01089), E[K] = 1.6401 \times 10^{-3}, (1.179 \times 10^{-3}), E[\Delta] = 0.3965(0.3660)$ and $E[P] = 2141.1(1426.8)$. Thus, the truncation procedure results in increases in the means for all of these 4 parameters.

4.1 Calculated extinction probabilities

In total, as described above for Methods 1,2 and 3, there were many different ways in which the parameters of the distributions of the randomized parameters were chosen. To illustrate, there are shown in Figure 1, the histograms for the parameter λ with truncated distributions according to Methods 1-3.

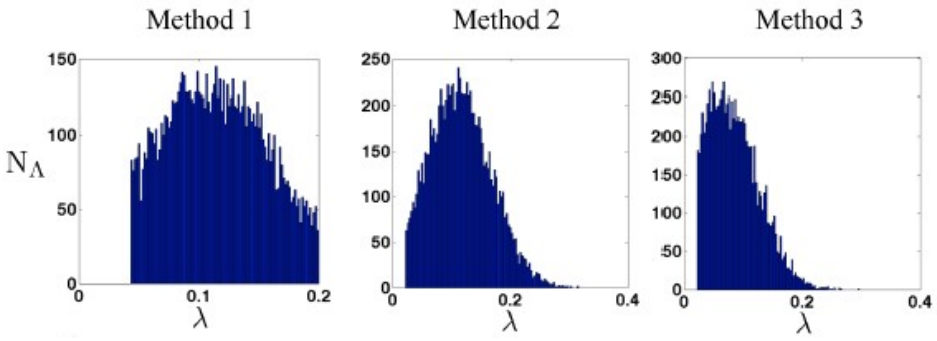

Figure 1: The truncated normal distributions of Λ according to the densities described in the text, with means chosen to be the values of Table 3.

For each Method and for each choice of parameterization of the distributions the calculated results for the probabilities of extinction p_E were as follows (Table 4). Furthermore, various combinations of confidence limits were used for the means so that in the Table 4, averages, minima and maxima over the various combinations are given.

Figures 2 and 3 show geometrically, by means of three-dimensional scatter diagrams, the situation with regard to the critical points in two extreme cases.

Table 4: Estimated extinction probabilities, p_E

	Method 1	Method 2	Method 3
Maximum value	0.0685	0.1354	0.1376
Minimum value	0.0063	0.0066	0.0158
Average value	0.0248	0.0450	0.0693

If P_2 falls outside the first octant then spontaneous recovery can, according to the model predictions, occur. In Figure 2 is shown the spatial distribution of P_1 and P_2 values when the probability of recovery is small, with most P_2-values falling in the first octant. In contrast, Figure 3 shows a case where the probability of recovery is much higher as many more P_2-values fall outside of the first octant. The sample sizes used for these figures were reduced to 2000 from the usual 10000 to make the figure files manageable.

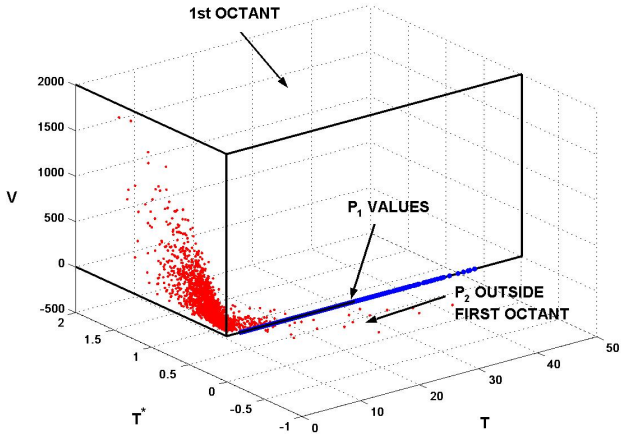

Figure 2: A sample distribution of the positions in (T, T^*, V)-space of the two critical points P_1 (blue circles) and P_2 (red circles) when the probability of recovery from HIV infection is very small. Only a relatively small number (about 1.5%) of points P_2 lie outside the first octant. Here the sample is generated by Method 1 using the actual minima, mean and maxima as given in Table 3 for the parameters of Stafford et al.[8] for use in the truncated normals. Sample size 2000.

We also explore calculations in which we shift the distributions to account

Table 5: Values of p_E, Method 4.

s_d	s_p	p_E
1.1	0.9	0.0253
1.2	0.8	0.0501
1.25	0.75	0.0671
1.3	0.7	0.0840
1.4	0.6	0.1414
1.5	0.5	0.2399

for bias in the Stafford data towards patients in which the virus persisted, which we have called Method 4. Results are given in Table 5 and see also Figure 3.

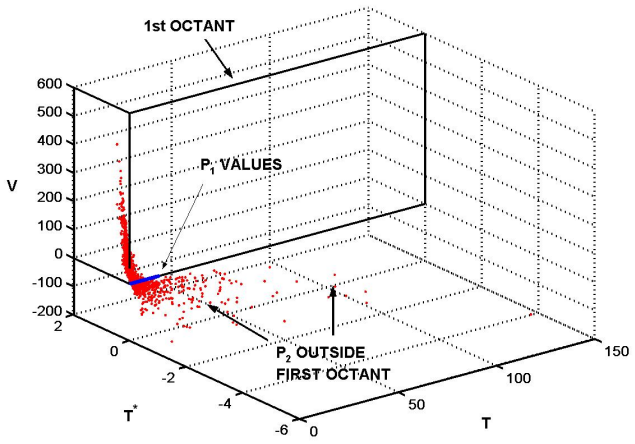

Figure 3: A sample distribution of the positions in (T, T^*, V)-space of the two critical points P_1 (blue circles) and P_2 (red circles) when the probability of recovery from HIV infection is relatively large. About 25% of the points P_2 lie outside the first octant. Here the sample is generated using Method 4 where the means and upper and lower truncation points for the distributions for k, λ, p are multiplied by 0.5 and those of μ and δ are multiplied by 1.5. Sample size 2000.

5 Discussion

The probabilities p_E determined above represent the chance that the parameters of the virus-immune system dynamics are such that the only equilibrium is at zero virions and hence the virus would, theoretically, be eliminated without medical intervention. The values of p_E given in Table 4 have approximate upper bounds of 0.07 for Method 1 and 0.14 for Methods 2 and 3. These probabilities are quite small, which is due, at least in part, to the fact that the estimated parameter distributions are biased, being derived from a sample of individuals, all of whom were infected by HIV for tracked periods of from 46 days to several hundred days.

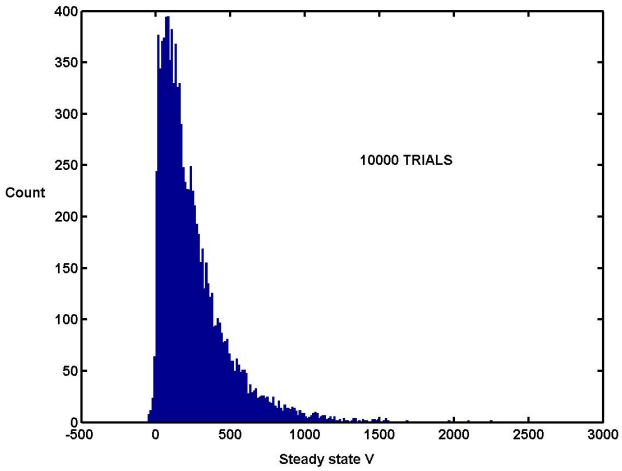

Figure 4: Histogram of steady state V values per μl when the parameter distributions are obtained by the conservative method 1.

A histogram of steady state $V = V_f$ values for Method 1, using the original means[8] and upper and lower experimental values for α and β (see Equ. (15)) is shown in Figure 4. Here a small fraction of values is less than or equal to zero giving a p_E value of 0.0136. Note that large variability in steady-state viral loads across patient populations was demonstrated in[32]. Here we may also point out that to be consistent, we have only used the data from[8] as the basis of the parameter distributions. Nevertheless, it is clear that other data sets would yield possibly quite different results. For example, values of c were reported as considerably higher in[33]. Changing c

from 3 to 5, for example, gives, with all other parameters unchanged, a value of $p_E = 0.0294$.

When the ranges of the parameters were extended by not extreme amounts in an attempt to counter the bias towards an infected group, values of p_E were obtained as high as about 0.24 (Table 5). Thus, in the general population, *within the framework of the standard 3-component model*, a considerable percentage of individuals could be infected by HIV but the virus would subsequently be eliminated without intervention which would constitute spontaneous recovery.

Much has been written concerning the feasibility of eradication of HIV with medical intervention, some authors considering that it could be done but would take years, and others declaring that it could not be achieved in the lifetime of a patient with presently used drug treatments[12–14,34,35]. Interestingly, related to this idea is the discussion in Ribeiro et al.[11] concerning the distribution of R_0. It was pointed out that if intervention could be carried out soon enough after initial infection, then R_0-values in some subjects could be driven below unity with subsequent possible elimination of the virus. The exploration of such possibilities and the experimental verification of the occurrence of a transient appearance of the virus in some subjects, followed by spontaneous elimination, would need frequent data collection in the early stages after an infectious incident.

It is further noted that the virus population in patient 3 of the Stafford et al. data had dwindled to 0.1% of its maximum after 50 days. Additionally, if one takes the values of the parameters for all 10 patients which lead to the smallest value $R_{0,min}$, of R_0, which are $\delta = 0.8$, $k = 0.00019$, $p = 98$ and the standard values $c = 3$ and $\mu/\lambda = 0.1$, then $R_{0,min} = 0.078$ which is considerably less than the value required to make the only equilibrium point the one at zero virions.

The probability of transmission of HIV has been estimated in various groups. Gray et al.[36] found an average value of 0.0011 per coital act in heterosexual couples in Rakai, Uganda and Wawer et al.[37] found a value of 0.0082 for a similar population. See also[38] who noted that in discordant couples transmission did not occur if the infectious partner had less than 1500 copies of HIV-1 RNA/ml serum[39]. Higher values, around 0.031, had been obtained for a group of male military trainees who interacted with female prostitutes in Thailand[40]. In the Ugandan studies, two of the main factors influencing transmission were time since infection of the index partner and degree of ulceration. However, in all these reports, the probability of trans-

mission involved not only the transfer of the virus, but also establishment of the virus in the new host, whereas only the latter is the subject of the present article.

Many findings reported in such articles, and in Downs et al.[41], concern transmission in stable monogamous discordant couples, in which one partner is HIV-positive and yet, despite frequent and long-term possibilities of transmission, the HIV-negative partner does not seroconvert, even in the absence of condom use. Similarly, in the metaanalytical study of Powers et al.[42], it was reported that there could be no transmission even after hundreds of contacts between members of discordant couples. Furthermore, transmission had been remarkably found to not occur in some individuals despite multiple high-risk sexual exposures[43,44]. In the latter study, CD8+ lymphocytes were found to have greater anti-HIV-1 activity than those from nonexposed controls. There is always the possibility that the non-transmission of the virus in discordant couples is due to properties of the infected partner, such as a low viral load. Nevertheless, it is feasible, though considered unlikely by HIV experimentalists and theorists, that in some of these long-term discordant couples, the non-index partner does become infected briefly, possibly repetitively, but the virus is subsequently eliminated as predicted by the standard model. The period(s) of infection could be brief and the viral load small so that the partner remained asymptomatic.

According to Haynes et al.[46], the existence of individuals who have been exposed multiple times to HIV and are persistently HIV-seronegative raises the possibility that a small percentage of them may be resistant to HIV, or may have been able to clear the infection. The situation is made less clear by virtue of the issues of viral loads below threshold for detection and other false negatives. Also pertinent are the rates of HIV infection in children born to HIV-infected parents. According to an analysis of Rowland-Jones et al.[45], 60-85% of children exposed either before or after birth to HIV were not infected. In a European study[47], a study of 165 HIV-affected families with 279 children, found that 68% of the children were HIV-negative.

Much has been written about host immune properties or properties of the virus which may lead to the fending off of HIV infection[46,48] or as in the case of elite controllers (sometimes called long term non progressors or just HIV controllers) who constitute about 5-10% of cases, maintaining low viral burdens and not converting to the AIDS regime. Genetic factors such as the gene encoding CCL3L1 have been shown to affect susceptibility to AIDS[49] and certain mutations in the gene encoding the protein CCR5 afford

immunity to HIV in mice[50].

There are evidently, however, no documented cases of clearance of HIV from an an individual with an established infection (Alan Perelson and Marc Pellegrini, personal communications). There were cases reported in the press of changes in individuals from HIV-positive to HIV-negative, the most noteworthy being that of Alan Stimpson. The standard model employed here predicts, under reasonable assumptions on the distributions of parameters, that a small percentage of the population might be able to clear HIV after infection. As pointed out above, it would be hard to verify or refute this prediction if the duration of infection and the viral load were both small. In actuality, there are several immune system components and reservoirs omitted in the standard 3-component model, such as latently-infected cells, cytotoxic T-cells (CD8+ T-cells, CTL), natural killer cells and dendritic cells. A stochastic model for the production of viruses from reservoirs of latently infected cells has been proposed in[51].

In depth discussions of these complicating factors including virus on the surface of follicular dendritic cells are given in references[13,14,26,34,35] and especially[12]. The inclusion of such reservoirs and sanctuaries would doubtless lead to smaller probabilities of eliminating the virus, with or without drug treatment, than those obtained in the present article using the simplified yet often-used standard three-component model. The incorporation of the many additional components would make the mathematical modeling much more complicated but would be worthwhile in that it may yield more insight into the possibility of an individual's clearing an HIV infection. Furthermore, an approach which combines the use of stochastic processes for virus and other system variables for infection within an individual and a distributional approach as employed in the present study would be even more complicated but also more capable of accurately predicting extinction probabilities across a population.

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