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Publication Date

1993-12-01

LBL-34952
Preprint

Lawrence Berkeley Laboratory
UNIVERSITY OF CALIFORNIA

Physics Division

Submitted to Journal of Aids

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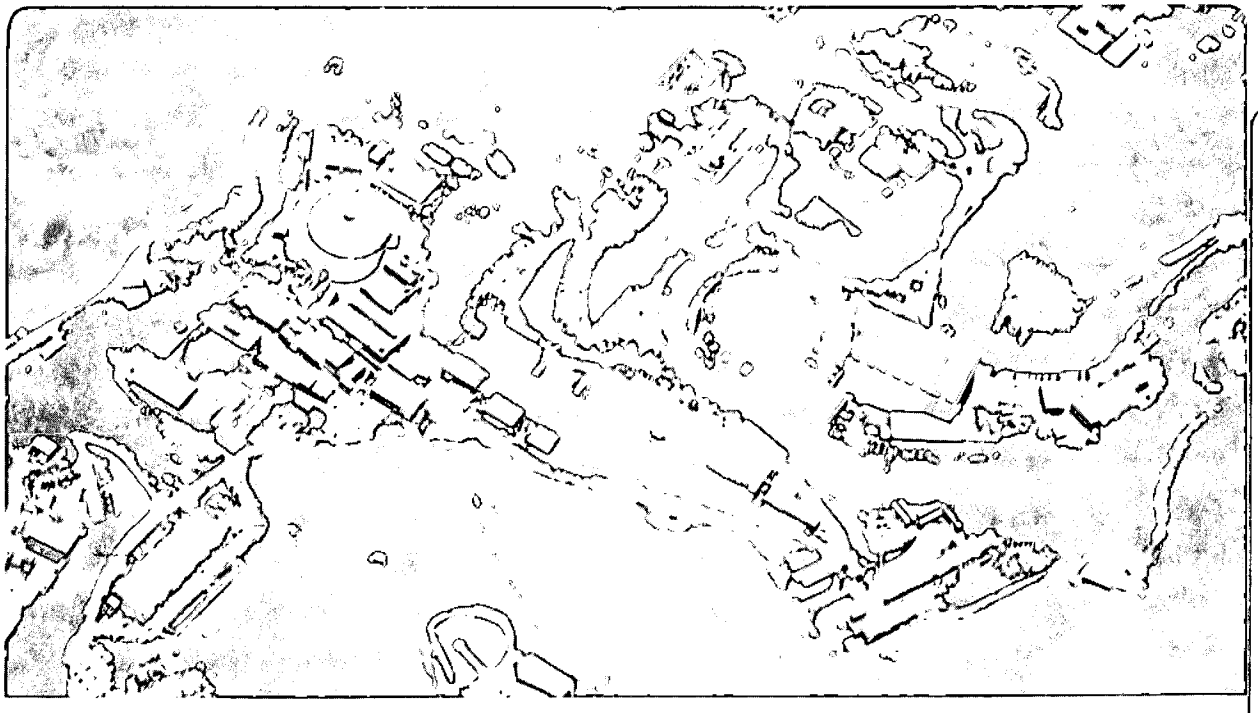
December 1993



Prepared for the U.S. Department of Energy under Contract Number DE-AC03-76SF00098

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LBL-34952

Localized or Systemic *In Vivo* Heat-Inactivation of Human Immunodeficiency Virus (HIV): A Mathematical Analysis

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This work was supported by National Institutes of Health grants AI 28433, GM 39723, and GM 49670, Augustine Medical, Inc., and the Director, Office of Energy Research, Office of High Energy and Nuclear Physics, High Energy Physics Division of the U.S. Department of Energy under Contract No. DE-AC03-76SF00098.

Abbreviated Title: HEAT-INACTIVATION OF HIV.

Abstract

Temperatures as low as 42°C, maintained for a little as 25 minutes, inactivate ≈25% of HIV. Furthermore, human immunodeficiency virus (HIV)-infected T-cells are more sensitive to heat than healthy lymphocytes and susceptibility increases when the cells are pre-sensitized by exposure to tumor necrosis factor. Thus, induction of a whole-body hyperthermia, or hyperthermia specifically limited to tissues having a high viral load, are potential antiviral therapies for acquired immunodeficiency disease (AIDS). Accordingly, we incorporated therapeutic hyperthermia into an existing mathematical model which evaluates the interaction between HIV and $CD4^+$ T cells. Given the assumptions and limitations of this model, the results indicate that a daily therapy, reducing the population of actively infected cells by 40% or infectious virus by 50%, would effectively reverse the depletion of T cells. In contrast, a daily reduction of 20% of either actively infected cells or infectious virus would have a marginal effect. However, reduction by 20% of both actively infected cells and infectious virus could restore T cell numbers, assuming that permanent damage had not been inflicted on the thymus. Whole-body hyperthermia seems unlikely to be clinically useful, unless it can be induced non-invasively without general anesthesia. In contrast, heating directed specifically to areas of viral concentration may be effective and have a suitable risk/benefit ratio.

Key words: HIV, AIDS, Mathematical Model, Heat Inactivation.

Introduction

In the ten years since its recognition, the human immunodeficiency virus (HIV) has infected more than 7 million people world-wide, and killed more than 2.5 million of them. The infection rate continues to increase nearly exponentially, and by the end of this decade, between 38 and 110 million people will be infected.[1] There currently is no cure for immune deficiency syndrome (AIDS); unless one is rapidly developed, nearly all HIV-infected individuals will die.[2] Furthermore, currently available treatments produce serious side-effects and only marginally impair progression of the syndrome.[3] Consequently, a relatively safe therapeutic intervention retarding the course of this disease would be welcome.

Temperatures near 60°C reliably inactivate HIV,[4] and such temperatures have been used to prevent transmission of the virus by isolated clotting components administered to hemophiliacs. Unfortunately, temperatures in this range also inactivate platelets and white blood cells, making this degree of hyperthermia (*i.e.*, using an extra-corporeal system) an unsuitable treatment for HIV infection. However, temperatures as low as 42°C, maintained for a little as 25 minutes, inactivate ≈25% of HIV.*[5] Furthermore, HIV-infected T-cells are more sensitive to heat than healthy lymphocytes and susceptibility increases when the cells are pre-sensitized by exposure to tumor necrosis factor.[6] This temperature only slightly exceeds the core hyperthermia produced by infectious fevers[7] and probably does not irreversibly damage most tissues including blood.[8] Thus, induction of whole-body hyperthermia is a potential antiviral therapy for AIDS. Moreover, HIV infection appears to be significantly concentrated in the lymphatic system,[9,10] raising the

* The authors thank Dr. Enok Tjotta for providing the raw data used in reference 5.

possibility that heating directed specifically at lymph nodes might also be effective, while perhaps substantially reducing the risks of whole-body hyperthermia.

A critical question in determining the likely effectiveness of hyperthermia — or any antiviral therapy — is whether the induced reduction in virus load is sufficient to decrease the negative effects of the infection, if not to eliminate the infection altogether. The data needed to estimate the ability of *in vivo* hyperthermia to eliminate virus and infected cells remains incomplete. Still, it is possible with present knowledge to mathematically model the effects of *in vivo* hyperthermia on HIV and relevant cell populations. Alternatively, we can estimate the amount of anti-viral effect a proposed therapy (*i.e.*, whole-body hyperthermia *vs.* specific heating of lymph nodes) must posses to eliminate virus and infected cells. Accordingly, we here incorporate therapeutic hyperthermia into an existing model which evaluates the interaction between HIV and $CD4^+$ T cells.

Methods

We model HIV infection of T lymphocytes as follows: Let T denote the concentration of uninfected T4 cells and let T^* and T^{**} denote the concentrations of latently infected and actively infected T4 cells, respectively. The concentration of free infectious virus particles is V. We assume that the dynamics of the various T4 cell populations is governed by the following differential equations:

$$dT/dt = s(V) - \mu_T T + rT\left(1 - \frac{T + T^* + T^{**}}{T_{max}}\right) - k_1 VT \quad (1)$$

$$dT^*/dt = k_1 VT + \mu_T T^* - k_2 T^*, \quad (2)$$

$$dT^{**}/dt = k_2 T^* - \mu_b T^{**}, \quad (3)$$

$$dV/dt = N\mu_b T^{**} - k_1 VT - \mu_v V. \quad (4)$$

The detailed derivation of these equations is described in Perelson, *et al.*[11] We begin by describing T cell population dynamics in uninfected individuals.

The first three terms in Eq. (1) represent the rates of production and destruction of T cells in uninfected individuals; s being the rate of supply of immunocompetent T cells from precursors in the thymus; μ_T represents the average per capita death rate of T cells. We have chosen s to be a decreasing function of V so that as the viral burden increases, infection of T cell precursors increases and the supply of T cells decreases. Here we assume $s(V) = Qs/(Q + V)$, where Q is a constant that determines the viral load needed to decrease s by a factor of two. In the absence of HIV, $s(V) = s =$ constant. The growth of T cells is modeled by a logistic equation, with r being the *per capita* T-cell growth rate in the absence of population limitation. The last term in the equation, proportional to k_1, represents T cell infection by HIV. In the absence of HIV, this equation describes the T cell population

level in blood. One can set the parameters, so that this level is maintained at 1000 cells/mm^3, as is typical in healthy people.

Virus isolated from patients at the final stages of the disease is often more pathogenic than the strain isolated initially from seropositive patient.[12,13] It may be that rapidly-replicating viruses (large N) are initially eliminated by an immune response, while slowly-replicating strains (small N) escape immune detection. A model exploring this view has been presented by Nelson and Perelson.[14] However, as the disease progresses, slowly growing viral strains apparently are replaced by faster growing or more pathogenic ones: *e.g.*, non-syncytium inducing strains may be replaced by syncytium inducing ones. Here we model this by replacing the constant N in Eq. 4 by a gradually increasing function of time

$$N(t) = N_0\left(1+\frac{at^n}{q^n+t^n}\right), \qquad \text{Eq. 5}$$

where N_0, n, a, and q are constants. One could also model the evolution of viral strains by replacing the constant [k_1] by a slowly increasing function of time, so that the infectivity increased as a function of time.

The solutions to Eqs. (1)-(4) were computed numerically, using a Gear's method, stiff differential equation solver (ddrvb3, Los Alamos National Laboratory Common Mathematical Software Library). Dependent variables and their initial values are shown in Table 1; the default or initial values for the parameters and constants are shown in Table 2.

To model the effects of a daily hyperthermic treatment, which kills a certain percentage of HIV virions and/or a percentage of actively infected T cells, the integration of Eqs. (1)-(4) was terminated at the end of each 24-h period, and then restarted with the appropriately reduced number of remaining infectious virions

and infected cells. For example, to evaluate a daily treatment which reduces the viral burden by 25%, we would integrate Eqs. (1)-(4) for one day, decrease V to 75% of its value at the end of that day, and then restart the integration.

Results

We first examine the case of disease progression without heat treatment. The model, given by Eqs. (1)-(4), with N constant, has two steady states, an uninfected state in which $V = 0$, $T = T_0 = 1000$, $T^* = T_0^* = 0$, and an endemically infected state in which $V > 0$. We have shown that if N, the number of infectious virions produced per actively infected cell, is less than some critical value, $N_{crit} = k_3(\mu_v + k_1T_0)/(k_2k_1T_0)$, then the infection will die out.[11] Conversely, if $N > N_{crit}$, then the infection will prosper, virus will survive and T-cell depletion will occur. When $N < N_{crit}$, virus infects cells, but the cells that are infected die before producing enough offspring to sustain the infection. The same type of phenomenon is observed in epidemics. If on average, infected people infect more than one other person the disease spreads and causes an epidemic; in contrast, the epidemic dies if each person on average infects fewer than one other person.

Figure 1 illustrates the predictions of the model for $N > N_{crit}$, where N is given by Eq. (5). Notice that initially, the amount of free virus declines as it infects cells, but it subsequently increases exponentially. While the virus level is low, T cells are infected but the level of infection is so low that T cell depletion is not noticeable. But ultimately, the virus population is sufficiently augmented to decrease the T-cell population. This decrease occurs gradually over a period of about eight years. The actual time course of this decrease depends on N(t), and hence, the viral strain. The model predicts that the fraction of latently infected T cells and actively infected T cells increases as the disease progresses but are consistent with the low values typically observed in patients, *e.g.*, on the order of 1 in a 100 T cells are latently infected[15] and 1 in 10,000 actively infected.[16]

Using this model, we now examine the effects of heat inactivation (or for that matter, any treatment that reduces the number of infectious virions and/or infected cells). In Figure 2, we show the predicted effects of a treatment that eliminates 0% (baseline), 20%, and 40% of the free infectious virus in the blood each day. Treatment is started in year 5 and continues through year 9. As is apparent, 40% removal leads to substantial recovery in the T-cell level. If 50% of the free virus is removed daily, the T cells recover to their normal level (not shown).

In Figure 3 we show the effects of a treatment given daily from years 5 through 9, that reduces the number of actively infected cells by 0%, 20%, and 40%. With 40% reduction, the level of uninfected T cells returns to 1000/mm^3 after a little more than one year of treatment. However, as in Figure 2, virus is not totally eliminated from the blood and once treatment is terminated, T-cell depletion continues so that by year 12, it is close to levels observed in untreated individuals. Thus, for improvement to continue, treatment at that level of efficacy may have to be sustained for the life of the patient.

Treatments that kill both actively infected cells and free virions give synergistic results. In Figure 4, we show the predicted effects of a daily treatment that eliminates 0%, 10%, and 20% of both free virus and actively infected T cells. Removing 20% of both populations now leads to complete recovery of the T cell population.

Discussion

HIV is an RNA virus that attaches to cells by interacting with CD4, a cell surface molecule.[17,18] After HIV binds to a cell, it becomes internalized, and infects the cell. Thus, $CD4^+$ T cells, as well as monocytes and macrophages which also express CD4, are targets of HIV infection. After HIV enters a cell, its RNA is "reverse transcribed" to produce a DNA copy of its genome, which may then integrate into the cells DNA. A cell containing the viral genome, called the provirus, but not producing new virus particles is considered *latently infected*. The provirus can remain latent, giving no sign of its presence for months or years.[19]

When a latently infected lymphocyte is stimulated by an antigen or mitogen, virus production may be initiated, causing virus particles to bud from the surface of the infected cell. The budding can be rapid, leading to the lysis of the host cell (as appears typical in T4-cell infection), or it can be slow and spare the host cell (as appears typical in macrophage and monocyte infection). Thus, immune activation of T cells, say by the T cells recognizing antigen, is required for converting a latently HIV infected cell into a proliferative state. Similar activation may also be required for integration of the HIV genome.

The simpler form of the model ignores the complexity of viral mutation. It is known that HIV can rapidly mutate and thus that there are many strains of HIV. Different strains of virus have different properties, and in particular different abilities to grow in T cells. Thus, the parameter N is a characteristic of a particular stain. Strains that are highly pathogenic might be envisioned as corresponding to high values of N.

The importance of including the evolution of the virus from slowing-replicating to rapidly-replicating strains in the model is illustrated by the differences

between Figures 1 and 2, and is consistent with recent data by Connor, *et al.*[12] showing that in some AIDS patients the T cell population declines precipitously over a period of one to two years, just as in our model. Furthermore, the period of T-cell decline in these patients correlates with a period of rapid increase in virus, as measured using the polymerase chain reaction.

Not all patients evaluated by Connor, *et al.* followed this pattern. One patient, for example, has had a nearly constant number of uninfected and latently infected T cells over a period of eight years. This patient may be generating an immune response preventing the virus from multiplying and/or becoming more pathogenic. In any event, our model, which does not incorporate an immune response to the virus, does not predict the relatively constant T cell and virus levels seen in this patient. Despite such occasional exceptions, this rather simple model of HIV infection of T cells mimics many of the quantitative observations made *in vivo*.

The model is based on quantitative data obtained in peripheral blood, and predicts observed values reasonably well. Recent studies suggest that many HIV-infected lymphocytes are sequestered in lymph nodes.[9,10] To the extent that peripheral blood T cell concentrations can be used to diagnose the stage and severity of the disease, our model may thus implicitly reflect the exchange between lymph nodes and blood, and hence the overall disease severity. In any event, the model is only indicative of the improvements in T cell numbers resulting from heat inactivation (or other therapies) that kill actively infected cells and/or free virus. The model ignores the long-term destruction of the follicular dendritic cell network and hence the decreased ability of lymph nodes to filter virus and stimulate immune responses.[9] Thus, it remains unlikely that full recovery of the immune system will occur, even if circulating T-cell counts are restored to normal. The model also ignores damage to the thymus, and thus optimistically assumes that

thymic function returns to normal if virus is cleared. Other models are currently under development in which this assumption is relaxed. Quantitative experiments certainly are needed to test our model and establish the effectiveness of heat treatment applied either to lymph nodes or to the entire body

Treatment of HIV with whole-body hyperthermia to 42°C has been attempted,[20] but the efficacy of the treatment has yet to be adequately evaluated. Obviously, any treatment requiring prolonged general anesthesia can only be applied at intervals far exceeding the 24 hours used in our calculations. Our model suggests that such infrequent treatments are unlikely to be effective. The extent to which lesser degrees of hyperthermia, *e.g.*, 39°C (which can easily be obtained by recreational immersion in a hot-tub[21] or by forced-air warming[22,23]), might prove beneficial remains unknown. However, based on the data of Tjotta, *et al.*[5], our model would predict an insignificant effect.

General anesthesia has been used in most previous hyperthermia studies[24] to avoid thermal discomfort and minimize active thermoregulatory vasodilation, which can increase cutaneous blood flow to as much as 7.5 liters/minute (equaling the entire resting cardiac output).[25] This increase is mediated by decreased systemic vascular resistance and requires a substantial — and stressful — compensatory increase in cardiac output.[26] However, it may be possible to avoid general anesthesia by administration of sedatives sufficient to raise the threshold for active vasodilation[27] (core temperature triggering thermoregulatory vasodilation[28]) to ≥42°C. Although propofol appears to inhibit thermoregulatory responses to hypothermia more than the volatile anesthetics,[29,30] our (unpublished) data suggests that it is less effective than other anesthetics[31] for preventing sweating and active vasodilation. The thermoregulatory effects of other sedative/hypnotic agents

have not been specifically tested during core hyperthermia, but barbiturates appear useful in some clinical protocols.[32]

Even if the direct autonomic responses to whole-body hyperthermia can be prevented pharmacologically, other potential complications including bleeding diathesis (mediated by excessive fibrinolysis,[33] decreased platelet number,[34] and disseminated intravascular coagulation[35]), baroreceptor malfunction,[36] and immune disturbances[37,38] may limit application of thermal treatments. An alternative is to focus application of heat to body regions most likely to benefit. In the case of HIV, the thoracic duct and major chain of lymph nodes surrounding the aorta might be appropriate targets. Such a system might include implanted heat exchangers or receivers for directed microwave radiation.[39] Naturally, routine clinical treatment of HIV with hyperthermia will required not only demonstration of efficacy, but also of a favorable risk/benefit ratio.

In summary, given the assumptions and limitations of this model, the results indicate that a daily therapy, reducing either the population of actively infected cells or infectious virus by 40%, would effectively reverse the depletion of T cells. In contrast, a daily reduction of either population by 20% would have a marginal effect. However, reduction of both populations by 20% daily would also reverse the depletion of T cells. Since all virus is not removed, therapy needs to be continued for the life of the patient. Because the quantitative predictions of this model depend on parameter values, one might expect variation from patient to patient. Only experimental tests can ultimately determine the efficacy of thermal treatments. Whole-body hyperthermia seems unlikely to be clinically useful, unless it can be induced non-invasively without general anesthesia. In contrast, heating directed specifically to areas of viral concentration may be effective and have a suitable

risk/benefit ratio. Even if heat-inactivation does not prove useful, the mathematical model presented here can be applied to other types of antiviral treatments.

Acknowledgment

We would like to acknowledge valuable conversations with Dorian King.

This work was supported by National Institutes of Health grants AI 28433, GM 39723, and GM 49670, Augustine Medical, Inc., and the Director, Office of Energy Research, Office of High Energy and Nuclear Physics, High Energy Physics Division of the U.S. Department of Energy under Contract No. DE-AC03-76SF00098.

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Figure Legends

Fig. 1. Predicted dynamics of HIV infection obtained by solving Eqs. (1)-(4) with parameters given in Table 2. Here N is an increasing function of time as given by Eq. (5), with N_0=250, a=3, n=3, and q=8 yr.

Fig. 2. The predicted effect of a treatment given daily from years 5 through 9 that reduces the number of actively infected cells by 0% (baseline), 20%, and 40%.

Fig. 3. The predicted effect of a treatment given daily from years 5 through 9 that reduces the number of free infectious virions by 0% (baseline), 20%, and 40%.

Fig. 4. The predicted effects of a treatment given daily from years 5 through 9 that reduces both the number of actively infected cells and the number of free infectious virions by 0%, 10%, and 20%.

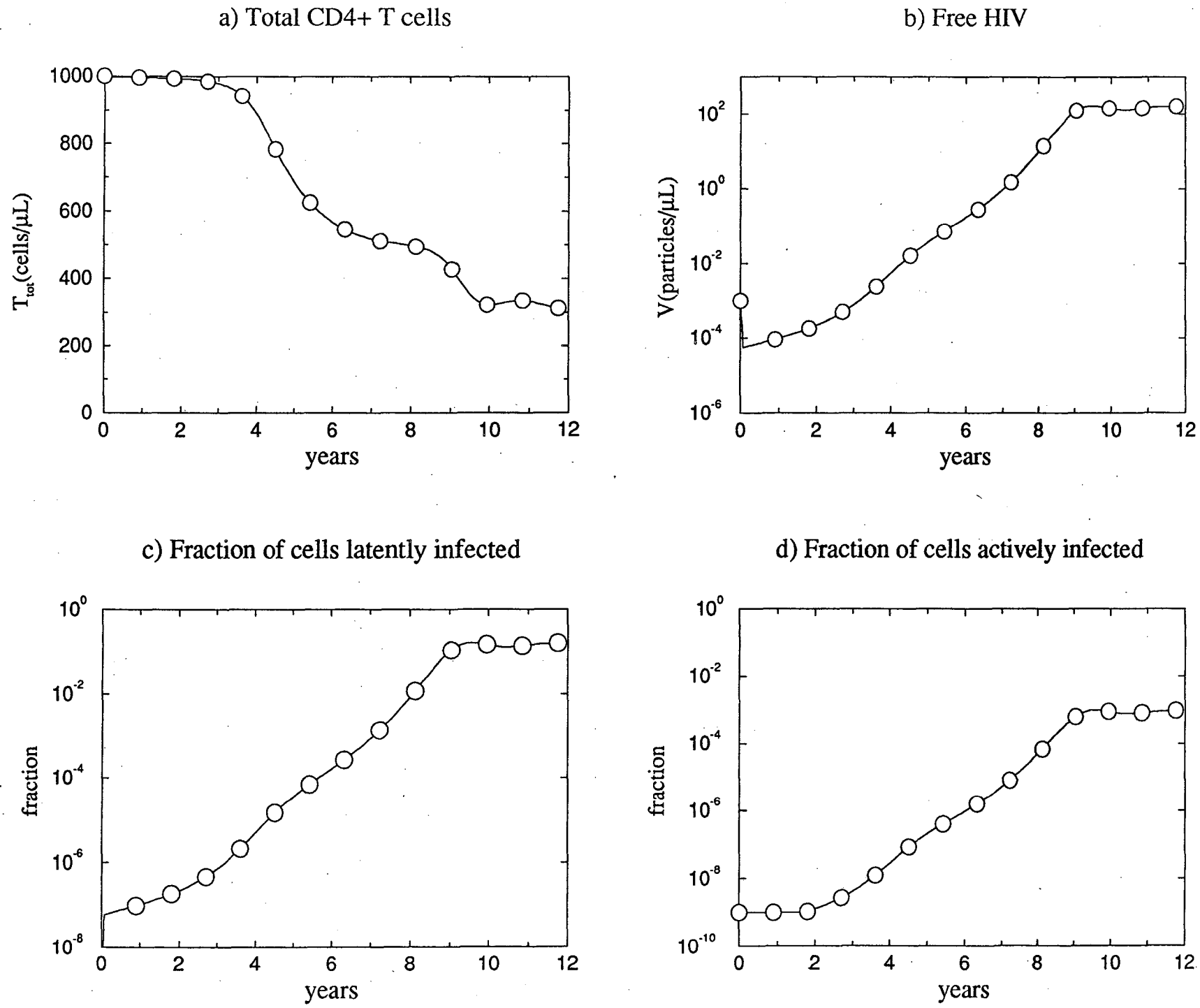
a) Total CD4+ T cells
b) Free HIV
c) Fraction of cells latently infected
d) Fraction of cells actively infected
T_{tot}(cells/μL)
V(particles/μL)
fraction
fraction
years
years
years
years

Figure 1

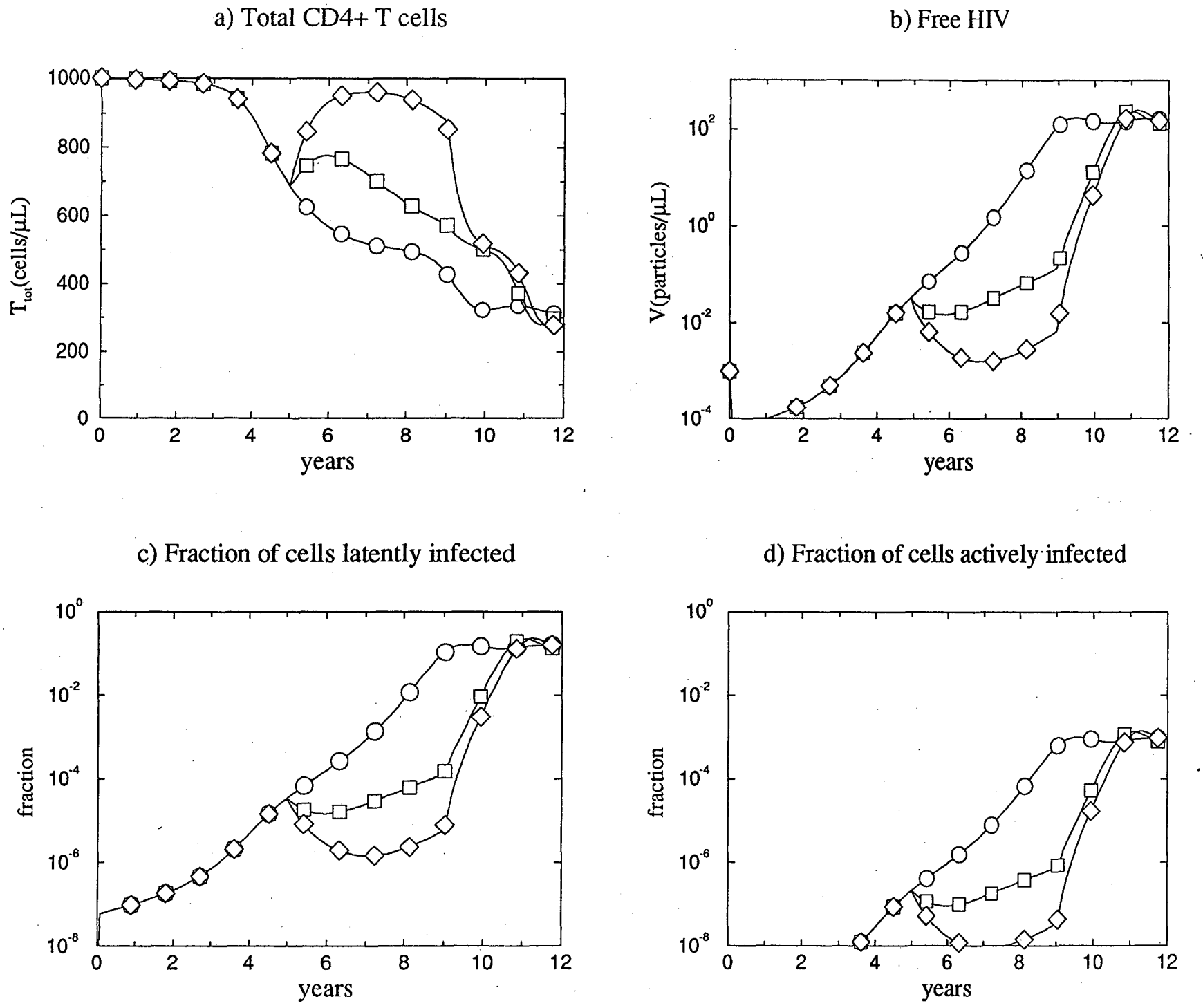
a) Total CD4+ T cells
T_{tot}(cells/μL)
1000
800
600
400
200
0
0
2
4
6
8
10
12
years
b) Free HIV
V(particles/μL)
10^{2}
10^{0}
10^{-2}
10^{-4}
0
2
4
6
8
10
12
years
c) Fraction of cells latently infected
fraction
10^{0}
10^{-2}
10^{-4}
10^{-6}
10^{-8}
0
2
4
6
8
10
12
years
d) Fraction of cells actively infected
fraction
10^{0}
10^{-2}
10^{-4}
10^{-6}
10^{-8}
0
2
4
6
8
10
12
years

Figure 2

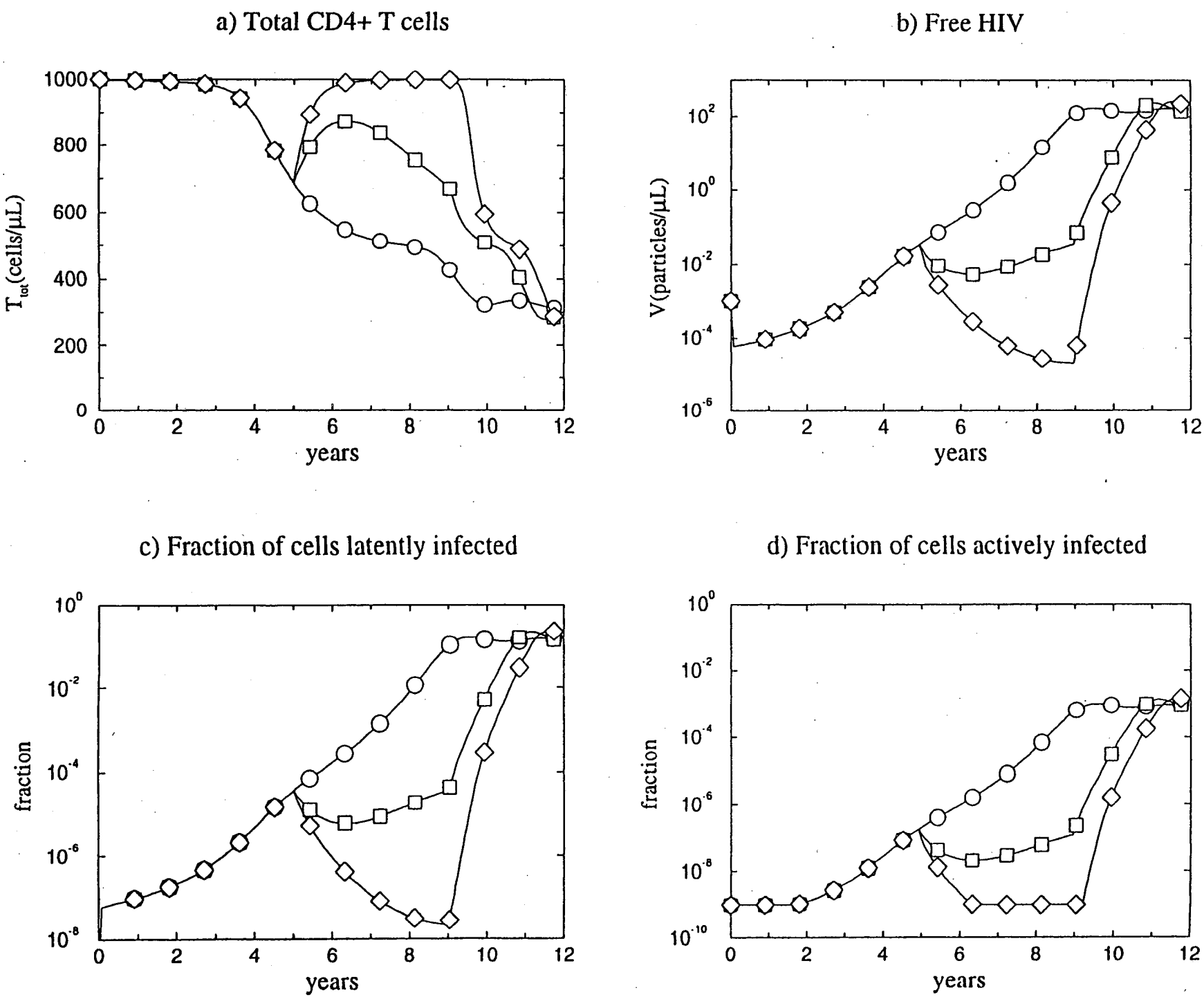
a) Total CD4+ T cells
T_{tot}(cells/μL)
1000
800
600
400
200
0
0
2
4
6
8
10
12
years
b) Free HIV
V(particles/μL)
10^{2}
10^{0}
10^{-2}
10^{-4}
10^{-6}
0
2
4
6
8
10
12
years
c) Fraction of cells latently infected
fraction
10^{0}
10^{-2}
10^{-4}
10^{-6}
10^{-8}
0
2
4
6
8
10
12
years
d) Fraction of cells actively infected
fraction
10^{0}
10^{-2}
10^{-4}
10^{-6}
10^{-8}
10^{-10}
0
2
4
6
8
10
12
years

Figure 3

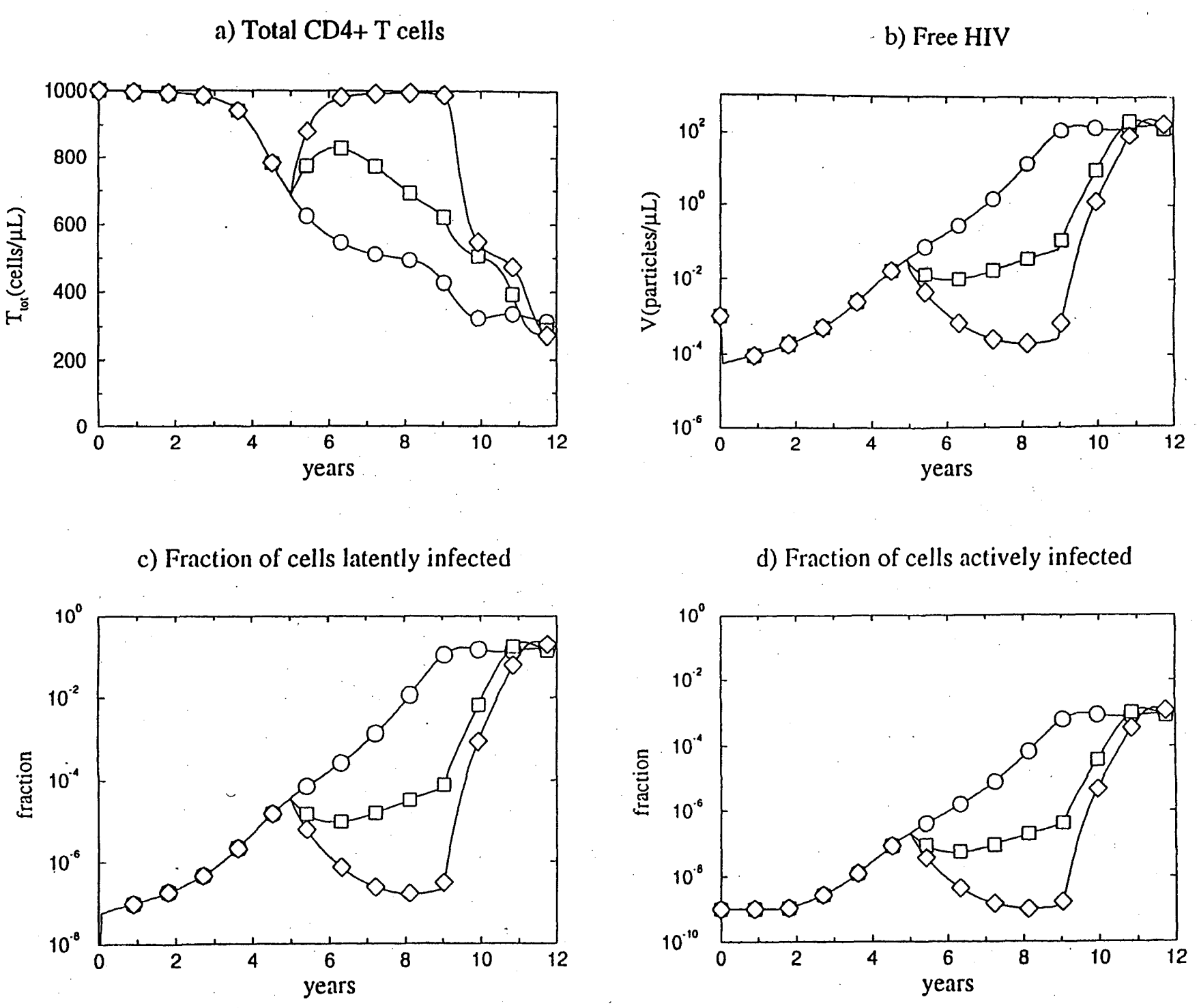
a) Total CD4+ T cells
T_{tot}(cells/μL)
1000
800
600
400
200
0
0
2
4
6
8
10
12
years
b) Free HIV
V(particles/μL)
10^{2}
10^{0}
10^{-2}
10^{-4}
10^{-6}
0
2
4
6
8
10
12
years
c) Fraction of cells latently infected
fraction
10^{0}
10^{-2}
10^{-4}
10^{-6}
10^{-8}
0
2
4
6
8
10
12
years
d) Fraction of cells actively infected
fraction
10^{0}
10^{-2}
10^{-4}
10^{-6}
10^{-8}
10^{-10}
0
2
4
6
8
10
12
years

Figure 4

Table 1. Dependent Variables.

Dependent Variables		Initial or Default Values
T	Uninfected $CD4^+$ cell population size	1000 mm^{-3}
T^*	Latently infected $CD4^+$ helper cell population	0
T^{**}	Actively infected $CD4^+$ helper cell population	0
V	HIV population size	10^{-3} mm^{-3}

Table 2. Parameters and Constants.

Parameters and constants		Initial or Default Values
s	Rate of supply of $CD4^+$ cells from precursors	10 $day^{-1} \cdot mm^{-3}$
r	Rate of growth of $CD4^+$ cells	0.03 day^{-1}
T_{max}	Maximum CD4 cell population level	1500 mm^{-3}
μ_T	Death rate of uninfected and latently infected CD4 cells	0.02 day^{-1}
μ_b	Death rate of actively infected CD4 cells	0.24 day^{-1}
μ_v	Death rate of free virus	0.35 day^{-1}
k_1	Rate constant for CD4 cells becoming infected by free virus	$2.4 \times 10^{-5} \cdot day^{-1} \cdot mm^3$
k_2	Rate latently infected cells convert to actively infected cells	$1.44 \times 10^{-3} \cdot day^{-1}$
N	Number of infectious virions produced by a CD4 cell	varies
Q	Viral concentration needed to decrease s to s/2	1 mm^{-3}

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