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THE ROLE OF LONG INCUBATION PERIODS IN THE DYNAMICS OF ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS). SINGLE POPULATION MODELS

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Abstract

In this study, we investigate systematically the role played by the reproductive number (the number of secondary infections generated by an infectious individual in a population of susceptibles) on single group population models of the spread of HIV/AIDS. Our results for a single group model strongly suggest that if R<1, the disease will die out; and if R>1 the disease will persist regardless of initial conditions. Our extensive (but incomplete) mathematical analysis and numerical simulations support the conclusion that the reproductive number R is a global bifurcation parameter. The bifurcation that takes place as R is varied is a transcritical bifurcation; in other words, when R crosses 1 there is a global transfer of stability from the infection-free state to the endemic equilibrium, and viceversa. These results do note depend on the distribution of times spent in the infectious categories (the survivorship functions). Furthermore, by keeping all the key statistics fixed, we can compare two extremes: exponential survivorship versus piecewise constant survivorship (individuals remain infectious for a fixed length of time). By choosing some realistic parameters we can see (at least in these cases) that the reproductive numbers corresponding to these two extreme cases do not differ by more than 18% whenever the two distributions have the same mean. At any rate a formula is provided that allow us to estimate the role played by the survivorship function (and hence the incubation period) in the global dynamics of HIV. The authors have obtained similar estimates for multiple group models.

These results strongly support the conclusion that single population models of this type are very robust and hence are good candidates as building blocks for the construction of multiple group models. Our understanding of the dynamics of HIV in the context of mathematical models for multiple groups is critical to our understanding of the dynamics of HIV in the presence of a highly heterogeneous population.

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Introduction:

AIDS, perhaps the most feared disease of this decade, has been estimated to at least 30% of those infected. By the middle of 1988 over 68,000 cases of people wit AIDS (with over 38,000 deaths) have been reported in the United States alone; the numbers in Africa and elsewhere tell an even more frightening story. However, despit these statistics, we do not have enough information to predict the eventual magnitude of this epidemic. Nevertheless, there has been increasing recognition that the dynamics will depend fundamentally on transmission within and among core subgroups, and that complex epidemiological models that account for this heterogeneous mixing are essential if one is to predict the time-course of the disease. In this paper, we examine prototypes of such models, extending those discussed by Anderson et al. (1988), Anderson and May (1987), and Pickering et al. (1986), and obtain threshold conditions for the maintenance of the disease.

Since the isolation and identification of this virus by Barre-Sinoussi et al. (1983 and Gallo et al. (1984), Gallo (1986,1987), and Wong-Staal and Gallo (1985), there has been rapid progress in understanding the structure of the Human Immunodeficiency Virus (HIV), the etiological agent of AIDS, and of the way it

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compromises the human immune system. Nonetheless, the epidemiology of the disease is still not well understood. A model geared towards determining the dynamics of AIDS must take into account, among other factors, recruitment of new susceptibles, high disease-related mortality, heterogeneous mixing (certain transfers among individuals are more likely than others), vertical transmission, a high number of asymptomatic carriers, variable infectivity for a single carrier during the course of the infection, and long time scales due to the incubation and infectious periods. This situation makes it difficult to formulate reliable models. In fact, since many important epidemiological parameters are not yet accurately known, prediction becomes an extremely problematical and dangerous enterprise.

The purpose of this paper is to formulate basic models for homogeneous populations, with the purpose of identifying the role played by the long period of incubation; other papers will do the same for heterogeneous populations (see Castillo-Chavez et al. 1988a, 1988b). The models can be used also as starting points for guided computer simulation of the dynamics of HIV, and our analytical results may provide useful comparisons in these future studies. The calculations are confined to appendices.

A detailed summary of the factors thought to be involved in the transmission of HIV can be found in the preliminary study of Anderson et al. (1988) or in the recent work of Hyman and Stanley (1988), and in the extensive references cited in those papers. We will consider primarily sexual transmission of AIDS, and will emphasize the role of three epidemiological parameters: the lengths of the latent period, the infectious period, and the incubation period. The latent period is the time from the acquisition of infection to the time when the host becomes infectious. The infectious period is the time during which the infected individual is capable of transmitting the disease. The incubation period is the time interval between the point of acquisition of infection and the appearance of symptoms. As Anderson et al. (1988), and Anderson

and May (1987) show, knowledge of these periods is critical to predicting the dynamics of the disease.

AIDS appears to have a short latent period, long incubation and infectious periods, and a variable transmission rate. The duration of the latent period is thought to be a few days to a few weeks (Anderson et al. 1988, Anderson and May 1988), and while the duration of the infectious period is not yet known, those individuals that develop full-blown AIDS have an average incubation period estimated variously at 35-47 months (Pickering et al. 1986), 66 months (Anderson et al. 1987), and as high as 96 months (Meddley et al. 1987). This estimate is continually being revised as information and experience accumulates. However, even the most conservative estimate suggests that it may be reasonable to approximate the infectious period by the incubation period; that is, to assume a negligible latent period. Pickering et al. (1986) stress that the ability to transmit HIV is not constant, as individuals are most infectious 3-16 months following exposure, and recent studies (Francis et al. 1984, Suluhuddin et al. 1984, Lange et al. 1986) report the existence of two peaks of infectiousness, one taking place a few weeks after exposure and the other before the onset of "full-blown" AIDS. The models in this study have been modified to take variable infectivity into consideration, with the intention of looking at how variable infectivity affects the conclusions in this paper (see Castillo-Chavez et al. 1988c).

A parameter of critical importance in the dynamics of a disease is its reproductive number; that is, the number of secondary infections generated by an infectious individual in a population of susceptibles. For our single population model, the reproductive number is given by

$$R = \lambda C(T) D,$$

where λ denotes the probability of transmission per partner, C(T) denotes the mean number of sexual partners an average individual has per unit time given that the population density is T, and D denotes the death-adjusted mean infectious period. For multiple group populations the reproductive number is given by an expression of the form

$$R_0 = \sum_{i=1}^{n} w_i R_i ,$$

where R_i denotes the reproductive number of group i and w_i is an appropriate weight factor (see Castillo-Chavez et al. 1988a, 1988b).

In this study, we investigate systematically the role played by the reproductive number on single group populations; in Castillo-Chavez et al. (1988a,1998b) we study its role for multiple group populations. Our results for a single group model strongly suggest that if R <1, the disease will die out; and if R >1 the disease will persist regardless of initial conditions. Our extensive (but incomplete) mathematical analysis and numerical simulations support the conclusion that the reproductive number R is a global bifurcation parameter. The bifurcation that takes place as R is varied is a transcritical bifurcation; in other words, when R crosses 1 there is a global transfer of stability from the infection-free state to the endemic equilibrium, and viceversa. These results do not depend on the distribution of times spent in the infectious categories (the survivorship functions). Furthermore, by keeping all the key statistics fixed, we can compare two extremes: exponential survivorship versus piecewise constant survivorship (individuals remain infectious for a fixed length of time). By choosing some realistic parameters we can see (at least in these cases) that the reproductive numbers corresponding to these two extreme cases do not differ by more than 18% whenever the two distributions have the same mean. At any rate a formula is provided that allow us to estimate the role played by the survivorhip function (and hence the incubation period) in the global dynamics of HIV. Similar estimates can also be obtained for our multiple group models (see Castillo-Chavez et al. 1988b).

These results strongly support the conclusion that single population models of this type are very robust and hence are good candidates (our "idealized" pendulums) for the construction of multiple group models. Our understanding of the dynamics of HIV in the context of mathematical models for multiple groups is critical to our understanding of the dynamics of HIV in the presence of a highly heterogeneous population (see Castillo-Chavez et al. 1988a, 1988b).

We must be aware, however, that the incorporation of a large number of groups may reduce predictive capability because of problems of parameter estimation and error propagation. We suggest the use of models with as few groups as possible as a compromise, with three groups the minimum needed to study realistically the dynamics of HIV in heterogeneous populations (see Castillo-Chavez, et al. 1988a, 1988b).

This paper is organized as follows: Section 1 introduces an epidemiological model that considers a single homogeneously-mixed population with constant rates of movement out of the infectious classes into the AIDS class or into the sexually-inactive category. This is a coarse first approximation useful as a starting point and as a reference model for comparison. This model is a variant and a generalization of those found in Anderson et al. (1988) and Anderson and May (1987). Section 1 assumes that the duration of infectiousness obeys a negative exponential distribution. In Section 2 we generalize this by assuming that the duration of infectiousness obeys an arbitrary distribution. We establish a threshold criterion for maintenance of the disease and analyze the stability properties of the endemic and infection-free states, and determine, when possible, the necessary and sufficient conditions for persistence of HIV. In Section 3, we compare briefly the consequences of assuming different distribution functions. Appendices A, B, C, and D collect some of the mathematical details.

Section 1. Constant removal rates

Our approach is to begin with the simplest model, and then add refinements as necessary in order to explore the effects of particular factors. Hence we start with a simple epidemic model that will allow us to compare easily the effects of long incubation periods. We consider a single homosexual population and concentrate on studying the dynamics of AIDS within this population. We divide this population into five classes. S denotes the number of susceptible individuals; I those infectious individuals that will go on to develop AIDS; Y those infectious individuals that will not develop full-blown AIDS; Z those former Y individuals that are no longer sexually active; and A those former I individuals that have developed full-blown AIDS (see Fig. 1). A and Z are cumulative classes; once individuals enter these classes, they no longer enter into the dynamics of the disease. However, in order to be able to compute the number of AIDS cases, we keep the A and Z individuals on record. We do not include a latent class (i.e., those exposed individuals that are not yet infectious), because the time spent in that class is so short. Furthermore, we assume that once an individual develops full-blown AIDS, he is not infectious because he has no sexual contacts. We also assume that all infected individuals become immediately infectious, and that they become sexually inactive or acquire AIDS with constant probabilities α_Y and α_I (respectively) per unit time; hence $1/\alpha_I$ denotes the average incubation period and $1/\alpha_Y$ denotes the average sexual-life expectancy.

Let Λ denote the recruitment rate into the susceptible class (defined to be those individuals who are sexually active); μ, the natural mortality rate; d, the disease-induced mortality due to AIDS; p, that fraction of the susceptibles that become infectious and will go into the AIDS class; and therefore $(1 - p)$ the fraction of susceptible individuals that do not. Following Anderson et al. (1988), May and

Anderson (1987), and using Figure 1, we arrive at the following simple epidemiological model with exponential removal:

$$(1.1)\quad \frac{dS(t)}{dt} = \Lambda - \lambda C(T(t))\frac{S(t)W(t)}{T(t)} - \mu S(t)\ ,$$

$$(1.2)\quad \frac{dI(t)}{dt} = \lambda p C(T(t))\frac{S(t)W(t)}{T(t)} - (\alpha_I + \mu)\, I(t)\ ,$$

$$(1.3)\quad \frac{dY(t)}{dt} = \lambda(1 - p)C(T(t))\frac{S(t)W(t)}{T(t)} - (\alpha_Y + \mu)\, Y(t)\ ,$$

$$(1.4)\quad \frac{dA(t)}{dt} = \alpha_I\, I(t) - (d + \mu)\, A(t)\ ,$$

$$(1.5)\quad \frac{dZ(t)}{dt} = \alpha_Y Y(t) - \mu\, Z(t)\ ,$$

where

$$(1.6)\quad W = I + Y \text{ and } T = W + S.$$

Here, the function C(T) denotes the mean number of sexual partners an average individual has per unit time, given that the population density is T, and λ (a constant) denotes the transmission probability per partner. We may think of λ as a product $\lambda = i\phi$ (see Hyman and Stanley 1988) where ϕ is the average number of contacts per sexual partner and i is the probability of infection from a sexual contact when the latter is infected. The parameter i is thus a biological one, whereas ϕ is a psychological or sociological one. Kingsley et al. (1987) have presented evidence that the probability of seroconversion (infection) increases with the number of infected sexual partners. With these observations, we then note that $\lambda C(T)$ gives the probability of transmission per unit time and $\lambda C(T)dt$ the probability that a given sexual partner will transfer the disease to a particular susceptible individual in the time dt.

The factor W/T is the probability that the contact of a susceptible with a randomly-selected individual will be with an infectious individual. Since individuals in classes A

and Z are not sexually active, $\lambda C(T)SW/T$ denotes the number of newly-infected individuals per unit time. C(T) is usually assumed to be of the form $c\,T^{\delta}$, $0 \le \delta \le 1$, where c is a constant ($C(T) = c$ if the actual number of sexual partners per individual is independent of population size). For AIDS, it may well be that $C(T) = c$ is more appropriate for large populations, and $C(T) = c\,T^{\delta}$, $0 < \delta \le 1$ for small ones. Hence, a case can be made for either form, or for hybrids. We use a general functional form for C(T) in order to determine how this assumption affects the conclusions. However, it is important to notice, as Anderson and May (1987) have shown, that in a homogeneous (one-group) model, C(T) should not be the mean number of sexual partners per unit time, but rather should be larger because of the important role played by highly active individuals who are more likely to acquire infection and are also more likely to transmit it. We note that some of our results partially overlap with and generalize those obtained simultaneously and independently by Blythe and Anderson (1988). Three cases of the system (1.1)-(1.6) are to be considered:

Case 1: $p = 1$. This, unfortunately, may be the most realistic as evidence accumulates that AIDS is a progressive disease. It now seems highly probable that most of the infected individuals will eventually develop "full-blown" AIDS (unless they die first from other causes). In this case, the Y and Z classes do not exist, and we may work only with equations (1.1), (1.2), (1.4) and with $W = I$, $T = W + S$.

Case 2: $0 < p < 1$, $\alpha_I = \alpha_Y$. In this case, we may interpret I as the class of infected individuals who develop "full-blown" AIDS and Y as the class of individuals who develop ARCS (AIDS-related complex). We assume that individuals with either AIDS or ARCS are no longer sexually active, so that $T = W + S$ is the total number of sexually-active individuals.

Case 3: $0 < p < 1$, $\alpha_I \neq \alpha_Y$. We may now interpret I as the class of individuals who spend a mean time $1/\alpha_I$ infected and then develop AIDS. The class Y consists of individuals who remain infective for a long time $1/\alpha_Y$ and then withdraw from the sexually active group into a group that does not develop AIDS symptoms. In this situation presumably $\alpha_I > \alpha_Y$. An alternative interpretation of the Z class is obtained i assuming that an individual moves into this group after testing seropositive, and then refrains from sexual intercourse. In this case we may have $\alpha_I < \alpha_Y$. Thus, it is appropriate again to take $T = W + S$ to be the number of sexually-active individuals.

The rest of this section, as well as some of the appendices, will describe mathematical results pertaining to these three cases. We now begin our analysis of th system (1.1)-(1.6) by making the following assumptions concerning C(T):

(H_1) $\quad C(T) > 0, \quad C'(T) \ge 0,$

$C'(T) > 0$, unless $C(T)$ is constant,

$(T/C)' \ge 0, \quad (T/C)'' \le 0,$

where the prime denotes the derivative with respect to T. An important class of functions that will satisfy these assumptions is $C(T) = c\,T^{\delta}$, where $0 \le \delta \le 1$ and c is a constant. Observe that the dynamics of S, Y, and I are governed independently of A and Z; therefore, it will suffice to analyze (1.1), (1.2), (1.3) with (1.6). It is not too difficult to show that the system is well-posed, in the sense that if $S(0) \ge 0$, $I(0) \ge 0$, $Y(0) \ge 0$ ther the solution exists and $S(t) \ge 0$, $I(t) \ge 0$, $Y(0) \ge 0$ for $t \ge 0$ (see Castillo-Chavez et al. 1988a).

The system (1.1)-(1.3) always has the equilibrium

$$(1.7) \qquad (S, I, Y) = \left(\frac{\Delta}{\mu}, 0, 0\right),$$

and also, under certain assumptions (discussed later) has a unique endemic equilibrium.

The stability of the disease-free equilibrium (1.7) is determined by the parameter

(1.8) $$R = \lambda\left(\frac{p}{\sigma_I} + \frac{1-p}{\sigma_Y}\right) C\left(\frac{\Lambda}{\mu}\right),$$

the basic reproductive number. Here $\sigma_I = \alpha_I + \mu$, $\sigma_Y = \alpha_Y + \mu$, and R denotes the number of secondary infections generated by a single infectious individual in a population of susceptibles. Note that R is given by the product of three key epidemiological parameters: λ (the probability of transmission per partner), $C(\Lambda/\mu)$ (the mean number of sexual partners an average susceptible individual has per unit time given that everybody is susceptible), and $D = \left(\frac{p}{\sigma_I} + \frac{1-p}{\sigma_Y}\right)$ (the overall death-adjusted mean infectious period). Further, $D = pD_I + (1-p)D_Y$, where D_I and D_Y denote the death-adjusted mean infectious periods, $1/\sigma_I$ and $1/\sigma_Y$, corresponding to the I and Y classes. This key parameter, $R = \lambda C(\Lambda/\mu)\, D$, allows us to establish our first result:

Theorem 1. If $R < 1$, then the equilibrium $\left(\frac{\Lambda}{\mu}, 0, 0\right)$ of the system(1.1)-(1.5) is globally asymptotically stable.

This theorem asserts that any solution of (1.1)-(1.3) (S(t), I(t), Y(t)) with $S(0) \geq 0$, $I(0) \geq 0$, $Y(0) \geq 0$ tends to $(\Lambda/\mu, 0, 0)$ as $t \to +\infty$. Thus the *condition $R < 1$ is sufficient to guarantee that the disease will eventually die out of the population.*

We have shown also that:

Theorem 2. If $R > 1$, there is a unique endemic equilibrium (S^*, I^*, Y^*), which is locally asymptotically stable, and the infection-free state $\left(\frac{\Lambda}{\mu}, 0, 0\right)$ is unstable.

In Appendix A, we collect the proofs of these results. In Appendix B, we show that when $\alpha_I = \alpha_Y$ or $p = 1$, and $R > 1$, the endemic equilibrium is actually globally stable. Furthermore, preliminary simulations suggest that even in the case $0 < p < 1$, the endemic state is globally asymptotically stable provided that $R > 1$. In mathematical terms, we have a transcritical bifurcation.

Combining the results of this section and Appendices A and B, we can describe the situation as follows:

The infection-free state of system (1.1)-(1.3) is globally asymptotically stable when $R < 1$ and unstable if $R > 1$. When $R > 1$, this system has a unique locally asymptotically stable endemic equilibrium. In others words, there is a transfer of stability to the endemic state as R crosses unity. Furthermore, when $\sigma_I = \sigma_Y$, that is when both death-adjusted mean infectious periods agree, and $R > 1$, then the endemic equilibrium is globally asymptotically stable.

The reproductive number R provides us with important information; we note that R increases proportionately to the transmission probability and to the average number of sexual partners, and may increase in proportion to the rate of recruitment of individuals to the susceptible class (through C(T)). Furthermore, R is an increasing

function of the mean infectious period D, and may be a decreasing function of the mortality rate (depending on the functional expression for C(T)).

Section 2. Distributed delay model

Exponential survival in the I and Y classes corresponds to the requirement that the removal rate from the I class (by the development of full-blown AIDS symptoms) into the A class is independent of the length of time that an individual has been infected. Although the distribution of times between infection and the onset of clinical AIDS is only partially known, it appears from available data that the rate of conversion from the I to the A class, or the Y to the Z class, has a more general distribution (see Anderson et al. 1987; Blythe and Anderson 1988). Therefore, in order to improve the model of Section 1 (a first approximation), we need to change from constant to variable removal rates.

This section introduces a single population model that incorporates variable periods of infectiousness. By assuming that individuals become immediately infectious (that is, by neglecting the latent period), we can concentrate on studying the effects of arbitrarily distributed infectious periods and arbitrarily distributed periods of sexual activity (for infectious I class and the life-long infectious Y class respectively) in the dynamics of HIV. We establish a threshold criterion for the maintenance of the disease and analyze to some extent the stability properties of the endemic and infection-free states. In Section 3, we compare briefly the consequences of assuming different distribution functions. Investigations of this type, but for specific distributions, have been carried out numerically, independently and simultaneously by Blythe and Anderson (1988).

Following our earlier approach, we divide our population into the previously defined classes: S, I, Y, Z, and A. The parameters $\lambda = i\phi$, Λ, μ, d, and p have the same meaning as Section 1. The model of Section 1 is now modified by introducing two functions, $P_I(s)$ and $P_Y(s)$ (see Fig. 2), which represent the proportion of those individuals that become I- or Y-infective at time t and that, if alive, are still infectious at time $t + s$; that is, they survive as infectious. Since P_I and P_Y are survivorship functions they are nonnegative and nonincreasing, and $P_I(0) = P_Y(0) = 1$. We assume further that

$$\int_0^\infty P_I(s)\,ds < \infty, \qquad \int_0^\infty P_Y(s)\,ds < \infty,$$

and thus, $-P'_I(x)$ and $-P'_Y(x)$ are the rates of removal of individuals from classes I and Y into classes A and Z, x time units after infection.

Defining C(T), W, and T as in Section 1, we have that the number of new infections occurring at time x is $\lambda\, C(T(x))\, S(x)\, W(x)/T(x)$, and therefore the rate of change of the susceptible class is given by the expression:

$$(2.1) \qquad \frac{dS(t)}{dt} = \Lambda - \lambda C(T(t))\, S(t)\, \frac{W(t)}{T(t)} - \mu\, S(t)\ ,$$

with

$$p \int_0^t \lambda\, C(T(x))\, S(x)\, \frac{W(x)}{T(x)}\, e^{-\mu(t-x)}\, P_I(t-x)\, dx$$

representing the number of individuals who have been infected from times 0 to t and are still in class I (with a similar expression for class Y). The factor $\exp(-\mu(t-x))$ takes account of removals due to deaths by natural causes (that is, in this case, not HIV). If $I_0(t)$ and $Y_0(t)$ denote those individuals that were in either class I or Y at time $t = 0$, and are still infectious, then the total number of I- and Y-infectives at time t are given by

$$(2.2) \qquad I(t) = I_0(t) + p \int_0^t \lambda C(T(x))\, S(x)\, \frac{W(x)}{T(x)}\, e^{-\mu(t-x)}\, P_I(t-x)\, dx\ ,$$

$$(2.3)\qquad Y(t) = Y_0(t) + (1-p)\int_0^t \lambda C(T(x))\, S(x)\, \frac{W(x)}{T(x)}\, e^{-\mu(t-x)} P_Y(t-x)\, dx\ ,$$

where $I_0(t)$ and $Y_0(t)$ are assumed to have compact support (that is, they vanish for large enough t).

The expression for A(t) is the sum of three terms. The first is $A_0 e^{-(\mu+d)t}$, where $A_0 = A(0)$, and represents those who had full-blown AIDS at time zero and are still alive. The second is the term $A_0(t)$, representing those initially in class I who have moved into class A and are still alive at time t. We assume that $A_0(t)$ approaches zero as t approaches infinity. Finally, the term representing those I infected after time t=0 is given by

$$\int_0^t \{ \int_0^\tau \lambda C(T(x))\, S(x)\, \frac{W(x)}{T(x)}\, e^{-\mu(\tau-x)} [-P_I'(\tau-x)\, e^{-(\mu+d)(t-\tau)}]\, dx \}\, d\tau,$$

where $-P_I'(\tau - x)$, denotes the rate of removal from the class I at time τ or $(\tau - x)$ units after infection and, therefore,

$$(2.4)\quad A(t) = p\int_0^t \{ \int_0^\tau \lambda C(T(x))\, S(x)\, \frac{W(x)}{T(x)}\, e^{-\mu(\tau-x)} [-P_I'(\tau-x)\, e^{-(\mu+d)(t-\tau)}]\, dx \}\, d\tau + A_0 e^{-(\mu+d)t} + A_0(t).$$

The corresponding expression for the Z-class is given by

$$(2.5)\quad Z(t) = (1-p)\int_0^t \{ \int_0^\tau \lambda C(T(x))\, S(x)\, \frac{W(x)}{T(x)}\, e^{-\mu(\tau-x)} [-P_Y'(\tau-x)\, e^{-\mu(t-\tau)}]\, dx \}\, d\tau + Z_0 e^{-(\mu+d)t} + Z_0(t).$$

System (2.1)-(2.5) is a system of nonlinear integral equations, and hence the standard results on well-posedness for these systems as found in Miller (1971) guarantee the existence and uniqueness of solutions as well as their continuous dependence on parameters. The proof of positivity is the same as that given in Castillo-Chavez (1988a) and therefore is omitted.

Observe that the dynamics of the classes S, Y, and I are governed autonomously, and hence we can restrict our analysis to the system (2.1)-(2.3). The basic reproductive number in this case is given by

$$(2.6)\qquad R = \lambda C(\frac{\Delta}{\mu}) \int_0^\infty [p P_I(x) + (1-p) P_Y(x)]\, e^{-\mu x}\, dx\ ,$$

where

$$\int_0^\infty [p P_I(x) + (1-p) P_Y(x)]\, e^{-\mu x}\, dx$$

denotes the death-adjusted mean infectious period D. In fact, if $P_I(x) = e^{-\alpha_I x}$, $P_Y(x) = e^{-\alpha_Y x}$, then (2.6) reduces to (1.8). Note that $D = p D_I + (1-p) D_Y$, where $D_I = \int_0^\infty P_I(s)\, e^{-\mu s} ds$ and $D_Y = \int_0^\infty P_Y(s)\, e^{-\mu s} ds$ denotes the mean infectious period of classes I and Y respectively.

The system (2.1)-(2.3) with $I_0(t) = Y_0(t) = 0$ alwys has the equilibrium

$$(2.7)\qquad (S, I, Y) = (\frac{\Delta}{\mu}, 0, 0)\ ,$$

but otherwise does not have a constant solution. Since $I_0(t)$ and $Y_0(t)$ are zero for large t, it could be expected that $(\Lambda/\mu, 0, 0)$ is an attractor or "asymptotic equilibrium" as $t \to +\infty$, under appropriate conditions. The following theorems show that the reproductive number R determines whether (2.7) is an attractor or not.

Theorem 3. If $R < 1$, then the infection-free state $(\frac{\Lambda}{\mu}, 0, 0)$ of the limiting system (2.1)-(2.3) is a global attractor; that is, $\lim_{t \to +\infty} (S(t), I(t), Y(t)) = (\frac{\Lambda}{\mu}, 0, 0)$ for any positive solution of system (2.1)-(2.3).

Theorem 4. If $R > 1$, then the infection-free state of thesystem (2.1)-(2.3) is weakly unstable, that is there exists a constant $W^0 > 0$, such that any positive solution (S(t), I(t), Y(t)), of (2.1)-(2.3) satisfies $\limsup_{t \to +\infty} [I(t) + Y(t)] \geq W^*$.

In other words, if $R > 1$, then the disease-free state (2.7) cannot be an attractor for any positive solution. In fact, every solution has approximately W^* infectives (this W^* is the same as that in the statement of Theorem 5 below), or more, for a sequence of times t tending to $+\infty$. It is then natural to ask wether S(t), I(t), Y(t), approach nonzero constants as $t \to +\infty$, when $R > 1$. If so, then it is known (see Miller (1971)) that these constants must satisfy the limiting system associated with (2.1)-(2.3), which is given by the following set of equations:

$$\frac{dS}{dt} = \Lambda - \lambda C(T(t))\, S(t) \frac{W(t)}{T(t)} - \mu S(t) , \tag{2.8}$$

$$I(t) = p \int_{-\infty}^{t} \lambda C(T(x))\, S(x) \frac{W(x)}{T(x)} e^{-\mu (t-x)} P_I(t-x)\, dx , \tag{2.9}$$

$$Y(t) = (1-p) \int_{-\infty}^{t} \lambda C(T(x))\, S(x) \frac{W(x)}{T(x)} e^{-\mu (t-x)} P_Y(t-x)\, dx , \tag{2.10}$$

If the equations for I and Y are added, we have

$$W(t) = \int_{-\infty}^{t} \lambda C(T(x))\, S(x) \frac{W(x)}{T(x)} e^{-\mu (t-x)} P(t-x)\, dx , \tag{2.11}$$

where

$$P(x) = p P_I(x) + (1-p) P_Y(x) .$$

The limiting system (2.8)-(2.11) is an autonomous system for which we have established the following result:

Theorem 5. If $R > 1$, then the limiting system (2.8)-(2.11) has a unique positive equilibrium (S^*, W^*) that is locally asymptotically stable (which we may call the endemic equilibrium).

Theorem 5 indicates that there is a switch of stability from $(\Lambda/\mu, 0)$ to (S^*, W^*) as R crosses one. We would also expect that the asymptotic dynamics of system (2.1)-(2.3) and the limiting system (2.8)-(2.11) agree. While this is not a proven fact, we believe that is a reasonable conjecture. An alternate, but perhaps not entirely satisfactory approach can be found in Hethcote et al. (1981). The proofs of these results can be found in Appendices C and D.

Section 3. Discussion

In this paper we have constructed a series of models with the purpose of determining the role of long incubation periods of the HIV virus in a single population.

The lack of enough information to determine the parameters needed for these models makes prediction impossible. However, much useful information can be obtained from these results. First of all, the long incubation periods do not result in periodic outbreaks. The disease either dies out or it remains endemic. The computations of the reproductive numbers allow us to understand the role of the different parameters in the maintenance or eradication of HIV. Behavior modification naturally plays a very important role, and the reproductive numbers help us to quantify the effects of behavior modification. Furthermore, the effects of different distributions for the incubation period can be estimated. Here, for example, we compare two extremes. First we assume that $P_I(x) = e^{-\alpha_I x}$, and $P_Y(x) = e^{-\alpha_Y x}$. The reproductive number, given by

$$R = \lambda C(\tfrac{\Delta}{\mu}) \int_0^\infty [p P_I(x) + (1-p) P_Y(x)] e^{-\mu x} dx,$$

now reduces to

$$R_1 = \lambda C(\tfrac{\Delta}{\mu}) \{p \frac{1}{\mu + \alpha_I} + (1-p) \frac{1}{\mu + \alpha_Y}\}.$$

If we take the other extreme and assume that $P_I(x) = H(x) - H(x - \omega)$, $P_Y(x) = H(x) - H(x - \tau)$, where $H(x)$ denotes the Heaviside function (the fact that $P_I(x)$ and $P_Y(x)$ are not continuously differentiable is just a technical nuisance), then

$$R_2 = \lambda C(\tfrac{\Delta}{\mu}) \{p \frac{1 - e^{-\mu\omega}}{\mu} + (1-p) \frac{1 - e^{-\mu\tau}}{\mu}\}.$$

Hence, we have that

$$\frac{R_1}{R_2} = \frac{p(\frac{1}{\mu + \alpha_I}) + (1-p)(\frac{1}{\mu + \alpha_Y})}{p(\frac{1 - e^{-\mu\omega}}{\mu}) + (1-p)(\frac{1 - e^{-\mu\tau}}{\mu})} = f(p).$$

Therefore if we take $p = .5$, $\omega = 10$ years ($= 1/\alpha_I$), $\tau = 30$ years ($= 1/\alpha_Y$), $(1/\mu) = 30$ years, then $R_1/R_2 \cong .82$. If, for example, $\omega = 6$ years, $\tau = 30$ years ($= 1/\alpha_Y$), $(1/\mu) = 30$ years, then

$$\frac{R_1}{R_2} = \frac{\frac{p}{6} + \frac{1-p}{2}}{p(1 - e^{-2}) + (1-p)(1 - e^{-1})}.$$

Hence f(1/3), the ratio of the reproductive numbers is approximately 0.81. A value of $p = 2/3$ gives a ratio of about 0.84, a value of $p = 8/9$ gives a ratio of about 0.88, and a value of $p = 1$ gives a ratio of about 0.92. In general, note that

$$f(p) = \frac{pD_{1,I} + (1-p) D_{1,Y}}{pD_{2,I} + (1-p) D_{2,Y}},$$

where the indices differentiate between the death-adjusted mean infectious periods for model 1 (exponential removal) and model 2 (fixed period of infectiousness). We further observe that f(p) is an increasing function of p provided that

$$\frac{\mu + \frac{1}{\tau}}{\mu + \frac{1}{\omega}} > \frac{1 - e^{-\mu\omega}}{1 - e^{-\mu\tau}},$$

which holds whenever $\tau > \omega$. Hence whenever $\tau > \omega$, f(p) satisfies

$$f(0) = \frac{D_{1,Y}}{D_{2,Y}} = \frac{\frac{1}{\mu + \alpha_Y}}{\frac{1 - e^{-\mu\tau}}{\mu}} \le f(p) \le f(1) = \frac{D_{1,I}}{D_{2,I}} = \frac{\frac{1}{\mu + \alpha_I}}{\frac{1 - e^{-\mu\omega}}{\mu}}, \quad 0 \le p \le 1.$$

Thus, even though the assumption of simple exponential removal underestimates the reproductive number, the above expression gives us a way to estimate the relative error relatively as the above two distributions represent the two

extremes. Hence, under the assumptions of the model, the "true" value of R lies somewhere in between. In addition, for a value p near unity (unfortunately not out of the realm of possibility), the qualitative dynamics predicted by these models is not very different. Furthermore, since the qualitative dynamics are governed largely by their reproductive numbers, and their values are not very different (at least for the realistic parameters chosen in the above examples), the effect of changing key parameters (once these are determined with higher accuracy) can be assessed readily. Note, however, that the transient dynamics could be quite different; this is partially due to the dimensionality of the system (finite vs infinite). If the infinite-dimensional model (that is the distributed delay model) is more realistic, then it will be extremely difficult to predict the transient dynamics; that is, short-term predictions become more difficult.

Finally, we note that in the models introduced here we have not only assumed homogeneous mixing (but see Castillo-Chavez et al. 1988a, 1988b), but also that an individual once infected is always equally infectious. Since there is some evidence that HIV carriers are not equally infectious (see Francis et al. 1984, Suluhuddin et al. 1984, Lange et al. 1986), then the relaxing of this assumption becomes of importance in order to estimate the effect of variable infectiousness in the reproductive number and therefore in the dynamics of HIV. Preliminary analysis suggests that variable infectiousnes does not have a significant effect on the qualitative dynamics of the distributed delay model, but this analysis is not yet complete (see Castillo-Chavez et al. 1988c).

Appendix A

Stability Results for the system (1.1)-(1.5)

In this appendix we collect the proofs of Theorems 1 and 2 of Section 1. We w repeat some statements to increase the clarity of the exposition.

Theorem 1. If $R < 1$, then the equilibrium $(\frac{\Delta}{\mu}, 0, 0)$ of the system(1.1)-(1.5) globally asymptotically stable.

Proof of theorem 1.

Let $Q = [0, \infty)^3$ be the nonnegative orthant in R^3. As we remarked above, if (S_0, I_0, Y_0) is in Q then $(S(t), I(t), Y(t))$ is in Q for $t \geq 0$ and any p, $0 \leq p \leq 1$. From (1.1), it follows that $\limsup_{t \to +\infty} S(t) \leq \frac{\Delta}{\mu}$. Hence for the discussion of the asymptotic behavior of solutions as $t \to +\infty$ we can (without loss of generality) assume that $S(t) \leq \Lambda/\mu$ when ≥ 0. Furthermore, since $C(T)/T$ is a nonincreasing function of T, and $C(T)$ is nondecreasing, then

$$\frac{C(T(t))\,S(t)}{T(t)} \leq \frac{C(S(t))\,S(t)}{S(t)} \leq C(\tfrac{\Delta}{\mu}).$$

If we now let $f(t) = \frac{I(t)}{\sigma_I} + \frac{Y(t)}{\sigma_Y}$, then

$$\begin{aligned}
\frac{df(t)}{dt} &= [\,(\frac{p}{\sigma_I} + \frac{1-p}{\sigma_Y})\,\lambda\,\frac{C(T(t))\,S(t)}{T(t)} - 1\,]\,W(t) \\
&\leq [\,(\frac{p}{\sigma_I} + \frac{1-p}{\sigma_Y})\,\lambda\,C(\tfrac{\Delta}{\mu}) - 1]\,W(t) \\
&\leq -(1-R)\,W(t) \leq -(1-R)\,\sigma\,f(t),
\end{aligned}$$

where $\sigma = \min\{\sigma_I, \sigma_Y\}$. Therefore $I(t) \to 0$ as $t \to +\infty$, hence $I(t) \to 0$, $Y(t) \to 0$, and $C(T)SW/T \to 0$ as $t \to +\infty$. From (1.1) it follows that $S(t) \to \Lambda/\mu$ as $t \to +\infty$, completing the proof.

When $R > 1$, the disease free equilibrium is unstable (Theorem 1); and furthermore, there exists a unique positive *endemic* equilibrium (S^*, I^*, Y^*). To establish this last result we begin with the following preliminary result:

Lemma A1. Suppose that β_1, β_2 and H are positive numbers, and that $C(\Lambda/\mu) > H$. Then there is a unique number $I^* > 0$ such that

$$C\left(\frac{\Delta}{\mu} - \beta_1 I^* + \beta_2 I^*\right)\left(\frac{\Delta}{\mu} - \beta_1 I^*\right) = H\left(\frac{\Delta}{\mu} - \beta_1 I^* + \beta_2 I^*\right), \quad \frac{\Delta}{\mu} - \beta_1 I^* > 0.$$

Proof. Let $M(T) = C(T)/T$ whenever $T > 0$, and let $g(I) = M(\Lambda/\mu - \beta_1 I + \beta_2 I)(\Lambda/\mu - \beta_1 I)$, with $0 \le I \le \Lambda/(\mu\beta_1)$. Observe that $g(0) = C(\Lambda/\mu) > H$ and $g(\Lambda/(\mu\beta_1)) = 0$. Since

$$\text{(A2)} \qquad \frac{dg}{dI} = \beta_2 \frac{\Delta}{\mu} M'(u) - \beta_1 [M(u) + u M'(u)], \quad u = \frac{\Delta}{\mu} - \beta_1 I + \beta_2 I.$$

Note that for $T > 0$, we have that

$$\text{(A3)} \qquad M(T) > 0, \; M'(T) \le 0, \; (TM(T))' > 0.$$

Therefore (A2) implies that $g(I)$ is a strictly decreasing function of I on the interval $[0, \Lambda/(\mu\beta_1)]$, and hence there is a unique I^* in the open interval $(0, \Lambda/(\mu\beta_1))$ such that $g(I^*) = H$ with $\Lambda/\mu - \beta_1 I^* > 0$.

Corollary A4. If $R > 1$, then there is a unique positive *endemic* equilibrium (S^*, I^*, Y^*).

Proof. In order to prove the existence of such equilibrium, we let $\beta_1 = \frac{1}{p\mu D_I}$, $\beta_2 = \frac{D}{pD_I}$, and $H = \frac{1}{\lambda D}$. Using the fact that $\beta_1 > 0$, $\beta_2 > 0$, and that $R = \lambda C(\Lambda/\mu) D$, we have that $C(\Lambda/\mu) = R/(D\lambda) > H$; hence by Lemma1, there is a unique I^* in $(0, \Lambda/(\mu\beta_1))$ such that

$$\text{(A5)} \qquad M(\Lambda/\mu - \beta_1 I^* + \beta_2 I^*)(\Lambda/\mu - \beta_1 I^*) = H \text{ and } \Lambda/\mu - \beta_1 I^* > 0.$$

Now let

$$\text{(A6)} \qquad S^* = \frac{\Delta}{\mu} - \frac{1}{\mu p D_I} I^*, \quad Y^* = \left(\frac{D}{pD_I} - 1\right) I^*, \quad W^* = I^* + Y^* = \frac{D}{pD_I} I^*.$$

Since $I^* < \Lambda/\mu\beta_1 = \Lambda p D_I$, then $S^* > 0$, and since $D/(pD_I) > 1$, then $Y^* > 0$. Therefore using (A6) we find that $T^* = S^* + W^* = \frac{\Delta}{\mu} - \beta_1 I^* + \beta_2 I^*$, which in combination with (A5) implies that $M(T^*) S^* = H$. Finally, it can be easily checked that (S^*, I^*, Y^*) is a positive equilibrium of (1.1)-(1.3).

To show uniqueness we proceed by letting $(S^\wedge, I^\wedge, Y^\wedge)$ denote a positive equilibrium. From (1.2), (1.3), we get $[(1 - p)/D_I] I^\wedge = [p/D_Y] Y^\wedge$, and $\lambda D M(T^\wedge) S^\wedge W^\wedge = I^\wedge + Y^\wedge = W^\wedge$.

Using

$$\text{(A7)} \qquad M(T^\wedge) S^\wedge = H = \frac{1}{\lambda D}, \quad Y^\wedge = \left(\frac{D}{pD_I} - 1\right) I^\wedge, \quad W^\wedge = \frac{D}{pD_I} I^\wedge,$$

where $W^\wedge = I^\wedge + Y^\wedge$, $T^\wedge = S^\wedge + W^\wedge$, and (1.1), it follows that

$$S^\wedge = \frac{\Delta}{\mu} - \frac{1}{p\mu D_I} I^\wedge, \; T^\wedge = S^\wedge + \frac{D}{pD_I} I^\wedge, \text{ and } M(T^\wedge) S^\wedge = H = \frac{1}{\lambda D}.$$

Hence, by Lemma 1, we have that $I^\wedge = I^*$, and therefore $Y^\wedge = Y^*$ and $S^\wedge = S^*$.

The nature of the stability of the endemic equilibrium is resolved in the following theorem:

Theorem 2. *If $R > 1$, then there is a unique endemic equilibrium (S^*, I^*, Y^*) which is locally asymptotically stable, and the equilibrium $(\frac{\Delta}{\mu}, 0, 0)$ is unstable.*

Proof of Theorem 2. The Jacobian matrix of the functions on the right side of (1.1)-(1.3) is

$$J = \frac{\partial(f_1,f_2,f_3)}{\partial(S,I,Y)} =$$

$$\begin{bmatrix} -\lambda W(M + SM') - \mu & -\lambda S(M + WM') & -\lambda S(M + WM') \\ p\lambda W(M + SM') & p\lambda S(M + WM') - \sigma_I & p\lambda S(M + WM') \\ (1-p)\lambda W(M + SM') & (1-p)\lambda S(M + WM') & (1-p)\lambda S(M + WM') - \sigma_Y \end{bmatrix}$$

where M' denotes $dM(T)/dT$. By evaluating this Jacobian at the disease-free equilibrium, that is, when $W = 0$, $S = \Lambda/\mu$, and therefore $SM = (\Lambda/\mu)\, M(\Lambda/\mu)) = C(\Lambda/\mu)$, we arrive at the corresponding characteristic equation:

$\det [zI - J] = (z + \mu)(z^2 + az + b) = 0$, where

$$a = \sigma_I + \sigma_Y + \lambda C(\tfrac{\Delta}{\mu}), \quad b = \sigma_I \sigma_Y [1 - \lambda C(\tfrac{\Delta}{\mu})(\frac{p}{\sigma_I} + \frac{1-p}{\sigma_Y})] = \sigma_I \sigma_Y (1 - R).$$

Since $b < 0$ whenever $R > 1$, the disease-free equilibrium is unstable. For the endem equilibrium (S^*, I^*, Y^*), the characteristic equation is the cubic $\det (zI - J) = z^3 + a_1 z^2 + a_2 z + a_3$. By letting $W^* = I^* + Y^*$, $T^* = S^* + W^*$, $M^* = M(T^*)$, and $M'^* = (dM/dT)(T^*)$, we obtain the following expressions for a_1, a_2, a_3, in which we have supressed the asterisks in order to simplify the typography.

$$a_1 = \sigma_I + \sigma_Y - \frac{1}{D} + \mu + \lambda WM = [p\frac{\sigma_Y}{\sigma_I} + (1-p)\frac{\sigma_I}{\sigma_Y}]\frac{1}{D} + \mu + \lambda WM$$

$$> [p\frac{\sigma_Y}{\sigma_I} + (1-p)\frac{\sigma_I}{\sigma_Y}]\frac{1}{D} + \mu > 0,$$

$$a_2 = \mu(\sigma_I + \sigma_Y) + (\sigma_I + \sigma_Y)\lambda(WM + SWM') + \sigma_I\sigma_Y$$

$$- [\mu + \sigma_I(1-p) + \sigma_Y p]\lambda(SM + SWM')$$

$$= \lambda(\sigma_I + \sigma_Y)(WM + SWM') + \mu(\sigma_I + \sigma_Y - \lambda SM) - \mu\lambda SWM'$$

$$- [\sigma_I(1-p) + \sigma_Y p]\lambda SWM',$$

where we have used the fact that

$$\sigma_I\sigma_Y - [\sigma_I(1-p) + \sigma_Y p]\lambda SM = 0.$$

Since $M' \le 0$ and $\sigma_1 + \sigma_2 - \lambda SM > 0$, we have that

$$a_2 > \lambda(\sigma_I + \sigma_Y)(WM + SWM') - [\sigma_I(1-p) + p\sigma_Y]\lambda SWM',$$

and that

$$a_3 = \lambda\sigma_I\sigma_Y(WM + SWM') + \mu[\sigma_I\sigma_Y - ((1-p)\sigma_I + p\sigma_Y)\lambda SM]$$

$$- \mu[(1-p)\sigma_I + p\sigma_Y]\lambda SWM' =$$

$$= \sigma_I\sigma_Y\lambda(WM + SWM') - \mu\lambda[\sigma_I(1-p) + p\sigma_Y]SWM' > 0.$$

Using these relations and

$$[p\frac{\sigma_Y}{\sigma_I} + (1-p)\frac{\sigma_I}{\sigma_Y}]\frac{1}{D}(\sigma_I+\sigma_Y) > \sigma_I\sigma_Y ,$$

one can show that $a_1 a_2 > a_3$. Therefore, the Routh-Hurwitz stability conditions are satisfied. This completes the proof of Theorem 2.

Appendix B

Global Stability for System (1.1)-(1.3)

Case : p = 1 or $\alpha_I = \alpha_Y$

When p =1 or $\alpha_I = \alpha_Y$ then the system (1.1)-(1.3) reduces to

$$(B1) \qquad \frac{dS}{dt} = \Lambda - \lambda C(T)\, S\frac{W}{T} - \mu S ,$$

$$(B2) \qquad \frac{dW}{dt} = \lambda C(T)\, S\frac{W}{T} - \sigma W , \text{ where } W = I + Y , \sigma = \alpha + \mu .$$

If $S(0) \geq S_0 \geq 0$, $W(0) \geq W_0 \geq 0$, then as we have seen $S(t) \geq 0$, $W(t) \geq 0$ for $t > 0$.

Moreover, $dS/dt \leq \Lambda - \mu S$ implies that that $\limsup_{t\to+\infty} S(t) \leq \frac{\Delta}{\mu}$. Hence we restrict our discussion to solutions that satisfy $0 < S(t) \leq \Lambda/\mu$.

We use the notation $M(T) = C(T)/T$, the fact that $S, W \leq T$, and the assumptions $M'(T) \leq 0$ and $(TM(T))' > 0$, to conclude that: $SM'(T) + M(T) \geq (TM(T))' > 0$, and $SM(S+W) \leq \frac{\Lambda M(\frac{\Delta}{\mu})}{\mu}$. Hence, $\frac{dW}{dt} \leq \sigma W(R-1)$. The same inequality holds when $C(T)$ is constant. Thus, if $R < 1$, we have $W(t) \to 0$ as $t \to +\infty$. Also, $S(t) = e^{-\mu t}(S_0 + \int_0^t e^{\mu x}[\Lambda - \lambda M(S+W)SW]\,dx)$. Since $SM(T)$ is bounded and W tends to zero, it follows that $S(t) \to \Lambda/\mu$ as $t \to +\infty$.

Next, suppose that $R > 1$. Then the system has a positive equilibrium (S^*, W^*). With $T = S + W$, the system (B1)-(B2) is equivalent to

(B3) $\frac{dT}{dt} = \Lambda - \mu T - \alpha W$,

(B4) $\frac{dW}{dt} = \lambda W [(T - W) M(T) - \frac{\alpha}{\lambda})$,

This system has the positive equilibrium (T^*,W^*) where $T^* = S^* + W^*$.

Using the equations satisfied by T^* and W^*, we may rewrite (B3)-(B4) in the form

(B5) $\frac{dT}{dt} = -\mu (T - T^*) - \alpha (W - W^*)$,

(B6) $\frac{dW}{dt} = \lambda W\{ (TM(T) - T^*M(T^*)) + W^*(M(T^*) - M(T))\} - \lambda WM(T)(W - W^*) =$

$= \lambda WG(T) - \lambda WM(T)(W - W^*)$,

where $G(T) = TM(T) - T^*M(T^*) + W^*(M(T^*) - M(T))$.

Since $TM(T) = C(T)$ is increasing, and $M(T)$ is nonincreasing by assumption (H_1), then $G(T)$ is positive when $T > T^*$ and negative when $T < T^*$. We now let

$$V(T,W) = \frac{\lambda}{\alpha}\int_{T^*}^{T} G(x)\,dx + W - W^* - W^* \ln\frac{W}{W^*}.$$

Then $V(T^*,W^*) = 0$, $V(T,W) > 0$ for other admissible T,W. Furthermore, the derivative of V along solutions of (B3)-(B4) (indicated by a bar over V) is given by

$\bar{V}(T,W) = -\frac{\lambda\mu}{\alpha} G(T)(T - T^*) - \lambda M(T)(W - W^*)^2$, which is < 0 whenever

$(T,W) \neq (T^*,W^*)$. Therefore, we get the following result:

Theorem B. If $R > 1$, then the equilibrium (T^*,W^*) for (B5)-(B6), and consequently the equilibrium (S^*,W^*) for (B1)-(B2), are globally asymptotically stable.

Appendix C

Stability and Instability for System (2.1)-(2.3)

In order to establish these results, we proceed to rewrite the system (2.1)-(2 introducing the following expressions:

(C1) $B(t) = \lambda C(T(t)) S(t) \frac{W(t)}{T(t)}$, $Q_J = P_J(s) e^{-\mu s}$, $J = I$ or Y.

Adding (2.2) and (2.3), and using (C1), we can rewrite the system (2.1)-(2.3) in the following way:

(C2) $\frac{dS}{dt} = \Lambda - B(t) - \mu S$,

(C3) $W(t) = W_0(t) + \int_0^t B(t - s)[p\,Q_I(s) + (1 - p)\,Q_Y(s)]\,ds$,

(C4) $W_0(t) = I_0(t) + Y_0(t)$, $W(t) = I(t) + Y(t)$.

Proof of theorem 3.

Because we are interested in the long-term behavior of system (C2)-(C4), we can make use of the fact that $W_0(t)$ has compact support and replace (C3) by

(C5) $W(t) = \int_0^t B(t - s)[p\,Q_I(s) + (1 - p)\,Q_Y(s)]\,ds$, for $t > t_0$ (large enough).

Just as in the proof of Theorem 1, we can assume that $S(t) \leq \Lambda/\mu$, and then show tha $B(t) \leq \lambda C(\Lambda/\mu)W(t)$, and therefore for $t > t_0$, we have that

$$W(t) \leq \lambda C(\frac{\Lambda}{\mu})\int_{0_-}^{t} W(t - s)[p\,Q_I(s) + (1 - p)\,Q_Y(s)]\,ds$$

$$= \lambda C(\frac{\Lambda}{\mu})\int_0^t W(t - s)[p\,Q_I(s) + (1 - p)\,Q_Y(s)]\,H(t - s)\,ds,$$

where H(s) denotes the Heaviside function (H(s) = 1 if s > 0, and zero otherwise). Hence, if $W = \limsup_{t \to +\infty} W(t)$, it follows that $W \le R\,W$, and therefore $W = 0$ whenever $R < 1$. This implies finally that $W(t) \to 0^+$ as $t \to +\infty$.

For the case R > 1, consider the limiting system of (C2)-(C3):

$$\text{(C6)} \qquad \frac{dS}{dt} = \Lambda - B(t) - \mu S ,$$

$$\text{(C7)} \qquad W(t) = \int_{-\infty}^{t} B(s)\, e^{\mu s} P(t-s)\, e^{-\mu t}\, ds ,$$

where,

$$P(t) = p\, Q_I(t) + (1-p)\, Q_Y(t) .$$

Lemma D8. If R > 1, then (C6)-(C7) has a unique endemic equilibrium (S^*, W^*)

The proof of this corollary is essentially the same as the proof of Corollary A4.

Proof. Let

$$\text{(C9)} \qquad S^* = \frac{\Delta}{\mu} - \frac{1}{\mu p D_I} I^* , \quad Y^* = \left(\frac{D}{pD_I} - 1\right) I^* , \quad W^* = I^* + Y^* = \frac{D}{pD_I} I^* ,$$

where D, D_I, and D_Y, have been previously defined in Section 2. Then the proof is the same as that of Appendix A.

We now proceed with the proof of Theorem 4. Since R > 1, then Lemma C* implies that there is a unique pair of positive numbers S^*, W^* with $S^* + W^* = T^* < \Lambda/\mu$, and satisfying the system

$$\text{(C10)} \qquad \Lambda - \lambda M(T) S W - \mu S = 0,$$

$$\text{(C11)} \qquad \lambda M(T) S D = 1,$$

where D denotes the overall death adjusted mean infectious period and M(T) = C(T)/T. We will show that $\limsup_{t \to +\infty} S(t) \ge W^*$.

Proof of Theorem 4. Assume that the conclusion of the theorem does not hold. Then there exist a $t^0 > 0$ and a $W' > 0$ ($W' < W^*$) such that $W(t) \le W'$ whenever $t \ge t^0$. Using the fact that T = S + W, we note that

$$\text{(C11)} \qquad \frac{\partial(M(S+W)S)}{\partial S} = \frac{d(M(T)T)}{dT} - \frac{dM(T)}{dT} W > 0,$$

$$\frac{\partial(M(S+W)W)}{\partial W} = \frac{d(M(T)T)}{dT} - \frac{dM(T)}{dT} S > 0 ,$$

whenever S > 0, and W > 0. Hence, if we define the function

$$L(S) = \Lambda - \lambda M(S + W^0)\, S\, W^0 - \mu S, \text{ for } S \ge 0, \text{ and } W' < W^0 < W^* ,$$

then since dL/dS is negative, it follows that L(S) is a strictly decreasing function of S. In addition since L(0) > 0, and $L(\Lambda/\mu) < 0$, then there exits an $S^0 > 0$ such that $L(S^0) = 0$.

Using (C11) we conclude that if $t \ge t^0$ and $S(t) \le S^0$, then

$$\frac{dS(u)}{dt} = \Lambda - \lambda S(u)W(u)M(u) - \mu S(u)$$

$$> \Lambda - \lambda M(T^0)\, S^0 W^0 - \mu\, S^0 = L(S^0) = 0,$$

where $T^0 = S^0 + W^0$. Hence, $\liminf_{t \to +\infty} S(t) \geq S^0 > 0$, and consequently, there is a $t^* > t^0$ such that $S(t) \geq S^0$, $t \geq t^*$. In addition, since

$$\mu (S^0 - S^*) = \lambda M(T^*) W^* S^* - \lambda M(T^0)\, S^0 W^0$$

$$> \lambda \{M(T^*) S^* W^* - M(S^0 + W^*) S^0 W^*\},\ T^* = S^* + W^*,$$

we must have that $S^0 > S^*$. Therefore, for all $t \geq t^*$, we have that $M(T(t))S(t) > M(S^0 + W(t))S^0 \geq M(T^*)S^*$, and hence there is a $\sigma > 0$ such that $M(T^0)S^0 = \sigma + M(T^*)S^*$.

Let $W^\wedge = \liminf_{t \to +\infty} W(t)$, and assume that $W^\wedge = 0$. Then there is a sequence $\{t_n\}$ such that $t_n \to +\infty$ as $n \to +\infty$, and $W(t) \geq W(t_n)$, $t_n/2 \leq t \leq t_n$. Hence, for large enough t_n, we have that

$$W(t_n) = \lambda \int_{\frac{t_n}{2}}^{t_n} M(T(s))S(s)W(s)\, e^{-\mu(t_n - s)}\, p(t_n - s)\, ds$$

$$= \lambda (M(T^*)S^* + \sigma) W(t_n) \int_0^{\frac{t_n}{2}} e^{-\mu s} p(s)\, ds,$$

where $p(s) = pP_1(s) + (1 - p)\, P_Y(s)$.

This implies that

$$1 \geq \lambda (M(T^*)S^* + \sigma) \int_0^{\frac{t_n}{2}} e^{-\mu s}\, p(s)\, ds,$$

and therefore, by letting $n \to +\infty$ we arrive at the contradictory statement that $R < 1$.

If $W^\wedge > 0$, then for any $\varepsilon > 0$, there exists a positive integer N such that

$$W(t) \geq (1 - \varepsilon)\, W(t_n) \text{ for all } \frac{t_n}{2} \leq t \leq t_n,\ n \geq N.$$

Using the same argument as above, we can then show that

$$W(t_n) \geq \lambda (M(T^*)S^* + \sigma)\, (1 - \varepsilon) W(t_n) \int_0^{\frac{t_n}{2}} e^{-\mu s}\, p(s)\, ds.$$ This implies that

$$1 \geq \lambda (M(T^*)S^* + \sigma)(1 - \varepsilon) \int_0^{\infty} e^{-\mu s} p(s)\, ds,$$ since ε is arbitrary this again implies that $R \leq 1$.

Appendix D

Asymptotic Stability of the Endemic Equilibrium

In Appendix C, it was proved in Lemma C8 that if $R > 1$, the limiting system has a unique positive equilibrium (S^*, W^*). We will now complete the proof of Theorem 5 by showing that this equilibrium is asymptotically stable for the system (2.8)-(2.9), or equivalently (C6)-(C7).

The proof of this result reduces to the study of the local stability of the trivial equilibrium ($X = 0$) for a Volterra integral equation of the type

$$(*) \qquad X(t) = F(t) + \int_0^t A(t-s)\, G(x(s))\, ds ,$$

where $X \in R^n$, $G(0) = 0$, $G \in C^1 (R^n \to R^n)$, $F \in C([0,\infty) \to R^n)$, A is an nxn matrix such that $A(t) \in L^1[0,t]$ for each $t > 0$. R^n denotes real n-space with a norm $|X|$ and $|A|$ denotes the corresponding matrix norm.

Theorem (Miller 1968; Theorem 4). Assume that the following conditions hold: (i) the Jacobian matrix $DG(0)$ is nonsingular,

(ii) $\det \left(I - \int_0^\infty e^{-z\tau} A(\tau)\, D\, G(0)\, d\tau \right) \neq 0$, for all z with $\mathrm{Re}\, z \geq 0$ where I denotes the nXn identity matrix), and (iii) there is a sufficiently small $\epsilon_0 > 0$ such that $\sup \{ |F(t)| : 0 \leq t < \infty \} \leq \epsilon_0$ and $F(t) \to 0$ as $t \to \infty$. Then $X(t) \to 0$ as $t \to \infty$

Proof of Theorem 5. First we rewrite (C6) as

$$(D1) \qquad S(t) = \frac{\Delta}{\mu} + \left[S(0) - \frac{\Delta}{\mu}\right] e^{-\mu t} - \int_0^t B(\tau)\, e^{-\mu (t-\tau)}\, d\tau ,$$

and as

$$(D2) \qquad B(\tau)\, e^{\mu \tau} = \Lambda\, e^{\mu \tau} - \frac{d(S(\tau)\, e^{\mu \tau})}{d\tau} .$$

Using these two expressions, we can write $W(t)$ as follows:

$$(D3) \qquad \begin{aligned} W(t) = {} & S(0)\, e^{-\mu t} P(t) - \frac{\Delta}{\mu} - \left[S(0) - \frac{\Delta}{\mu}\right] e^{-\mu t} \\ & + \int_0^t B(\tau)\, e^{-\mu (t-\tau)} p(t-\tau)\, d\tau + \int_{-\infty}^{t} B(\tau)\, e^{-\mu (t-\tau)} d\tau \\ & + \int_0^t \Lambda\, e^{-\mu \tau} P(\tau)\, d\tau - \int_0^t S(\tau)\, e^{-\mu (t-\tau)} \frac{dP(t-\tau)}{d\tau}\, d\tau . \end{aligned}$$

We let $W^\wedge(t) = W(t) - W^*$ and $S^\wedge(t) = S(t) - S^*$ denote perturbations from the endemic equilibrium. By substituting $W^\wedge$ and $S^\wedge$ into (D1) and (D2) (which are satisfied by S^* and W^*), we arrive at the following system for $S^\wedge$ and $W^\wedge$:

$$(D4) \qquad S^\wedge(t) = S^\wedge(0)\, e^{-\mu t} - \int_0^t [B^\wedge(\tau) - B^*]\, e^{-\mu (t-\tau)}\, d\tau ,$$

$$(D5)\qquad W^{\wedge}(t) = S^{\wedge}(0)\,[P(t) - 1]\,e^{-\mu t} + \int_0^t [B^{\wedge}(\tau) - B^{*}]\,e^{-\mu(t-\tau)}\,d\tau - \int_0^t S^{\wedge}(\tau)\,e^{-\mu(t-\tau)}\,\frac{dP(t-\tau)}{d\tau}\,d\tau + \int_{-\infty}^{0} [B^{\wedge}(\tau) - B^{*}]\,e^{-\mu(t-\tau)}\,\rho(t-\tau)\,d\tau,$$

where $B^{*} = \lambda\, M[T^{*}]\, S^{*} W^{*}$, $B^{\wedge} = \lambda\,[S^{\wedge} + S^{*}][W^{\wedge} + W^{*}]M[T^{\wedge} + T^{*}]$, $T^{\wedge} = T - T^{*}$, $T = S + W$, and $T^{*} = S^{*} + W^{*}$. Finally, by letting

$$(D6)\qquad F(t) = \begin{bmatrix} S^{\wedge}(0)\,e^{-\mu t} \\ S^{\wedge}(0)\,[P(t) - 1]\,e^{-\mu t} + \int_{-\infty}^{0} [B^{\wedge}(\tau) - B^{*}]\,e^{-\mu(t-\tau)}\,\rho(t-\tau)\,d\tau \end{bmatrix},$$

$$(D7)\qquad G(S^{\wedge}, W^{\wedge}) = \begin{bmatrix} B^{\wedge} - B^{*} \\ S^{\wedge} \end{bmatrix}$$

$$(D8)\qquad A(\tau) = \begin{bmatrix} -e^{-\mu\tau} & 0 \\ e^{-\mu\tau} & -e^{-\mu\tau}\,\dfrac{dP(\tau)}{d\tau} \end{bmatrix},$$

$$(D9)\qquad X(t) = \begin{bmatrix} S^{\wedge} \\ W^{\wedge} \end{bmatrix}$$

then the system (C13)-(C14) is in the form needed to apply Miller's theorem.

It remains to show that the conditions specified in Miller's theorem are satisf

We start by showing that DG(0) is non-singular. First note that

$$DG(0) = \begin{bmatrix} \lambda W^{*}(M(T^{*}) + S^{*}M'(T^{*})) & \lambda S^{*}(M(T^{*}) + W^{*}M'(T^{*})) \\ 1 & 0 \end{bmatrix},$$

and since $(TM(T))' \geq 0$ and $M'(T) \leq 0$, then $\det\{DG(0)\} \neq 0$.

Next we show that $\det\left(I - \int_0^{\infty} e^{-z\tau} A(\tau)\, D\, G(0)\, d\tau\right) \neq 0$, for all z with Re z ≥

First, we note that $H(z) = \det\left(I - \int_0^{\infty} e^{-z\tau} A(\tau)\, D\, G(0)\, d\tau\right)$

$$= \det \begin{bmatrix} 1 + m_1 \int_0^{\infty} e^{-(\mu+z)\tau}\,d\tau & m_2 \int_0^{\infty} e^{-(\mu+z)\tau}\,d\tau \\ -m_1 \int_0^{\infty} e^{-(\mu+z)\tau}\,d\tau + \int_0^{\infty} e^{-(\mu+z)\tau}\,\dfrac{dP}{d\tau}\,d\tau & 1 - m_2 \int_0^{\infty} e^{-(\mu+z)\tau}\,d\tau \end{bmatrix},$$

where $m_1 = \lambda W^{*}(M(T^{*}) + S^{*}M'(T^{*}))$, $m_2 = \lambda S^{*}(M(T^{*}) + W^{*}M'(T^{*}))$. After expanding and collecting terms, we have that

$$H(z) = 1 + \frac{m_1}{\mu + z} - m_2 \int_0^{\infty} e^{-(\mu+z)\tau} P(\tau)\,d\tau.$$

Observe that (C7) implies that $1 = \lambda S^{\wedge} M(T^{\wedge}) \int_0^{\infty} e^{-\mu\tau} P(\tau)\, d\tau$. Using this equality, we can show that whenever $\mathrm{Re}\, z \geq 0$, $|H(z)| \geq |1 + \frac{m_1}{\mu + z}| - |m_2| \int_0^{\infty} e^{-\mu\tau} P(\tau)\, d\tau > 0$.

Furthermore, clearly for any $\varepsilon_0 > 0$, there is a $\delta_0 > 0$ such that $\sup\{|F(t)| : 0 \leq t < \infty\} \leq \varepsilon_0$ and $F(t) \to 0$ as $t \to \infty$, for any $|S^{\wedge}(\tau)| \leq \delta_0$, $|W^{\wedge}(\tau)| \leq \delta_0$, $-\infty \leq \tau \leq 0$.

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Literature Cited

Anderson, R. M. 1988. The epidemiology of HIV infection: variable incubation plus infectious period and heterogeneity in sexual activity (ms.)

Anderson, R.M. and R. M. May. 1987. Transmission dynamics of HIV infection. *Nature.* 326, March 12: 137-142.

Anderson, R.M., et. al. 1988. A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV), the causative agent of AIDS." *IMA J. Math. Med. Biol.* (in press).

Barre-Sinoussi, F. et al. 1983. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 220, : 868-70.

Blythe, S. P. and R. M. Anderson. Distributed incubation and infectious periods in models of the transmission dynamics of the Human Immunodeficiency Virus (HIV). *IMA J. Math. Med. Biol.*(In press).

Castillo-Chavez, C., Cooke, K., Huang, W. and Levin, S.A. 1988a.The role of infectious periods in the dynamics of acquired immunodeficiency syndrome (AIDS). In: Mathematical Approaches to Ecological and Environmental Problem Solving (C. Castillo-Chavez, S. A. Levin, and C. Shoemaker, eds.). Lecture Notes in Biomathematics, Springer-Verlag (in preparation)

Castillo-Chavez, C., Cooke, K., Huang, W. and Levin, S.A. 1988b. The role of infectious periods in the dynamics of HIV/AIDS. Part 2 : multiple group models (in preparation).

Castillo-Chavez, C., Cooke, K., and H. Thieme. 1988c. The role of long periods of infectiousness and variable infectivity in the dynamics of HIV/AIDS in a homogeneously mixed group (in preparation).

Francis, D.P. et al. 1984. Infection of chimpanzees with lymphadenopathy-associated virus. *Lancet*, December 1: 1276-77.

Gallo, R. C. 1986. The first human retrovirus. *Scientific American*. December: 88-98.

Gallo, R.C. 1987. The AIDS virus. *Scientific American*. January: 47-56.

J. K. Hale. 1977. *Theory of Functional Differential Equations*. Springer Verlag. New York, Heidelberg, and Berlin.

Hethcote, H. W., H. W. Stech, and P. van den Driessche. 1981. Nonlinear oscillations in epidemic models. SIAM J. Appl. Math. 40, 1-9.

Hyman, J. M. and E. A. Stanley. 1988. A risk base model for the spread of the AIDS virus. *Math. Biosci.* (in press).

L. A. Kingsley et al.1987. Risk factors for seroconversion to human immunodeficiency virus among male homosexuals. *The Lancet*. Feb 14: 345-348.

Lange, J. M. A., et. al. 1986. Persistent HIV antigenaemia and decline of HIV core antibodies associated with transition to AIDS." *Br. Med. J.* 293: 1459-62.

Meddley, G. F., R. M. Anderson, D. R. Cox, and L. 1987. Billard. Incubation period of AIDS in patients infected via blood transfussons. *Nature* 328, 719-21.

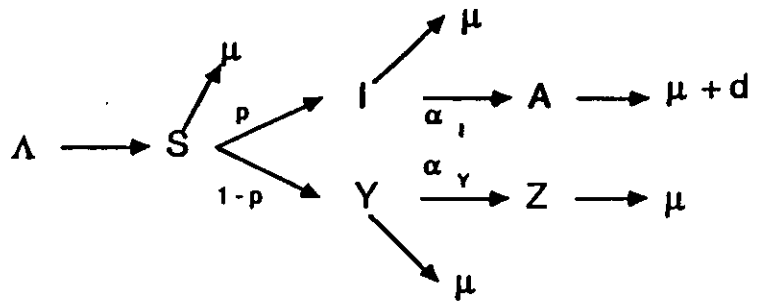
R. K. Miller. 1968. On the linearization of Volterra integral equations. *J. Math. Anal. Appl.* 23: 198-208.

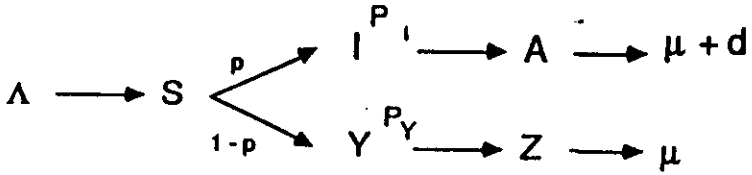
R. K. Miller. 1971. *Nonlinear Volterra Integral Equations*, W. A. Benjamin. Menlo Park, CA.

Pickering J., J. A. Wiley., and Padian, N. S., et al.1986. Modeling the incidence of Acquired Immunodeficiency Syndrome (AIDS) in San Francisco, Los Angeles, and New York. *Math. Modelling* 7 :661-688 (1986)

Suluhuddin, S.Z. et al. 1984. HTLV-III in symptom-free seronegative persons. *Lancet*. December 22-29: 1418-20.

Wong-Staal, F. and R. C. Gallo. 1985. Human T-lymphotropic retroviruses. *Nature*. 317: 395-403.





Legends of Figures

Fig. 1: Flow diagram for a single group model with exponential removal, for details see the text.

Fig. 2: Flow diagram for a single group model with distributed periods of infectiousness, for details see the text.