UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION
INTERNATIONAL CENTRE FOR THEORETICAL PHYSICS
I.C.T.P., P.O. BOX 586, 34100 TRIESTE, ITALY, CABLE: CENTRATOM TRIESTE

SMR.478 - 38

THIRD AUTUMN COURSE ON MATHEMATICAL ECOLOGY

(29 October - 16 November 1990)

"On the possible effects of infection-age-dependent infectivity in the dynamics of HIV/AIDS"

C. CASTILLO-CHAVEZ
Cornell University
Centre for Applied Mathematics
Biometrics Unit
Ithaca, NY 14853-7801
U.S.A.

These are preliminary lecture notes, intended only for distribution to participants.

On the possible effects of infection-age-dependent infectivity in the dynamics of HIV/AIDS

Hörst R. Thieme
Department of Mathematics
Arizona State University
Tempe, AZ 85287

Carlos Castillo-Chavez
Biometrics Unit, Center
for Appl. Math., and Population
and Development Program
Cornell University
Ithaca, NY 14853-7801

Abstract

Epidemiological and behavioral factors crucial to the dynamics of HIV/AIDS include long and variable periods of infecciousness, variable infectivity, and the processes of pair formation and dissolution. Most of the recent mathematical work on AIDS models has concentrated on the effects of long periods of incubation and heterogeneous social mixing in the transmission dynamics of HIV. In this paper we explore the role of variable infectivity in combination with a variable incubation period in disease dynamics in a homogeneously mixing population. We keep track of time since infection, that is, the age of infection of infected individuals, and assume a nonlinear functional relationship between mean sexual activity and the size of the sexually-active population T that saturates at large values of T. We show that if the basic reproductive number $R_0 < 1$, the disease dies out, whereas if $R_0 > 1$ the incidence rate converges to or oscillates around a uniquely determined nonzero equilibrium. We study the stability of this equilibrium and provide the analytical results necessary to explore the region of parameter space in which this equilibrium is locally asymptotically stable. We observe that oscillations cannot be excluded in all cases but may occur if the variable infectivity is concentrated at an early part of the incubation period. Whether oscillations are possible in the presence of two infectivity peaks as observed in HIV infected individuals has yet to be determined.

1. Introduction

Declines in the incidence of a particular disease may be difficult to explain in some cases, for example, one may ask whether the recent decline of AIDS (acquired immunodeficiency syndrome) incidence in homosexuals in the U.S. is due entirely to effective behavioral changes and preventive measures or whether is partially due to the oscillatory behavior inherent in disease dynamics: Our results strongly suggest the possibility of observing oscillations in the incidence rate because of interacting epidemiological and behavioral factors.

Early analyses of similar models (see Castillo-Chavez *et al.*, 1989a, b, c, d) has shown that the long incubation period (time from infection to appearance of symptoms) of AIDS cannot excite oscillations alone (at least not by a *Hopf* bifurcation). The early HIV (human immunodeficiency virus, the etiological agent for AIDS) infectivity experiments of Francis *et. al.* (1984), Salahuddin *et. al.* (1984), and Lange *et. al.* (1986) suggest the existence of two infectivity peaks, one taking place a few weeks after exposure and the other one year or so before the onset of "full-blown" AIDS. Numerical simulations of models that incorporate variable infectivity (see Anderson and May 1989, Blythe and Anderson 1989b; Hyman and Stanley, 1988, 1989) demonstrate that the initial transient dynamics are very sensitive to the timing and the shape of the first peak; however, all show the same qualitative dynamics (even in the presence of heterogeneity in sexual behavior), that is, a steady approach to a unique endemic equilibrium. The model of this paper extends the model of Castillo-Chavez *et al.* (1989b) by incorporating infection-age-dependent-infectivity to study analytically the validity of these results in the presence of variable infectivity.

Various mechanisms have been found to cause undamped oscillations in time-autonomous epidemic models (see Hethcote *et al.*, 1981, and Hethcote and Levin 1989, for surveys). We particularly mention the work by Gripenberg (1980, 1981), Diekmann *et al.* (1982, 1984), and Hethcote and Thieme (1985), because they find periodic solutions for models with infection-age-dependent infectivity. The most commonly found reason for undamped oscillations is the return of infectives into the susceptible class with or without having spent a period of immunity. Anderson *et. al.* (1981) have found undamped oscillations in a fox rabies model, which were caused by the combined effects of the rapid

turnover of the fox population and the relatively long latency period of fox rabies. Liu *et. al.* (1986, 1987) have shown, in their work on influenza, that generalized nonlinear incidence rates can also generate sustained oscillations. Castillo-Chavez *et. al.* (1988, 1989) and Andreasen's (1988, 1989) work on influenza strongly suggests that the interaction between multiple viral-related strains of influenza type A, the host immune system(cross-immunity), and age-dependent host's mortality are needed to generate sustained oscillations.

All these mechanisms obviously do not operate in AIDS dynamics. Further, the models described above (except for the rabies model) assume that the disease is essentially nonfatal and the population size is constant, assumptions that are not realistic in HIV modeling. In our model the occurrence of undamped oscillations will depend mainly on the following epidemiological entities: the length distribution of the sexual activity period of exposed individuals, the distribution of infectivity over that period, and the functional relationship between the per capita number of contacts $C = C(T)$ and the number of sexually-active individuals T. Undamped oscillations can be ruled out if the probability that an infected individual is still sexually active is a convex function of infection age or if the infectivity is sufficiently evenly distributed over the activity period (as is already suggested by the findings of Castillo-Chavez *et al.* (1989)) or if $C(T)/T$ is close to the constant, i.e., there is no saturation in partner acquisition. Undamped oscillations may occur if

(i) the probability that an infected individual is still sexually active is sufficiently far away from being a convex function of infection age.

(ii) there is sufficient saturation in partner acquisition, i.e., the number C(T) of actual partners per capita is rather independent of slight changes in the number of available partners T.

(iii) the period of sexual activity is not too short for infected individuals in relation to uninfected ones.

(iv) the fraction of infected individuals in the sexually-active population is neither too low nor too high.

(v) the infection-age-distributed infectivity is concentrated at an early part of the incubation period.

The conditions (i) and (ii) appear to be realistic for AIDS; condition (v) is rather extreme and

had to be chosen because this paper completely relies on analytical methods, and represents our first step towards the study of the effects of variable infectivity. Sustained oscillations can be ruled out if any of the conditions (i) – (iv) are not satisfied. Future numerical work has to show whether or not undamped oscillations also occur for infection-age-distributions with an early and a late peak.

Apart from this we can show the same phenomena as for the by Castillo-Chavez *et al.* model (1989b), that is, we can identify a basic reproductive numer R_0 in terms of the model parameters such that for $R_0 < 1$, the disease dies out and for $R_0 > 1$, the disease persists in the population. In the latter case there is a unique endemic equilibrium which is locally asymptotically stable for R_0 slightly larger than 1, but which may lose stability if R_0 increases. Even if unstable, the endemic equilibrium may be some indicator of the severity of the disease because (as we show) the incidence rate, for example, oscillates around its equilibrium value.

This paper is organized as follows: Section 2 introduces our model with infection-age-dependent infectivity, Section 3 deals with the existence and stability of stationary states, Secion 4 discusses the epidemiological significance of our stability results, Sections 5 and 6 establish the validity of our claims, and Section 7 discusses the significance of our results and our plans for future work. Most of the results of this paper were stated, without proofs, in Thieme and Castillo-Chavez (1989).

2. Model with infection-age-dependent infectivity

The transmission dynamics of HIV in a homogeneously-mixing male homosexual population is modeled through the incorporation of the following ingredients:

- A nonlinear functional relationship between mean sexual per capita activity and the size of the sexually-active population T. We assume that it increases for small population values while saturating for large values of T.
- A stratification of the infected part of the sexually-active population according to infection age, i.e., time since the moment of infection.

- An infection-age-dependent rate of leaving the sexually-active population due to disease progression.
- An infection-age-dependent infectivity .

The model of this section shares the first three features with the models considered by Castillo-Chavez *et al.* (1989 a, b, c, d) though the stratification according to infection age is not explicit there. The key modification, infection-age dependent infectivity, has been added in order to study its effect in combination with the other mechanisms. This model does not include heterogeneities other than through the infection-age-dependent infectivity and through the population-size dependent per capita average sexual activity C(T). Further, by restricting itself to the homosexual part of a population which is replenished by constant recruitment, it does not reflect the joint effects of HIV dynamics and the population dynamics of its population (see Anderson and May 1989; Busenberg *et al.* 1989).

We divide the homosexually-active population under consideration into three groups: S (uninfected but susceptible, that is, sexually active), I (HIV infected with hardly any symptoms), and A (fully developed AIDS symptoms, and hence ill). A-individuals are assumed to be sexually inactive and sexually-active individuals (S and I) are supposed to choose their partners at random (although the rate of partnership change depends on T = S + I).

We use the following notation: t denotes time and τ denotes time since the moment of infection. Our time unit is given by the average length of the period of sexual activity for healthy individuals. Individuals are recruited into the sexually-active population at a constant rate A, and the length of the sexually-active period is exponentially distributed such that healthy individuals become sexually inactive at a constant rate μ, and since the average length $1/\mu$ of the sexually-activite period is 1, $\mu = 1$. Infected individuals with infection-age τ become sexually inactive by force of the disease at a rate $\alpha(\tau)$, and consequently the proportion of those individuals still sexually active given that they were infected τ time units ago is given by

$$\exp\left(-\tau - \int_0^\tau \alpha(\rho)\mathrm{d}\rho\right).$$

We stratify the infected part of the population according to age of infection through the infection-age density $i(t,\tau)$, and therefore

$$I(t) = \int_0^\infty i(t,\tau)d\tau$$

denotes the number of infected individuals that are sexually active.

The proportion of sexually-active infected individuals with infection-age τ in the age interval $[\tau, \tau+\delta\tau]$ is

$$\frac{i(t,\tau)}{T(t)}\,\delta\tau,$$

with $T = S + I$ being the size of the sexually active population. We assume that a typical susceptible (since we assume homogeneous mixing, everybody is typical) contracts the disease from a typical infected partner with age of infection τ at a mean risk $\lambda(\tau)$. The proportion of typical susceptible individuals being infected at time t, under the condition that they had a sexual contact at that time, is given by

$$\frac{W(t)}{T(t)},$$

where

$$W(t) = \int_0^\infty \lambda(\tau)i(t,\tau)d\tau;$$

that is, W(t) weights each infected individual by his infectivity.

The mean per capita sexual activity is measured in terms of the mean number of sexual contacts C(T) that a typical sexually-active individual has per unit of time. We assume that C(T) is a function of the size of the sexually-active population: $T = S + I$. Putting all the above together, we arrive at the following expression for the incidence rate (number of new cases of infection per unit time):

$$B(t) = C(T(t))S(t)\,\frac{W(t)}{T(t)},$$

and we also arrive at the following model for the transmission dynamics of HIV/AIDS with infection-age-dependent infectivity:

$$\frac{dS(t)}{dt} = \Lambda - B(t) - S(t)\ ; \tag{1}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}\right) i(t,\tau) = -\Big(1 + \alpha(\tau)\Big)\, i(t,\tau)\ ; \tag{2}$$

$$i(t,0) = B(t) = S(t)C(T(t))\frac{W(t)}{T}; \tag{3}$$

$$T = I + S; \tag{4}$$

$$I(t) = \int_0^\infty i(t,\tau)d\tau; \tag{5}$$

$$W(t) = \int_0^\infty \lambda(\tau)i(t,\tau)d\tau; \tag{6}$$

$$\frac{d}{dt}A(t) = \int_0^\infty \alpha(\tau)i(t,\tau)d\tau - (1+\nu)A(t).$$

Despite the fact that A, the number of individuals with fully developed AIDS symptoms (that are supposedly too ill to be sexually active), does not play any further role in the dynamics of the epidemic, we give the formula for its incidence (new number of AIDS cases per unit time) because it can be compared to data. AIDS causes a very high degree of mortality (most individuals with AIDS die within two years of the appearance of severe symptoms); hence in our model ν denotes the rate at which individuals with fully developed AIDS symptoms die from the disease or from an opportunistic infection.

Note that in contrast to earlier models of Anderson and May (1987), Blythe and Anderson (1988a), and Castillo-Chavez *et al.* (1989a, b), this model does not assume that at the moment of infection an individual follows a severe or a mild course of the disease. However, by assuming that

$$\int_0^\infty \alpha(\tau)d\tau < \infty,$$

this model, albeit with a different mechanism, takes into consideration the possibility that not all individuals may develop "full-blown" AIDS.

We assume that $\alpha(\tau)$ is a nonnegative measurable function; $\lambda(\tau)$ is a nonnegative integrable function of infection age, and that C(T) is a nondecreasing function of T, where $C(T) > 0$ whenever $T>0$. Later we assume that

$$M(T) = \frac{C(T)}{T}$$

is a nonincreasing function of T, i.e., that C(T) increases in a sublinear way reflecting some kind of saturation effect.

There are various ways of handling problem (1),···,(6). The first reformulates (1),···,(6) as an

abstract ordinary differential equation (see Thieme 1989a, b, in particular Section 7) providing a dynamical system, in terms of S and I, useful in the study of the instability and persistence of solutions. A second approach consists in integrating (1),⋯,(6) along characteristic lines (see Webb 1985), generating the same dynamical system but in a different way. Thirdly, one uses integration along characteristic lines to reduce the system (1),⋯,(6) to the following set of integral equations:

$$S = \Lambda - B * P_1 + f_1 , \tag{7}$$

$$V = B * P_{\alpha+1} + f_2 , \tag{8}$$

$$W = B * Q + f_3 , \tag{9}$$

$$B = SM(S + V)W . \tag{10}$$

We have used the following notation:

$$P_\alpha(\tau) = \exp\left(-\int_0^\tau \alpha(s)ds\right), \tag{11}$$

$$Q(\tau) = \lambda(\tau)P_{\alpha+1}(\tau) , \tag{12}$$

$$(B * P)(t) = \int_0^t B(t-s)P(s)ds , \tag{13}$$

$$f_1(t) = \left(S(0) - \Lambda\right)e^{-t} , \tag{14}$$

$$f_2(t) = \int_t^\infty i(0,\tau-t)\frac{P_{\alpha+1}(\tau)}{P_{\alpha+1}(\tau-t)}d\tau , \tag{15}$$

$$f_3(t) = \int_t^\infty i(0,\tau-t)\lambda(\tau)\frac{P_{\alpha+1}(\tau)}{P_{\alpha+1}(\tau-t)}d\tau , \tag{16}$$

$$M(T) = \frac{C(T)}{T} . \tag{17}$$

Note that

$$f_j \to 0, \quad t \to \infty, \tag{18}$$

and that P_1 and $P_{\alpha+1}$ are defined in analogy to P_α.

Some of the expressions just defined above have intuitive meanings. For example, $P_1(s) = e^{-s}$ gives the proportion of healthy individuals that remain sexually active s time units after having entered the active population, while $P_{\alpha+1}(\tau)$ gives the proportion of those infected individuals of infection age

τ that are still sexually active.

Substituting Equation (10) into Equations (7), (8), and (9) yields a system of Volterra integral equations of convolution form for which a well-developed theory is available (see Miller 1971, or Londen 1981); while the substitution of Equations (7), (8), and (9) into Equation (10) yields a scalar integral equation which is not of common Volterra type.

We can then easily check, from the various equations, that nonnegativity is preserved under the solution flow. Integrating Equation (2) over τ and combining it with (1) yields the differential inequality

$$\frac{d}{dt}T \leq \Lambda - T\,, \tag{19}$$

that provides us with the important *a priori* estimate

$$S(t),I(t) \leq T(t) = S(t) + I(t) \leq \Lambda + \Big(T(0) - \Lambda\Big)e^{-t}\,. \tag{20}$$

Using the theory found in Webb (1985) or Thieme (1985, 1989a, b) or applying standard fixed point arguments to (7),$\cdots$,(10), one easily shows that our model is well posed (i.e., there is a unique nonnegative solution for given nonnegative initial conditions). Furthermore, the mathematical theory shows that the solution depends continuously on the initial conditions, and the functions S, I, W, B are continuous and satisfy the estimate given by the inequality (20).

3. Stationary states, stability, and the basic reproductive number

In this section we concentrate in the study of of the existence and stability of stationary states, that is, equilibria or time-independent solutions. It turns out that there are only two kinds of equilibria: the infection-free state and the endemic state. Until recently, it was believed that most epidemic models had at most two equilibria, an infection-free state and (under certain assumptions) a unique endemic equilibrium. Earlier studies (see Hethcote and Yorke 1984, Castillo-Chavez *et. al.* 1988, 1989, and references therein) supported this belief even for heterogeneously mixing populations; however, recent studies (see Castillo-Chavez *et. al.* 1989c, d; Huang 1989; and Huang *et. al.* 1990) have

shown that multiple endemic equilibria are possible.

Steady states are important because their existence is usually intimately connected to the basic reproductive number R_0, which can be determined in terms of model parameters and because they are candidates for the asymptotic behavior of the model. We show that for $R_0 < 1$, the disease dies out while for $R_0 > 1$, the disease persists in the population. These basic stability results provided us with a starting point for the development and evaluation of control measures, and has provide us with useful results that have been applied in disease management (see Hethcote and Yorke 1984, and references therein.)

When $R_0 > 1$, there is a unique endemic equilibrium which is locally asymptotically stable provided that R_0 is slightly larger than 1, but which might lose stability if R_0 increases (see Section 4). Even if possibly unstable, knowledge of the existence of the endemic equilibrium is very useful as it provides us with an indicator of the severity of the disease because, as we show later, the incidence rate fluctuates around the endemic equilibrium value.

Clearly, the system (1),$\cdots$,(6) always has the infection-free state with coordinates

$$S_0 = A,\ I_0 = 0,\ W_0 = 0,\ B_0 = 0,\ i_0 = 0, \tag{21}$$

as a steady state. However, to determine the existence of an endemic equilibria of system (1),$\cdots$,(6) we have to look for solutions of the following nonlinear system of algebraic equations:

$$S^* = A - B^*\,, \tag{22}$$

$$I^* = B^*\hat{P}_{\alpha+1}(0)\,, \tag{23}$$

$$W^* = B^*\hat{Q}(0)\,, \tag{24}$$

$$B^* = \frac{S^*}{T^*}C(T^*)W^*, \quad T^* = S^* + I^* \tag{25}$$

Here we have used the *Laplace* transform notation i.e.,

$$\hat{Q}(z) = \int_0^\infty e^{-z\tau}Q(\tau)d\tau\,, \tag{26}$$

$$\hat{P}_{\alpha+1}(z) = \int_0^\infty e^{-z\tau}P_{\alpha+1}(\tau)d\tau, \tag{27}$$

only to simplify the notation.

If we substitute Equation (24) into (25) and dividing by B^* (which is assumed to be positive, as otherwise there is no endemic equilibrium), we obtain the following stability equation:

$$1 = \frac{S^*}{T^*}C(T^*)\hat{Q}(0), \tag{28}$$

hence reducing the study of the existence of endemic equilibria to the study of positive roots of Equation (28). To facilitate the study of the roots of this equation, we introduce a dimensionless quantity, namely the fraction of infected individuals,

$$\xi = \frac{I^*}{T^*}. \tag{29}$$

Manipulation of Equations (22), (23), and the second equation in (25) leads to the following expressions for T^*:

$$\frac{S^*}{T^*} = 1 - \xi, \quad T^* = \frac{\Lambda}{1 + \left(\frac{1}{\hat{P}_{\alpha+1}(0)} - 1\right)\xi}. \tag{30}$$

Substitution of (30) into (28) results in the following reformulation of Equation (28):

$$1 = (1-\xi)C\left(\frac{\Lambda}{1 + \left(\frac{1}{\hat{P}_{\alpha+1}(0)} - 1\right)\xi}\right)\hat{Q}(0), \tag{31}$$

or alternatively we can also consider

$$1 = \frac{\Lambda - B^*}{\Lambda - B^*\left(1 - \hat{P}_{\alpha+1}(0)\right)} C\left[\Lambda - B^*\left(1 + \hat{P}_{\alpha+1}(0)\right)\right]\hat{Q}(0), \tag{32}$$

which we obtain by fitting (22), (23), (24) into (25). Hence we conclude that the existence of a unique endemic equilibrium is intimately connected to the properties of C(T). Therefore, since C(T) is a monotone nondecreasing function and since clearly $1>\hat{P}_{\alpha+1}(0)$, we have that the right-hand side of (31) is a strictly decreasing function of ξ, and consequently, for $\xi = 0$, the right-hand side of (31) gives the basic reproductive number R_0 of the disease-free population (in its equilibrium):

$$R_0 = C(\Lambda)\hat{Q}(0)\,. \tag{33}$$

Biologically, R_0 gives the average number of secondary infections that a typical infectious individual can produce if introduced into the disease-free population. A direct application of the intermediate

value theorem leads us to the following existence result:

Theorem 1. *If $R_0 \leq 1$, there exists only the disease-free equilibrium. If $R_0 > 1$, there is a unique endemic equilibrium.*

Theorem 1 is a static result that does not provide us with a relation between the basic reproductive number and the actual disease dynamics. It only provides us with information regarding the existence of a unique state in which the disease persists. The following theorem, however, partially connects the basic reproductive number to the HIV dynamics:

Theorem 2. *Assume that $R_0 < 1$, then the disease-free equilibrium is globally attractive. Specifically, we have that*

$$B(t),\ I(t),\ \text{and}\ W(t) \to 0;\ \text{and that}\ S(t) \to \Lambda \quad \text{when}\ t \to +\infty .$$

Proof:. The proof follows through a direct application of Fatou's lemma to (9) and (10), use of the estimate (20), and the fact that C(T) is nondecreasing. We can easily see that

$$\limsup_{t\to\infty} B(t) \leq R_0 \limsup_{t\to\infty} B(t),$$

from where the assertion of this theorem follows.

In most cases, it is not possible to obtain a global convergence result if $R_0 > 1$. For this model, however, we can show that if a trajectory is not attracted to the endemic equilibrium then it has to oscillate around it.

Theorem 3. *Let $R_0 > 1$. The following holds:*

(a)
$$\limsup_{t\to\infty} B(t) \leq B^* .$$

(b) Let $\lambda(\tau) \not\equiv 0$ and $\tau_\dagger$ be the smallest $\bar{\tau}$ such that $\lambda(\tau) = 0$ for a.a. $\tau \geq \bar{\tau}$. *Let*

$$\int_0^{\tau_\dagger} i(0,\tau)d\tau > 0 .$$

Then

$$\limsup_{t\to\infty} B(t) \geq B^* .$$

Proof. Let us show the validity of (b) first. If the assertion is wrong, we can find $\tilde{B} < B^*$ and $\tilde{t} > 0$ such that

$$B(t+s) \geq \frac{\Lambda - \tilde{B}}{\Lambda - \tilde{B}\left(1 - \hat{P}_{\alpha+1}(0)\right)} C\left[\Lambda - \tilde{B}\left(1 - \hat{P}_{\alpha+1}(0)\right)\right] \times$$

$$\left(\int_0^t B(t+s-a)Q(a)da + \int_0^{\tilde{t}} B(s-a)Q(a+t)da\right)$$

for $t \geq 0$, $s \geq \tilde{t}$. It follows from the assumption in (b) that the initial infectives produce secondary cases. Actually one can readily show that the existence of some $\tilde{s}$ such that

$$B(t) > 0 \quad \text{for} \quad t \geq \tilde{s},$$

and hence, if we choose s large enough we have that

$$\int_0^{\tilde{t}} B(s-a)Q(a+t)da > 0 \qquad \text{for some } t > 0 .$$

Since $\tilde{B} < B^*$, one sees from the expression for T^* in (30) that

$$B(t+s) \geq \beta \int_0^t B(t+s-a)Q(a)da + g(t)$$

with

$$\beta\hat{Q}(0) > 1, g \geq 0, g \not\equiv 0 .$$

It then follows from the celebrated renewal theorem – formulated by Lotka and first proved rigorously by Feller (see Webb 1985, Theorem 4.10, for a proof and references)– that B(t) goes to infinity if $t \to +\infty$, in contradiction to our assumption.

To prove assertion (a) we proceed as follows: if the assumption in (b) is not satisfied there will be no secondary cases and the disease will die out anyhow, and therefore we assume that (b) holds and use the fact that

$$\tilde{B} = \limsup_{t\to\infty} B(t) > 0 .$$

Applying Fatou's lemma to (32) we find that

$$\bar{B} \leq \frac{\Lambda - \underline{B}}{\Lambda - \underline{B}\left(1 - \hat{P}_{a+1}(0)\right)} C\left(\Lambda - \underline{B}\left(1 - \hat{P}_{a+1}(0)\right)\right)\hat{Q}(0)\bar{J}$$

with

$$\underline{B} = \liminf_{t\to\infty} B(t) .$$

Dividing this inequality by $\bar{B}$, which is positive, and comparing it to (32) yields that $\underline{B} \leq B^*$.

Analogous statements can now be derived for S, I, and W. Theorem 3 does not yet answer the question of whether I, the total number of infected individuals, will be bounded away from zero if $R_0 > 1$, and whether this bound does or does not depend on the initial conditions. Both questions can be better handled in the framework of dynamical systems theory, i.e., by looking at the formulation (1), ···, (6) rather than (7), ···, (10). Fortunately, through Theorem 3 we satisfy condition (4.2) in Theorem 4.1 of the persistence theory for dynamical systems found in Hale and Waltman (1989). This theory allows us to show the existence of a positive lower bound for I(t). The argument goes as follows: from the apriori estimate provided by (20) it follows that the solution flow has a bounded attractor. The asymptotic smoothness of the solution flow can be established in the same way as in the proof of the Proposition 3.16 found in Webb (1985), and we note that the boundary flow $-\ I \equiv 0-$ is attracted to the disease-free equilibrium. From the above discussion and Theorem 4.2 in Hale and Waltman (1989) we obtain the following result:

Theorem 4. *Let* $\lambda(a) \not\equiv 0$ *and* $a_\dagger$ *be the smallest* $\tilde{a}$ *such that* $\lambda(a) = 0$ *for* a.a. $a \geq \tilde{a}$. *Let*

(3.2)
$$\int_0^{a_\dagger} I(0,a)da > 0 .$$

Then

$$\liminf_{t\to\infty} I(t) > \epsilon > 0$$

with ϵ *not depending on the initial conditions.*

The persistence theory of dynamical systems does not give us information, however, as to whether B and W are bounded away from zero too.

4. Stability of the endemic equilibrium: The epidemiology

The stability of endemic equilibria of epidemiological models is of biological interest for at least two reasons. First, in case of locally asymptotic stability, in many instances it is the ultimate state of the epidemic, though only a global stability analysis would provide a definite answer to this question. In our model, this is a definite possibility, as there is only one endemic equilibrium and the disease-free equilibirum becomes a repellor as soon as the endemic equilibrium comes into existence. Secondly, if an endemic equilibrium is unstable, then undamped oscillations of the disease dynamics around this equilibrium are very likely. From Theorem 3, one sees intuitively that local asymptotic stability means that once the course of the disease comes close to the endemic equilibrium it remains close and finally approaches it. The precise definition can be given most nicely in reference to the model formulation (1), ···, (6).

Definition (a) The endemic equilibrium S^*, I^*, W^*, B^*, i^* of (1), ···, (6) with

$$i^*(a) = B^* P_{\alpha+1}(\tau)$$

is ***locally asymptotically stable*** if and only if the following two properties hold:

(i) For any $\epsilon > 0$ there is some $\delta > 0$ such that if

$$|S(0) - S^*| + \int_0^\infty |i(0,a) - i^*(\tau)|\, d\tau \leq \delta$$

then

$$|S(t) - S^*| + \int_0^\infty |i(t,\tau) - i^*(\tau)|\, d\tau \leq \epsilon \quad \text{for all} \quad t \geq 0 .$$

(ii) There exists $\delta_0 > 0$ with the property that if

$$|S(0) - S^*| + \int_0^\infty |i(0,\tau) - i^*(\tau)|\, d\tau \leq \delta_0 ,$$

then

$$|S(t) - S^*| + \int_0^\infty |i(t,\tau) - i^*(\tau)|\, d\tau \to 0 \quad \text{for} \quad t \to \infty .$$

(b) The endemic equilibrium is called ***unstable*** if the following holds: there exists a sequence of solutions S_n, i_n to (1), ···, (6), a sequence of times $t_n \to \infty$, and a positive number $\epsilon_0 > 0$ such that

$$\left|S_n(0) - S^*\right| + \int_0^\infty \left|i_n(0,\tau) - i^*(\tau)\right| d\tau \to 0 \qquad \text{for} \qquad n \to \infty,$$

but

$$\left|S_n(t_n) - S^*\right| + \int_0^\infty \left|i_n(t_n,\tau) - i^*(\tau)\right| d\tau \geq \epsilon_0 \qquad \text{for all} \qquad n \in N .$$

The discussion of the stability and instability of the endemic equilibria is facilitated by switching from the original parameters of the model to the following nondimensional ones:

$$\xi = \frac{I^*}{T^*} = \frac{I^*}{S^* + I^*}, \tag{34}$$

$$\gamma := -\frac{T^* M'(T^*)}{M(T^*)}, \tag{35}$$

and

$$\sigma := \frac{1}{\hat{P}_{\alpha+1}(0)}. \tag{36}$$

Note that ξ gives the fraction of infected individuals in the sexually-active population and therefore is a dimensionless parameter satisfying

$$0 < \xi < 1 .$$

Even though all values of ξ in the interval $0 < \xi < 1$ are feasible (as one can see from (31) and (33) by choosing $R_0 > 1$) not all them are realistic. Note that $\frac{1}{\sigma} = P_{\alpha+1}(0)$ can be interpreted as the average length of the effecive sexually-active period of infected individuals (relative to the average length of the sexually-active period of healthy individuals, our time unit). Hence it is intuitively clear (and this follows from the definition of $P_{\alpha+1}$ - see (11)) that $\sigma > 1$. The average infection has been estimated to be about 10 years (see May and Anderson 1989 and references therein). If we assume that the mean of the sexually-active period lies in the interval [15 years, 30 years], then we obtain values of $1/\sigma$ in the interval [1.5, 3]. We observe tha γ is also a dimensionless parameter, and since $M(T) \doteq \frac{C(T)}{T}$ is

nonincreasing and C is nondecreasing, we see that

$$0 \leq \gamma \leq 1 .$$

The following choices for C(T) may give us a feeling for a reasonable range for γ.

(a) *Mass-action type contact law*

The classical epidemiological contact law is $C(T) = \beta T$, where M = constant and $\gamma = 0$. This contact law is more appropriate for communicable diseases such as influenza (see Castillo-Chavez *et al.* 1988, 1989).

(b) *C = constant*

This may be a good approximation if the number of available partners is large enough and everybody can make more contacts than is practically feasible. Note that in this case $\gamma = 1$.

(c) *Michaelis Menton-type contact law*

The Michaelis Menton type contact law or Holling functional response type 1 combines the two previous formulations by assuming that, if the number of available partners is low, the number of actual per capita partners C(T) is proportional to T, whereas if the number of available partners is large, there is a saturation effect which makes the number of actual partners constant. In situations like this, we may take

$$C(T) = \frac{\beta T}{1 + \kappa T},$$

for which

$$\gamma = \frac{kT^*}{1 + \kappa T^*},$$

and consequently, γ covers the range from 0 to 1 when T^* covers the range from 0 to ∞, that is, any value of γ is feasible (as one can see from (30)).

In view of this discussion, we call γ the *saturation index* of the number of partners at the endemic equilibrium. If $\gamma = 0$, there is no saturation at all because the number of actual partners is proportional to the number of available partners while if $\gamma = 1$, there is a complete saturation because

the number of new actual partners per unit time hardly changes if the number of available partners does. In Sections 5 and 6 we prove the following result:

Theorem 5. *The endemic equilibrium is locally asymptotically stable if one of the following holds:*

a) ξ *is sufficiently close to 0 or to 1.*

b) σ *is sufficiently large.*

c) γ *is sufficiently close to 0.*

d) $\lambda = const.$

e) $P_{\alpha+1}$ *is convex.*

From this thorem, we conclude that the endemic equilibrium is locally asymptotically stable if the fraction of infected individuals is either low or high, or if the length of the effective sexually-active period of infected individuals is short compared with the length of the sexually-active period of the susceptible individuals, or if the saturation index is low. Further, we have local stability if the infectivity is evenly distributed over the period of sexual activity. Although $P_{\alpha+1}$ may be convex, for example, if the length of the sexually-active period of infected individuals is exponentially distributed, this is, of course, not always the case.

Conversely, the following result, whose proof is provided in the next sections, holds:

Theorem 6. *Let* $\gamma > 0$ *and*

$$\int_0^\infty cos(sy)P_{\alpha+1}(s)ds < 0 \quad for\ some\ y\ . \tag{37}$$

If Q is concentrated sufficiently close to 0, one can find ξ *and* σ $(0 < \xi < 1,\ \sigma > 1)$ *such that the corresponding endemic equilibrium is unstable.*

From this result we see that actually, the saturation index has a destabilizing effect. The closer it is to 1, the more likely the endemic equilibrium will be unstable. The requirement that Q is concentrated at 0, i.e., that the infectivity is concentrated in the early part of the incubation period, emphasizes the importance of an infection-age-dependent infectivity. Future numerical studies have to show whether or not more realistic infectivity distributions (one early and one late peak) induce instability. We conclude our discussion with an example for which (37) holds.

We assume that the incubation period is divided into two periods: a fixed period of length τ during which no symptoms show up but after which severe symptoms (leading to an end of sexual activity) occur at a fixed rate $\rho > 0$. This is mathematically realized by setting

$$\alpha(\tau') = \begin{cases} 0 & , \ 0 \le \tau' \le \tau \\ \rho & , \ \tau' > \tau \end{cases}, \tag{38}$$

and consequently from (11) we obtain

$$P_{\alpha+1}(\tau') = \begin{cases} e^{-\tau'} & , \ 0 \le \tau' \le \tau \\ e^{-\tau'} e^{\rho(\tau-\tau')} & , \ \tau' \ge \tau . \end{cases} \tag{39}$$

Hence

$$\int_0^\infty \cos(sy) P_{\alpha+1}(s)ds = \frac{1}{1+y^2}\left(1 - e^{-\tau}\right) + \frac{y}{1+y^2} e^{-\tau} \sin(y\tau)$$

$$+ \frac{\rho+1}{(\rho+1)^2+y^2} e^{-\tau} \cos(y\tau) - \frac{y}{(\lambda+1)^2+y^2} e^{-\tau} \sin(y\tau),$$

from where we may have that

$$\int_0^\infty \cos(sy) P_{\alpha+1}(a)ds < 0$$

if $y\tau = \left(2n - \frac{1}{2}\right)\pi$ with n being sufficiently large.

In the next sections we prove the results just presented and lay the analytical foundations for a future numerical computation of the stability boundaries in the $\xi\sigma$ plane.

5. Stability of the endemic equilibrium and the characteristic equation

Using the abstract results in the theory of ordinary differential equations, specifically, Corollary 4.3 and Section 7 in Thieme (1989 a,b) or Theorem 4.13 in Webb (1985) it is possible to approach the

stability of the endemic equilibrium for (1), ···, (6) in the same way as for a "classical" ordinary differential equation. Hence we set

$$S = S^* + s, \quad i = i^* + u, \quad I = I^* + v, \quad W = W^* + w$$

and consider the variational equations for s, u, v, w related to (1), ···, (6), in other words, we linearize the dynamical system (1), ···, (6) around the endemic equilibrium

$$\frac{d}{dt}s(t) = -u(t,0) - s(t)\ , \tag{40}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right)u(t,a) = -[\alpha(a) + 1]u(t,a)\ , \tag{41}$$

$$u(t,0) = s(t)F(T^*)W^* + (s + v)S^*F'(T^*)W^* + wS^*F(T^*)\ , \tag{42}$$

where

$$v(t) = \int_0^\infty u(t,a)da \tag{43}$$

$$w(t) = \int_0^\infty \lambda(a)u(t,a)da\ . \tag{44}$$

To study the stability of this linear system, we look for solutions to (40), ···, (44) of the exponential form

$$s(t) = e^{zt}\tilde{s},\ u(t,a) = e^{zt}\tilde{u}(a), \tag{45}$$

where z is a complex number, and $s \neq 0$ or $u \not\equiv 0$.

The endemic equilibrium will be locally asymptotically stable provided all such solutions have a strictly negative real part while it will be unstable if there is at least one such solution with the real part of z being strictly positive.

Plugging (45) into (40), ···, (44) yields

$$z\tilde{s} = -\tilde{u}(0) - \tilde{s}, \tag{46}$$

$$z\tilde{u}(a) + \frac{d}{da}\tilde{u}(a) = -[\alpha(a) + 1]\tilde{u}(a), \tag{47}$$

$$\tilde{u}(0) = \tilde{s}W^*M(T^*) + (\tilde{s} + \tilde{v})S^*M'(T^*)W^* + \tilde{w}S^*M(T^*), \tag{48}$$

$$\tilde{v} = \int_0^\infty \tilde{u}(a)da, \tag{49}$$

$$\tilde{w} = \int_0^\infty \lambda(a)\tilde{u}(a)da. \tag{50}$$

From (46) we obtain

$$\tilde{s} = \frac{\tilde{u}(0)}{1+z}, \tag{51}$$

and solving (47) for $\tilde{u}$ and substituting this result into (49) and (50) yields

$$\tilde{v} = \tilde{u}(0)\hat{P}_{\alpha+1}(z), \tag{52}$$

and

$$\tilde{w} = \tilde{u}(0)\hat{Q}(z)\ . \tag{53}$$

Note that $\tilde{u}(0)$ has to be different from 0 because otherwise both $\tilde{s} = 0$ and $\tilde{u} \equiv 0$. Fitting (51), (52), and (53) into (48) and dividing by $\tilde{u}(0) \neq 0$ yields the *characteristic equation*

$$1 = -\frac{W^*}{1+z}\Big(M(T^*) + S^*M'(T^*)\Big) + S^*M'(T^*)W^*\hat{P}_{\alpha+1}(z) + S^*M(T^*)\hat{Q}(z)\ . \tag{54}$$

We note that the same characteristic equation is obtained after linearizing the limiting equations associated with (7), $\cdots$, (10) around the endemic equilibrium and looking for solutions of exponential form (45). Finally, we arrive at the following relation between the stability of the endemic equilibrium and the roots of the characteristic equation (54).

Theorem 7. (a) *The endemic equilibrium is locally asymptotically stable if all the roots of the characteristic equation have strictly negative real parts.*

(b) *The endemic equilibrium is unstable if the characteristic equation has at least one root with a strictly positive real part.*

6. Analysis of the characteristic equation

The difficulty in analyzing (54) along the lines proposed by Theorem 7 lies in the fact that W^*,

S^*, T^* are related by the steady state equations (22), ⋯, (25). In this section we incorporate these relations into (54) while trying to keep as few parameters as possible (all of which can be modified independently of each other.)

From (25), (17), (23), (29) we obtain

$$W^*M(T^*) = \frac{B^*}{S^*} = \frac{I^*}{S^*}\frac{1}{1-\hat{P}_{\alpha+1}(0)} = \frac{\xi}{1-\xi}\frac{1}{1-\hat{P}_{\alpha+1}(0)}.$$

From (24), (28), (17), (29) we get

$$S^*W^* = S^*B^*\hat{Q}(0) = \frac{B^*}{M(T^*)} = \frac{I^*}{M(T^*)1-\hat{P}_{\alpha+1}(0)} = \frac{T^*}{M(T^*)}\frac{\xi}{1-\hat{P}_{\alpha+1}(0)};$$

and from (28)

$$S^*M(T^*) = \frac{1}{\hat{Q}(0)}.$$

Substituting these relations into the characteristic equation (54) yields

$$1 = \frac{1}{1+z}\frac{\xi}{1-\hat{P}_{\alpha+1}(0)}\left(\frac{1}{1-\xi}+\frac{T^*M'(T^*)}{M(T^*)}\right)+\xi\frac{T^*M'(T^*)}{M(T^*)}\frac{1-\hat{P}_{\alpha+1}(z)}{1-\hat{P}_{\alpha+1}(0)}+\frac{\hat{Q}(z)}{\hat{Q}(0)}. \tag{55}$$

Further, we define the probability densities

$$p(s) \equiv \frac{1-\hat{P}_{\alpha+1}(s)}{1-\hat{P}_{\alpha+1}(0)}, \tag{56}$$

and

$$q(s) \equiv \frac{Q(s)}{\hat{Q}(0)}, \tag{57}$$

and set

$$\gamma \equiv \frac{T^*M'(T^*)}{M(T^*)} \tag{58}$$

and

$$\sigma \equiv \frac{1}{1-\hat{P}_{\alpha+1}(0)}. \tag{59}$$

Equation (55) takes the form

$$1 = \frac{\sigma\xi}{1+z}\left(\frac{1}{1-\xi} - \gamma\right) - \xi\gamma\hat{p}(z) + \hat{q}(z)\,. \tag{60}$$

From the definition of $P_{\alpha+1}$ – see (11) – it follows that $\sigma > 1$. We assume here, however, that $\sigma > 2$ because (as discussed earlier) the duration of the effective sexually-active period of healthy (that is, susceptible) individuals seems to be more than twice that of infected individuals. Note that p and q are probability densities in dimensionless time related to the average duration of the effective sexually active period of infected individuals, while γ (given by 58) is a dimensionless parameter already. Since M(T) = C(T)/T is nonincreasing and C is nondecreasing we have that $0 \leq \gamma \leq 1$ (see the discussion in Section 4 concerning the dependence of γ on the functional relation C between the numbers of actual and potential partners and on the equilibrium value T^*.)

We now let $z = x + iy$ and separate (60) into real and imaginary parts:

$$1 - \int_0^\infty e^{-xs}\cos(sy)q(s)ds = \frac{1+x}{(1+x)^2+y^2}\sigma\xi\left(\frac{1}{1-\xi} - \gamma\right) - \xi\gamma\int_0^\infty e^{-xs}\cos(sy)p(s)ds \tag{61}$$

and

$$\int_0^\infty e^{-xs}\sin(sy)q(s)ds = \frac{y}{(1+x)^2+y^2}\sigma\xi\left(\frac{1}{1-\xi} - \gamma\right) + \xi\gamma\int_0^\infty e^{-xs}\sin(sy)p(s)ds\,. \tag{62}$$

Using the fact that q is a probability density, we see that the left-hand side of (61) is strictly positive. Further, by the Riemann & Lebesgue lemma we conclude that

$$\int_0^\infty e^{-xs}\sin(sy)p(s)ds \to 0,\ \int_0^\infty e^{-xs}\sin(sy)q(s)ds \to 0,\ |y| \to \infty, \tag{63}$$

provided that λ is of bounded variation, and of course the same result holds if sine is replaced by cosine. Note further that

$$\int_0^\infty e^{-sx}\sin(sy)p(s)ds > 0\,, \tag{64}$$

because p is nonincreasing. This implies that the roots of (61) and (62) satisfy $x < 0$ if ξ (>0) is small enough. Further, one can easily show that there exist no roots with $y = 0$. Suppose that there exists some $0 < \xi < 1$ such that (61) and (62) can be solved with $x,y > 0$. Since the roots of the characteristic equation depend continuously on ξ by Rouché's theorem, and lie in the left half plane for

small $\xi > 0$, they must cross the imaginary axis as ξ increases ($y \to \infty$ is excluded by (63).) Consequently, for some $0 < \xi < 1$ (different from the one we started with) (61) and (62) are solved with $x = 0$, $y > 0$, i.e.,

$$1 - \int_0^\infty \cos(sy)q(s)ds = \frac{1}{1+y^2}\sigma\xi\left(\frac{1}{1-\xi} - \gamma\right) - \xi\gamma\int_0^\infty \cos(sy)p(s)ds \tag{65}$$

and

$$\int_0^\infty \sin(sy)q(s)ds = \frac{y}{1+y^2}\sigma\xi\left(\frac{1}{1-\xi} - \gamma\right) + \xi\gamma\int_0^\infty \sin(sy)p(s)ds\,. \tag{66}$$

We can solve for ξ by multiplying (65) by y and adding the two equations together:

$$\xi = \frac{y\left(1 - \int_0^\infty \cos(sy)q(s)ds\right) + \int_0^\infty \sin(sy)q(s)ds}{\gamma\left(\int_0^\infty \sin(sy)p(s)ds - y\int_0^\infty \cos(sy)p(s)ds\right)}\,. \tag{67}$$

Substituting (66) into (67) makes it possible to solve for σ:

$$\sigma = \frac{\int_0^\infty \sin(sy)q(s)ds - \xi\gamma\int_0^\infty \sin(sy)p(s)ds}{\frac{y}{1+y^2}\left(\frac{\xi}{1-\xi} - \xi\gamma\right)}\,. \tag{68}$$

If we take into account the fact that $0 < \xi < 1$, $0 \le \gamma \le 1$, and that $\sigma > 1$, we have the following result:

Proposition. There are no roots of (61) or (62) with $x \ge 0$ if one of the following holds:

(a) ξ is sufficiently close to 0 or to 1.

(b) σ is sufficiently large.

(c) γ is sufficiently close to 0.

(d) There is no $y > 0$ satisfying the following simultaneously:

$$\int_0^\infty \cos(sy)q(s)ds > 0\,,$$
$$\int_0^\infty \sin(sy)q(s)ds > 0\,,$$
$$\int_0^\infty \cos(sy)p(s)ds < 0\,,$$

$$y\left(1 - \int_0^\infty \cos(sy)q(s)ds\right) + \int_0^\infty \sin(sy)q(s)ds$$
$$< \gamma\left(\int_0^\infty \sin(sy)p(s)ds - y\int_0^\infty \cos(sy)p(s)ds\right) \quad < 0\,.$$

(e) $\lambda = \text{const.}$

(f) p is convex.

Proof. The statements a), b), c) are consequences of (61), ···, (64). Statement d) follows from the arguments preceding Proposition 7 and (65), ···, (68). The statements e) and f) are consequences of d). If $\lambda = \text{const}$, then $q(s) = \lambda p(s)$, so the relative integrals cannot have different signs. This is the case considered in Castillo-Chavez *et al.* (1989). If p is convex, then $\int_0^\infty \cos(sy)p(s)ds = \int_0^\infty \frac{1}{y}\sin(sy)[-p'(s)]ds > 0$.

Actually, it is possible to obtain additional information by fitting ξ into (68), but the formulas become so complicated that they are of little use. One easily realizes that for (ξ,σ) satisfying (67) and (68) one finds $(\xi,\tilde{\sigma})$ and $(\xi,\check{\sigma})$ close by satisfying (61) or (62) with $x > 0$ or $x < 0$, respectively.

Actually (67) and (68) provide a curve of points (ξ,σ) for which the characteristic equation has roots on the imaginary axis and beyond with the endemic equilbirum being unstable. It is questionable, however, whether there are points (ξ,σ) for which the characteristic equation has roots in the right-half plane and which lie in a realistic parameter range with $0 < \xi < 1$, as $\sigma > 1$ is the minimum requirement. One realizes from (67) and (68) that this is possible if

$$\int_0^\infty \cos(sy)p(s)ds < 0 \tag{69}$$

and the probability density q is concentrated close to 0. The second condition means epidemiologically that the infectivity is concentrated in an early part of the incubation period. Future numerical studies have to show how far this condition can be relaxed.

7. Conclusions

Several mathematical studies of epidemic models have identified both mechanisms capable and incapable of generating sustained oscillations (see Hethcote *et al.* 1981, and Hethcote and Yorke 1989

for a survey), and as discussed in the introduction of this paper, most of these mechanisms are inadequate in the case of HIV. In our model, the saturation of mean per capita sexual activity interacts with an infection-age-dependent rate (at which infected individuals are removed from sexual activity by the disease) and an infection-age-dependent infectivity of infected individuals. We have shown in this paper that the unique endemic equilibrium can loose its stability (thus generating sustained oscillations) by a rather unique combination of conditions (see Section 1). Sustained oscillations can be ruled out if any of the reasonable conditions (i) – (iv) are not satisfied. Condition (v) represents our first step towards the analysis of the effects of variable infectivity on HIV dynamics. The analysis of Castillo-Chavez *et al.* (1989a, b, c, d) which assumes constant infectivity, suggests that sustained oscillations can be ruled out if the infectivity is rather evenly distributed over the activity period. Our condition (v) – the infection-age-distributed infectivity is concentrated at an early part of the incubation period – emphasizes the possible relevance of variable infectivity on the dynamics of an HIV epidemic. Relying on analytical techniques exclusively, we have shown the possibility of sustained oscillations if the infectivity distribution only has an early peak. Although, we have not analyzed the possibility of sustained oscillations in the presence of two infectivity peaks (one early and one late), our results show that the stability of the endemic state in the latter case cannot be taken for granted. We plan to study numerically whether or not undamped oscillations also occur for models with an early and a late infectivity peak. Our stability criterion will be the analytical basis for numerically exploring the parameter range in which oscillations occur. The ξ, σ curves generated by equations (67) and (68) will help to find the boundary of the ξ, σ region within which (if at all) the endemic equilibrium is unstable. This procedure will demand intensive numerical studies as it will have to be repeated for different choices of γ, p and q. This paper supports the selection of a saturation index $\gamma = 1$ and whether or not the endemic equilibrium is unstable in a realistic ξ, σ range will depend crucially on the shape of p, q as we recognize from (i) and (v). We don't know whether or not the shape of p, q for which the endemic equilibrium is unstable is realistic as our analytic results so far suggest instability if the age-infected infectivity is concentrated at an early part of the incubation period. The *limited* numerical simulations of models that incorporate variable infectivity by Anderson and May (1989),

Hyman and Stanley (1988, 1989), Blythe and Anderson (1988b) suggest that the endemic equilibrium is stable for realistic infectivity functions, and therefore, further numerical and analytical investigations are needed. Numerical studies can be carried more easily and more effectively through the exploration of the parameter range of possible sustained oscillations using the ξ-σ curves just described. Simulations of the full model are indispensable for showing whether the amplitudes of the oscillations are large enough to be epidemiologically significant, however, we feel that they need to be guided by the previous exploration of the critical parameter range.

The uncertainty of whether or not the endemic equilibrium is stable raises the question of whether or not it should be discarded as some kind of measure of the severity of the disease when unstable. However, its usefulness has been established by our proof that the incidence rate either converges to its uniquely determined endemic equilibrium (provided that it exists) or it fluctuates around it. Of course, it would be more useful to know whether or not the time averages converge (as time tends to infinity) towards the endemic equilibrium.

We remark that variable infectivity is just one of the important factors involved in HIV dynamics. Heterogeneity in sexual behavior is also of crucial importance in the transmission dynamics of HIV (see Blythe and Castillo-Chavez 1989; Castillo-Chavez and Blythe 1989; Busenberg and Castillo-Chavez 1989, 1990; Castillo-Chavez *et al.* 1990; Castillo-Chavez and Busenberg 1990, Sattenspiel and Castillo-Chavez 1990, and references therein). The analytical study of a model that incorporates variable infectivity and heterogenous mixing looks like a formidable task. However, mathematical studies of submodels of this general model are central to the execution of extensive numerical simulations of more detailed models.

We conclude with a not very optimistic view of the predictive value of mathematical models for HIV transmission. The recent literature in HIV modeling reveals a *potentially* very complex picture: multiple endemic equilibria and possibility of oscillations. This dynamic behavior is not observed in less detailed versions of these models (see Castillo-Chavez 1989a, b) indicating that very aggregated versions of these models may not be adequate. Unfortunately, more detailed models required more data (most of which is not only unavailable but unfortunately of not enough high quality) and as

Ludwig (1985, 1989) has shown, these demands put very severe limits on our ability to generate accurate predictions. The theoretical value of these models is nevertheless very important.

ACKNOWLEDGMENTS

This research has been partially supported by NSF grant DMS-8906580 and Hatch project grant NYC 151-409, USDA awarded to Carlos Castillo-Chavez. We are grateful to K. L. Cooke and S. Busenberg for their stimulating conversations.

REFERENCES

Anderson, R.M., H.C. Jackson, R.M. May, and A.D.M. Smith. (1981). Population dynamics of fox rabies in Europe. *Nature* 289, 765-771.

Anderson, R.M. and R.M. May. (1987). Transmission dynamics of HIV infection. *Nature* 326, 137-142.

Anderson, R.M., R.M. May, and G.F. Medley. (1986). A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV), the causative agent of AIDS. *IMA J. Math. Med. Biol.* 3, 229-263.

Andreasen, V. (1988). Dynamical models of epidemics in age-structured populations: Analysis and simplifications. Ph.D. Thesis, Cornell University.

Andreasen, V. (1989). Multiple time scales in the dynamics of infectious diseases. In *Mathematical Approaches to Problems in Resource Management and Epidemiology*, C. Castillo-Chavez, S.A. Levin, and C. Shoemaker (eds.). Lecture Notes in Biomathematics 81. Springer-Verlag, Berlin, Heidelberg, New York, Tokyo.

Blythe, S.P. and R.M. Anderson. (1988a). Distributed incubation and infectious periods in models of the transmission dynamics of the human immunodeficiency virus (HIV). *IMA J. Math. Med. Bio.* 5, 1-19.

Blythe, S.P. and R.M. Anderson. (1988b). Variable infectiousness in HIV transmission models. *IMA J. of Mathematics Applied in Med. and Biol.* 5, 181-200.

Blythe, S.P. and C. Castillo-Chavez. (1989). Like-with-like preference and sexual mixing models. *Math. Biosci.* 96, 221-238.

Busenberg, S. and C. Castillo-Chavez. (1989). Interaction, pair formation and force of infection terms in sexually transmitted diseases. In (C. Castillo-Chavez, ed.) *Mathematical and Statistical Approaches to AIDS Epidemiology.* Lecture Notes in Biomathematics 83, Springer-Verlag, Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong: 289-300

Busenberg, S. and C. Castillo-Chavez. (1990). On the role of preference in the solution of the mixing problem, and its application to risk- and age- structured epidemic models. (To appear in *IMA J. of Math. Applic. to Med. and Biol.*)

Busenberg, S., K.L. Cooke, and H.R. Thieme. (1989). Interaction of population growth and disease dynamics for HIV/AIDS in a heterogeneous population. (Preprint.)

Castillo-Chavez, C. (1989a). Review of recent models of HIV/AIDS transmission. In (S. A. Levin, T. G. Hallam, and L. J. Gross, eds.) *Applied Mathematical Ecology*, Biomathematics 18, Springer-Verlag, Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong, 253-262.

Castillo-Chavez, C. (ed.) (1989b). *Mathematical and Statistical Approaches to AIDS Epidemiology.* Lecture Notes in Biomathematics 83, Springer-Verlag, Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong.

Castillo-Chavez, C. and S. P. Blythe. (1989). Mixing framework for social/sexual behavior. In (Castillo-Chavez, ed.) *Mathematical and Statistical Approaches to AIDS Epidemiology.* Lecture Notes in Biomathematics 83, Springer-Verlag, Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong: 275-288.

Castillo-Chavez C, Busenberg S, Gerow K. (1990). Pair formation in structured populations. In: *Proceedings of International Conference on Differential Equations and Applications* (W. Schappacher, ed.), Retzhof, Austria 1989. (in press.)

Castillo-Chavez, C., K.L. Cooke, W. Huang, and S.A. Levin. (1989a). On the role of long periods of infectiousness in the dynamics of acquired immunodeficiency syndrome (AIDS). In *Mathematical Approaches to Problems in Resource Management and Epidemiology,* C. Castillo-Chavez, S.A. Levin, and C. Shoemaker (eds.). Lecture Notes in Biomathematics 81, Springer-Verlag, 177-189.

Castillo-Chavez, C., K.L. Cooke, W. Huang, and S.A. Levin. (1989b). One the role of long incubation periods in the dynamics of acquired immunodeficiency syndrome (AIDS), Part 1. Single population models. *J. Math. Biol. 27, 373-398.*

Castillo-Chavez, K.L. Cooke, W. Huang, and S.A. Levin. (1989c). Results on the dynamics for models for the sexual transmission of the human immunodeficiency virus. *Applied Mathematics Letters.* (In press.)

Castillo-Chavez, C., K.L. Cooke, W. Huang, and S.A. Levin. (1989d). On the role of long incubation periods in the dynamics of acquired immunodeficiency syndrome (AIDS), Part 2. Multiple group models. In *Mathematical and Statistical Approaches to AIDS Epidemiology,* C. Castillo-Chavez (ed.). Lecture Notes in Biomathemtics, Springer-Verlag. (This volume.)

Castillo-Chavez, C., H.W. Hethcote, V. Andreasen, S.A. Levin, and W.M. Liu. (1989). Epidemiological models with age structure, proportionate mixing, and cross-immunity. *J. Math. Biol.* 27, 233-258.

Castillo-Chavez, C., H.W. Hethcote, V. Andreasen, S.A. Levin, and W.M. Liu. (1988). Cross-immunity in the dynamics of homogeneous and heterogeneous populations. In *Mathematical Ecology,* L. Gross, T.G. Hallam, and S.A. Levin (eds.). Proceedings of the Autumn Course Research Seminars, Trieste 1986 and World Scientific Publ. Co., Singapore.

Diekmann, O. and S.A. van Gils. (1984). Invariant manifolds for Volterra integral equations of convolution type. *J. Diff. Equa.* 54, 189-190.

Diekmann, O. and R. Montijn. (1982). Prelude to Hopf bifurcation in an epidemic model: analysis of a characteristic equation associated with a nonlinear Volterra integral equation. *J. Math. Biol.* 14, 117-127.

Francis, D.F., P.M. Feorino, J.R. Broderson, H.M. McClure, J.P. Getchell, C.R. McGrath, B. Swenson, J.S. McDougal, E.L. Palmer, A.K. Harrison, F. Barré-Sinoussi, J.C. Chermann, L. Montagnier, J.W. Curran, C.D. Cabradilla, and V.S. Kalyanaraman. (1984). Infection of chimpanzees with lymphadenopathy-associated virus. *Lancet* 2, 1276-1277.

Gripenberg, G. (1980). Periodic solutions to an epidemic model. *J. Math. Biol.* 10, 271-280.

Gripenberg, G. (1981). On some epidemic model. *Appl. Math.* 39, 317-327.

Hale, J.K. and P. Waltman. (1989). Persistence in infinite-dimensional systems. *SIAM J. Math. Anal.* 20, 388-395.

Hethcote, H.W. and S.A. Levin. (1989). Periodicity in epidemiological models. In *Applied Mathematical Ecology*, S.A. Levin, T.G. Hallam, and L.J. Gross (eds.). Biomathematics 18, Springer-Verlag, Heidelberg.

Hethcote, H.W., H.W. Stech, and P. van den Driessche. (1981). Periodicity and stability in epidemic models: a survey. In *Differential Equations and Applications in Ecology, Epidemics and Population problems*, S. Busenberg and K.L. Cooke (eds.). Academic Press, New York.

Hethcote, H.W. and H.R. Thieme. (1985). Stability of the endemic equilibrium in epidemic models with subpopulations. *Math. Biosci.* 75, 205-227.

Hethcote, H.W. and J.A. Yorke. (1984). Gonorrhea, transmission dynamics, and control. Lecture Notes in Biomathematics 56. Springer-Verlag, Berlin, Heidelberg, New York, Tokyo.

Holling, C.S. (1966). The functional response of invertebrate predators to prey density. *Mem. Ent. Soc. Canada* 48.

Huang, W. (1989). Studies in differential equations and applications. Ph. D. Thessis, The Claremont Graduate School (December 1989), Claremont CA.

Huang, W., K. Cooke, and C. Castillo-Chavez. (1990). Stability and befurcation for a multiple group model for the dynamics of HIV/AIDS transmission. (Submitted SIAM J. of Applied Mathematics.)

Hyman, J.M. and E.A. Stanley. (1988). A risk base model for the spread of the AIDS virus. *Math. Biosci.* 90, 415-473.

Hyman, J.M. and E.A. Stanley. (1989). The effects of social mixing patterns on the spread of AIDS. In *Mathematical Approaches to Problems in Resource Management and Epidemiology*, C. Castillo-Chavez, S.A. Levin, and C. Shoemaker (eds.). Lecture Notes in Biomathematics 81, Springer-Verlag, Berlin, Heidelberg, New York and Tokyo.

Lange, J.M.A., D.A. Paul, H.G. Huisman, F. De Wolf, H. Van den Berg, C.A. Roel, S.A. Danner, J. Van der Noordaa, and J. Goudsmit. (1986). Persistent HIV antigenaemia and decline of HIV core antibodies associated with transition to AIDS. *Brit. Med. J.* 293, 1459-1462.

Liu, W-m., H.W. Hethcote, and S.A. Levin. (1987). Dynamical behavior of epidemiological models with nonlinear incidence rates. *J. Math. Biol.* 25(4), 359-380.

Liu, W-m., S.A. Levin, and Y. Iwasa. (1986). Influence of nonlinear incidence rates upon the behavior of SIRS epidemiological models. *J. Math. Biol.* 23, 187-204.

Londen, S.O. (1981). Integral equations of Volterra type. *Mathematics of Biology.* Liguori Editore, Napoli, Italia.

Ludwig D, Walters C. (1985). Are age structured models appropriate for catch-effort data? *Can. J. Fish. Aquat. Sci.* 40, 559-569.

Ludwig D. (1989). Small models are beautiful: efficient estimators are even more beautiful. In (C. Castillo-Chavez, S.A. Levin, and C. Shoemaker, eds.) *Mathematical Approaches to Problems in Resource Management and Epidemiology.* Lecture Notes in Biomathematics 81, Springer-Verlag, Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong, 274-283.

May, R.M. and R.M. Anderson. (1989). The transmission dynamics of human immunodeficiency virus (HIV). *Phil. Trans. R. Soc. London B* 321, 565-607.

May, R.M., R.M. Anderson, and A.R. McLean. (1988). Possible demographic consequences of HIV/AIDS epidemics: I. Assuming HIV infection always leads to AIDS. *Math. Biosci.* 90, 475-506.

May, R.M., R.M. Anderson, and A.R. McLean. (1989). Possible demographic consequences of HIV/AIDS epidemics: II. Assuming HIV infection does not necessarily lead to AIDS. In *Mathematical Approaches to Problems in Resource Management and Epidemiology.* C. Castillo-Chavez, S.A. Levin, and C. Shoemaker (eds). Lecture Notes in Biomathematics 81, Springer-Verlag, Berlin, Heidelberg, New York and Tokyo.

Miller, R.K. (1971). *Nonlinear Volterra Integral Equations.* Benjamin, Menlo Park.

Salahuddin, S.Z., J.E. Groopman, P.D. Markham, M.G. Sarngaharan, R.R. Redfield, M.F. McLane, M. Essex, A. Sliski, and R.C. Gallo. (1984). HTLV-III in symptom-free seronegative persons. *Lancet* 2, 1418-1420.

Sattenspiel, L. and C. Castillo-Chavez. (1990). Environmental context, social interactions, and the spread of HIV. *American Journal of Human Biology,* Volume 2, Number 4 (in press).

Thieme, H.R. (1989a). Semiflows generated by Lipschitz perturbations of non-densely defined operators. I. The theory. (Preprint.)

Thieme, H.R. (1989b). Semiflows generated by Lipschitz perturbations of non-densely defined operators. II. Examples. (Preprint.)

Thieme, H.R. and C. Castillo-Chavez. (1989). On the possible effects of infection-age-dependent infectivity in the dynamics of HIV/AIDS. (Manuscript.)

Webb, G.F. (1985). *Theory of Nonlinear Age-Dependent Population Dynamics.* Marcel Dekker, New York.