ON THE ROLE OF VARIABLE INFECTIVITY IN THE DYNAMICS OF THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC

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Abstract

In this paper, we study the effects of variable infectivity in combination with a variable incubation period on the dynamics of HIV (the human immunodeficiency virus, the etiological agent for AIDS, the acquired immunodeficiency syndrome) in a homogeneously mixing population. In the model discussed here, the functional relationship between mean sexual activity and size of the population is assumed to be nonlinear and to saturate at high population sizes. We identify a basic reproductive number R_0 and show that the disease dies out if $R_0 < 1$. If $R_0 > 1$ the incidence rate converges to or oscillates around a uniquely determined nonzero equilibrium, the stability of which is studied. Our findings provide the analytical basis for exploring the parameter range in which the equilibrium is locally asymptotically stable. Oscillations cannot be excluded in general, and may occur in particular, if the variable infectivity is concentrated at an earlier part of the incubation period. Whether they can also occur for the reported two peaks of infectivity observed in HIV-infected individuals has to be the subject of future numerical investigations.

1. Introduction

Most epidemiological models for the transmission of infectious diseases have assumed that all infectious individuals are equally so. This assumption has proved to be reasonable in the study of the dynamics of communicable diseases such as influenza (see Castillo-Chavez et al. 1988, 1989 and references therein) or in the study of sexually transmitted diseases such as gonorrhea (see Hethcote and Yorke 1984 and references therein).

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The AIDS epidemic, however, has forced researchers to look more closely at the role played by variable infectivity in the transmission of HIV. The experimental work reported in Francis et al. (1984), Salahuddin et al. (1984), and Lange et al. (1986) has begun to clarify the possible shape of the infectivity curve, supporting the hypothesis that there are two infectivity peaks. Once an individual has been infected, s/he experiences a short latency period of about two months, followed by a rise of virus titer (first peak). This period of infectivity is believed to last about six months, after which the individual's virus titer decreases and stays at a reduced level for a long period of time (presumably for an average of about seven to eight years). Finally, about a year before the onset of "full-blown" AIDS, a substantial increase in virus titer is observed (second peak). Though it may be premature to identify virus titer levels with infectivity levels, there is reason enough to study the possible effects of variable infectivity at this stage of affairs in order to clarify how important a good knowledge of the infectivity curve is for the understanding of the dynamics of the epidemic.

Numerical simulations of models that incorporate variable infectivity (see Anderson and May (1989); Hyman and Stanley 1988, 1989; Blythe and Anderson 1988b) demonstrate that the initial (transient) dynamics are very sensitive to the shape and timing of the first infectivity peak. Furthermore, all the published numerical simulations show the same qualitative dynamics, namely a steady approach to a unique endemic equilibrium. Hyman and Stanley's simulations (1988, 1989) indicate the same qualitative dynamics even in the presence of a high degree of heterogeneity in sexual behavior. The mathematical analysis of Castillo-Chavez et al. (1989a, b, c, and this volume) proves that the interactions between a distributed incubation period and a nonlinear mean sexual activity (as a function of population size) are not enough to excite undamped oscillations (at least not by a Hopf Bifurcation). In this paper, we will discuss whether and how these results change if we add variable infectivity results for the special case of a homogeneously mixing homosexual population.

The main body of the paper is organized as follows: Section 2 introduces a model for the sexual transmission of HIV that incorporates age of infection and variable infectivity and shows that this model is well-posed (i.e, its solutions exist and make epidemiological sense). Section 3 discusses the existence of stationary states and disease persistence in connection with the basic reproductive number, while Section 4 presents our stability results as well as the discussion of the possibility of sustained oscillatory behavior. The technical details will be published elsewhere. In the concluding discussion, we briefly review conditions upon which epidemiological models have been found to exhibit sustained oscillations, compare them to our results, and project future work.

2. Model description and well-posedness

In order to mimic HIV dynamics in a homogeneously mixing male homosexual population, we incorporate the following particular ingredients in our mathematical model:

- A nonlinear functional relationship between mean sexual per capita activity and the size of the sexually active population.
- 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 considered here shares the first three features with the models considered by Castillo-Chavez et al. (1989 a, b, c and this volume) though the stratification according to infection age is not explicit there. The fourth feature has been added in order to study the kind of effects infection-age-dependent infectivity produces in combination with the other mechanisms. The model does not include heterogeneities other than infection-age-dependent infectivity and, by restricting itself to the homosexual part of a population which is replenished by constant recruitment, does not reflect the mutual effects of HIV dynamics and the dynamics of the total population (see Anderson and May 1989; Busenberg et al. 1989).

More specifically, we divide the population into three groups: S (uninfected, but susceptible), I (HIV infected), and A (fully developed AIDS symptoms). A-individuals are assumed to be sexually inactive and sexually active individuals (S and I) are supposed to choose their partners at random.

In our model, t denotes time, whereas τ denotes time since the moment of being infected, i.e., infection-age. As time unit we choose the average length of the period of sexual activity for healthy individuals. Individuals are recruited into the sexually active population at a constant rate Λ. We assume that the length of the sexually active period is exponentially distributed such that healthy individuals become sexually inactive at a constant rate μ. As we have chosen the average length $1/\mu$ of the activity period to be 1, $\mu = 1$. Infected individuals with infection-age τ stop being sexually active by force of the disease at a rate $\alpha(\tau)$. So the chance of an individual still being sexually active if he has been 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 such that

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

with $i(t,\tau)$ denoting the infection-age density. The chance that a randomly chosen partner is infected and has infection-age τ is

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

with $T + S + I$ being the size of the sexually active population. We assume that an average susceptible contracts the disease from an infected partner with age of infection τ at a mean risk $\lambda(\tau)$. So the chance of an average susceptible individual being infected at time t (under the condition that he has had a sexual contact at that time) is given by

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

where

$$T = S + I ,$$

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

The mean per capita sexual activity is measured in terms of the mean number of sexual contacts C(T) that an average individual has per unit of time. We assume that this number is a function of the size of the sexually active population: $T = S + I$.

We arrive at the following expression for the incidence rate (number of new cases of infection per unit time):

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

The dynamical model can now be formulated as follows:

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

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

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

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

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

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

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

Though A, the number of individuals with fully developed AIDS symptoms (that are supposed to be too ill to be sexually active), is not assumed to play any further role in the dynamics of the epidemic, we give the formula here because it is one of the epidemiological entities which

can be compared to data. ν denotes the rate at which an individual with fully developed AIDS symptoms dies from the disease.

Note that, in contrast to 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. By assuming that

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

this model, albeit with a different mechanism, takes into account the possibility that some individuals may not develop "full-blown" AIDS. Also, note that this model extends that of Blythe and Anderson (1988b). Furthermore, when this approach is combined with that of Castillo-Chavez et al. (this volume), the resulting model generalizes that of Hyman and Stanley (1988, 1989). We do not write a model of this generality because this paper is concerned with the mathematical analysis of the least complex model. Once we fully understand the dynamics of this model, we will proceed to the analysis of more detailed models.

Throughout this paper, we assume that $\alpha(\tau)$ is a nonnegative measurable function; $\lambda(\tau)$ is a nonnegative integrable function of infection age. C(T) is assumed to be a nondecreasing function of T, where $C(T) > 0$ whenever $T > 0$. Later we will assume that

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

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

There are different ways of handling problem (1),⋯,(6), each of which has its definite advantages. The first approach reformulates (1),⋯,(6) as an abstract ordinary differential equation. See Thieme (1989a, b), in particular Section 7. This approach provides a dynamical system in terms of S and I useful in proving instability and persistence. A second approach consists of integrating (1),⋯,(6) along characteristic lines (see Webb 1985) generating the same dynamical system but in a different way. Thirdly, one can use integration along characteristic lines to reduce the system (1),⋯,(6) to the following set of integral equations:

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

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

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

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

Here we have used the following notation:

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

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

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

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

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

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

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

Note that

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

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

Some of the entities defined above have an intuitive meaning. We mention that $P_1(s) = e^{-s}$ gives the chance a healthy individual has of still being sexually active s time units after having entered the active population. $P_{\alpha+1}(\tau)$ gives the chance an infected individual of infection age τ has of still being sexually active. Fitting 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). Substituting Equations (7), (8), and (9) into equation (10) yields an integral equation which is not of common Volterra type, but has the advantage of being scalar.

From (1) we realize that S(t) remains positive (nonnegative) if S(0) has the corresponding property. We can then easily check, from the various equations, that nonnegativity is preserved under the solution flow. Integrating (2) over τ and combining it with (1) yields the differential inequality:

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

and, as a result, the *a priori* estimate

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

By using the theory found in Webb (1985) or Thieme (1989a, b) 1985) or by applying standard fixed point arguments to (79),$\cdots$,(10), it is shown that the model is well posed (i.e., there is a unique nonnegative solution for given nonnegative initial conditions). Furthermore, the solution depends continuously on the initial conditions, and the functions S, I, W, B are continuous and satisfy the estimate given by (20).

3. Stationary states, the basic reproductive number, and disease persistence

This section begins with a discussion of possible stationary states: the infection-free state and the endemic state. These solutions are important because their feasibility (i.e., existence) is usually intimately connected to the basic reproductive number R_0, (which can be determined in terms of model parameters and is a starting point for the development and evaluation of control measures) 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. In the latter case, there is a unique endemic equilibrium which is locally asymptotically stable for R_0 being slightly larger than 1, but which might lose stability if R_0 increases (see Section 4). Even if possibly unstable, the endemic equilibrium may be an indicator of the severity of the disease because (as we show) the incidence rate fluctuates around the endemic equilibrium value.

We start our analysis by noting that the system (1),⋯,(6) always has the infection-free state

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

In order to determine the existence of the endemic equilibria of (1),⋯,(6) we have to look for solutions of the following algebraic system of equations:

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

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

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

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

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

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

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

Substituting Equation (24) into (25) and dividing by B^* (which is assumed to be positive), we obtain the following:

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

We introduce a dimensionless quantity, namely the fraction of infected individuals,

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

and note from (22), (23), and the second equation in (28) that

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

Fitting these into (28) we arrive at

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

Recalling that C(T) is a monotone nondecreasing function and that $1 > \hat{P}_{\alpha+1}(0)$, we realize that the right-hand side of (31) is a strictly decreasing function of ξ. For $\xi = 0$, the right-hand side of (31) gives the basic reproductive number R_0 of the disease-free population (in its equilibrium):

$$R_0 = C(\Lambda)\hat{Q}(0) . \tag{32}$$

R_0 gives the average number of secondary infections that a typical infectious individual can produce if it is introduced into the disease-free population. From the intermediate value theorem we arrive at the following 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 does not provide us with a relation between the basic reproductive number and the actual disease dynamics. It only provides information regarding the existence of a state in which the disease persists. The next theorem, however, partially connects the basic reproductive number.

Theorem 2. *Let $R_0 < 1$. Then the disease-free equilibrium is globally attractive. In particular we have*

$$B(t), I(t), W(t) \to 0, \quad S(t) \to \Lambda \quad \text{for } t \to \infty .$$

Proof. Applying Fatou's lemma to (9) and (10) and using the estimate (20) and the fact that C is nondecreasing, we obtain

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

This implies the assertion.

In general, it is not possible to obtain a global convergence result if $R_0 > 1$. One can show, however, that if a trajectory is not attracted to the endemic equilibrium, 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* $\tilde{\tau}$ *such that* $\lambda(\tau) = 0$ *for* a.a. $\tau \geq \tilde{\tau}$. *Let*
$$\int_0^{\tau_\dagger} i(0,\tau)d\tau > 0 .$$

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

The proof of this result can be found in Thieme and Castillo-Chavez (1989).

Analogous statements can now be derived for S, I, and W. Note, however, that Theorem 3 does not yet answer the question of whether I, the total number of infected individuals, is bounded away from zero whenever $R_0 > 1$, as well as whether or not this bound depends on the initial conditions. To address this question, it is better to look at the initial formulation (1),$\cdots$,(6) given in a framework suitable for dynamical systems theory. See Hale and Waltman's (1989) theory of persistence and note that part b of our Theorem 3 implies the satisfaction of condition (4.2) of their Theorem 4.1. Combining these observations with Equation (20), we see that the solution flow has a bounded attractor. Using the approach found in Webb (1985, proposition 3.16) we can show also that the solution flow is asymptotically smooth. Furthermore, the boundary flow, i.e., i = 0, is attracted to the infection-free state. Hale and Waltman's result (1989, Theorem 4.2) leads us to the following result:

Theorem 4. *Let* $R_0 > 1$ *and* $\lambda(\tau) \not\equiv 0$, *and let* $\tau_\dagger$ *be the smallest* $\tilde{\tau}$ *such that* $\lambda(\tau) = 0$ *for* a.a. $\tau \geq \tilde{\tau}$. *If*
$$\int_0^{\tau_\dagger} i(0,\tau)d\tau > 0 .$$

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

with ϵ *not depending on the initial conditions.*

Unfortunately, the dynamical systems persistence theory does not give us information as to whether or not B and W are bounded away from zero.

4. Stability of the endemic equilibrium

The stability of the endemic equilibrium is of epidemiological interest for two reasons:

First, in the case of local asymptotic stability, there is some reason to believe that it really is the ultimate state of the epidemic because the disease-free equilibrium is a repellor and there is no third equilibrium. But only global stability could answer this question (e.g., there could be a "blue sky" bifurcation of periodic orbits). Secondly, if the endemic equilibrium is unstable, this strongly suggests undamped oscillations of the disease dynamics around the equilibrium. Recall Theorem 3.2. Intuitively, 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 model formulation (1),⋯,(6) is the most appropriate framework for a precise definition.

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

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

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

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

This implies that

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

(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

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

b) The endemic equilibrium is called *unstable* if 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

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

but

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

To facilitate the discussion of the stability and instability of the endemic equilibria, we switch from the original parameters of the model to the following nondimensional ones:

$$\xi = \frac{I^*}{T^*} = \frac{I^*}{S^* + I^*} , \tag{33}$$

$$\gamma := - \frac{T^* M'(T^*)}{M(T^*)} , \tag{34}$$

and

$$\sigma := \frac{1}{\hat{P}_{\alpha+1}(0)} . \tag{35}$$

ξ, the fraction of infected individuals in the sexually active population, is a very convenient dimensionless parameter satisfying

$$0 < \xi < 1 .$$

Note that all ξ in the interval $0 < \xi < 1$ are feasible (as one can see from (31), (32) by choosing $R_0 > 1$ accordingly) albeit not all are realistic. In addition, we observe that $\frac{1}{\sigma} = P_{\alpha+1}(0)$ denotes the average length of the 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 σ in the interval [1.5, 3]. γ is a dimensionless parameter also, and since $M(T) = \frac{C(T)}{T}$ 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 $C(T) = \beta T$, i.e., M = constant and $\gamma = 0$. This contact law is more appropriate for casual contact diseases like influenza (see Castillo-Chavez et al. 1988, 1989).

b) C = constant

If the number of available partners is large enough and everybody can make more contacts than is practically feasible, this may be a good approximation in some situations. 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 approaches 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. We may take

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

In this case,

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

and γ covers the range from 0 to 1 when T^* covers the range from 0 to ∞. Therefore any value of γ is feasible (as one can see from (30), although not necessarily realistic).

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. If $\gamma = 1$, there is a complete saturation because the number of actual partners hardly changes if the number of available partners does. Thieme and Castillo-Chavez (1989) 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.*

Thus the endemic equilibrium is locally asymptotically stable if the fraction of infected individuals is either low or high, or if the length of the sexually active period of infected individuals is short compared with the length of the sexually active period of the healthy 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. $P_{\alpha+1}$ may be convex (e.g., if the length of the sexually active period of infected individuals is exponentially distributed). This of course, may not be the case.

Conversely, the following holds (see Thieme and Castillo-Chavez 1989):

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

$$\int_0^\infty cos(sy)P_{\alpha+1}(s)ds < 0 \quad \text{for some } y\,. \tag{36}$$

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.*

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 more realistic infectivity distributions (one early and one late peak) induce

instability. An example for which (36) holds is given in Thieme and Castillo-Chavez (1989).

Theorems 5 and 6 follow from studying the roots of the characteristic equation

$$1 = -\frac{\sigma\xi}{1+z}\left(\frac{1}{1-\xi} - \gamma\right) - \xi\gamma\hat{p}(z) + \hat{q}(z) \tag{37}$$

with

$$p(s) = \frac{P_{\alpha+1}}{\hat{P}_{\alpha+1}(0)}\,, \tag{38}$$

and

$$q(s) = \frac{Q(s)}{\hat{Q}(0)}\,. \tag{39}$$

Actually they represent special cases of the following more technical result which follows from linearizing (1),⋯,(6) around the endemic equilibrium and applying Theorem 4.13 in Webb (1985) or Corollary 4.3 and Section 7 in Thieme (1989 a, b) (see Thieme and Castillo-Chavez 1989):

Theorem 7. *a) The endemic equilibrium is locally asymptotically stable if all the roots of the characteristic equation* (37) *have strictly negative real parts.*

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

The characteristic equation can be used to trace the parameters ξ, σ for which the endemic equilibrium changes (if at all) its stability. In this case, the root of the characteristic equation with largest real part crosses the imaginary axis. Setting $z = jy$ with $j = \sqrt{-1}$ being the imaginary unit and separating real and imaginary part of the characteristic equation, we obtain

$$1 - \int_0^\infty \cos(sy)q(s)ds = -\frac{1}{1+y^2}\,\sigma\xi\left(\frac{1}{1-\xi} - \gamma\right) - \xi\gamma\int_0^\infty \cos(sy)p(s)ds \tag{40}$$

$$\int_0^\infty \sin(sy)q(s)ds = \frac{y}{1+y^2}\,\sigma\xi\left(\frac{1}{1-\xi} - \gamma\right) + \xi\gamma\int_0^\infty \sin(sy)p(s)ds\,. \tag{41}$$

We can solve for ξ by multiplying (40) by y and adding the two equations together:

$$\xi = \frac{y\left(1 - \int_0^\infty \cos(sy)q(s)ds\right) + \int_0^\infty \sin(sy)q(s)ds}{\gamma\left(\int_0^\infty \sin(sy)p(s)ds - y\int_0^\infty \cos(sy)p(s)ds\right)}\,. \tag{42}$$

Fitting (42) into (41) makes it possible to solve for σ:

$$\sigma = \frac{\int_0^\infty \sin(sy)q(s)ds - \xi\gamma \int_0^\infty \sin(sy)p(s)ds}{\frac{y}{1+y^2}\left(\frac{\xi}{1-\xi} - \xi\gamma\right)} . \tag{43}$$

Note that only ξ, γ and σ satisfying $0 < \xi < 1$, $0 \leq \gamma \leq 1$ and $\sigma > 1$ make epidemiological sense in the framework of our model. Hence equations (40),$\cdots$,(43) provide the following technical stability result which implies Theorem 5 d, e.

Theorem 8. *The endemic equilibrium is locally asymptotically stable if there is no* $y > 0$ *satisfying the following simultaneously*:

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

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

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

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

$$< \gamma\left(\int_0^\infty \sin(sy)p(s)ds - y\int_0^\infty \cos(sy)p(s)ds\right) .$$

The equations (42), (43) provide a curve $\xi = \xi(y)$, $\sigma = \sigma(y)$, $y > 0$ which traces the parameters ξ, σ for which the characteristic equation has roots on the imaginary axis. From the shape of this curve, it should be possible to decide in which ξ, σ range, for given γ, p and q, the characteristic equation has roots z in the right-half plane implying that the endemic equilibrium is unstable. Again one has to keep in mind that only ξ, σ satsifying $0 < \xi < 1$, $\sigma > 1$ are meaningful, and the realistic parameter range is much narrower than this. It is not too difficult to see from (42), (43) that the endemic equilibrium is unstable for realistic values of ξ, σ if the assumptions of Theorem 5 are satisfied.

5. Discussion and projected future work

The mathematical analysis of epidemic models has identified both mechanisms capable and incapable of generating sustained oscillations (see Hethcote et al. 1981, and Hethcote and Levin 1989 for a survey). One of the most common mechanisms known to be capable of exciting oscillations derives from the return of infectives into a susceptible class (with or without having experienced a period of temporary immunity). Anderson et al. (1981) found,

for a fox rabies model, that sustained oscillations can be generated by the combined effects of a rapid turnover of the fox population and the relatively long latency and the high fatality of fox rabies. Liu et al. (1986, 1987), in their work on influenza, have shown 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. Epidemic models which incorporate time since infection – age of infection – do or do not exhibit sustained oscillations: this depends on the form of the infection-age dependent infectivity curve and the distribution of the length of the infection period (see Diekmann et al. 1982, 1984; Gripenberg 1980, 1981; Hethcote and Thieme 1985).

The mechanisms found to generate sustained oscillations for the models described above do not operate in the case of HIV dynamics. But these models (rabies exempted) are different from any realistic HIV model in one respect: they assume that the disease is essentially nonfatal and the population size is constant. Though our model assumes a constant recruitment rate into the sexually active population, the population size will vary with time due to the disease fatalities. So how the per capita number of sexual contacts $C = C(T)$ depends on the number of sexually active individuals T becomes crucial for the dynamics of the disease. For sexually transmitted diseases, it seems reasonable to assume a saturation effect for partner acquisition, namely that $C(T)$ becomes largely independent of T if the population size T is large.

In our model, the saturation of mean per capita sexual activity interacts with an infection-age-dependent rate (at which infected individuals are sexually inactivated by the disease) and an infection-age-dependent infectivity of infected individuals. We find that the endemic equilibrium can lose its stability (thus generating sustained oscillations) by a rather unique combination of conditions:

(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 largely 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 any early part of the incubation period.

Sustained oscillations can be ruled out if any of the conditions (i), (ii), (iii), or (iv) are not satisfed. But actually, they do not seem unreasonable for a model of HIV transmission. Condition (v) represents our first step towards an analysis of the effects of variable infectivity on HIV dynamics. As sustained oscillations can be ruled out if the infectivity is rather evenly distributed over the activity period (as suggested by the analysis in Castillo-Chavez et al. 1989 a, b, c, and this volume, where it is assumed to be constant), condition (v) emphasizes the possible relevance of variable infectivity for the dynamics of the epidemic. Relying on analytical techniques, so far we have found sustained oscillations only if the infectivity distribution has one (early) peak instead of one early and one late peak. But this is warning enough not to take stability of the endemic equilibrium for granted. Actually, stability will depend on the choice of the model parameters. Future numerical work will attempt to see whether or not undamped oscillations also occur for models with an early and a late infectivity peak. The above mentioned stability criterion will be the analytical basis for numerically exploring the parameter range in which oscillations occur. The ξ, σ curves generated by equations (42) and (43) will help to find the boundary of the ξ, σ region within which (if at all) the endemic equilibrium is unstable. This procedure has to be repeated for different choices of γ, p and q producing different curves, of course. A saturation index $\gamma = 1$ will be a reasonable first choice (see our discussion in the previous section). Whether the endemic equilibrium is unstable in a realistic ξ, σ range will crucially depend on the shape of p, q as we recognize from (i) and (v). The shape of p, q for which the endemic equilibrium is unstable may or may not be realistic. Our analytic results so far suggest instability if the age-infected infectivity is concentrated at an early part of the incubation period. The numerical simulations of models that incorporate variable infectivity by Anderson and May (1989), Hyman and Stanley (1988, 1989), Blythe and Anderson (1988b) rather suggest that the endemic equilibrium is stable for realistic infectivity functions.

Here further investigations are needed. These can be done much easier and more effectively by first exploring the parameter range of possible sustained oscillations using the ξ, σ curves just described. Although simulations of the full model are indispensable for showing whether the amplitudes of the oscillations are large enough to be epidemiologically significant, 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 it has to be totally discarded as some kind of measure of the severity of the disease when unstable. We have shown, however, that the incidence rate either converges to its (uniquely determined) endemic equilibrium or fluctuates around it (provided that an endemic equilibrium exists). This at least gives some information. It would be more useful to know whether the time averages converge (as time tends to infinity) towards the endemic equilibrium. This stronger statement may or may not be true.

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