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The Invasion Problem for the HIV Infection in a Homosexual Community

Hisashi Inaba (稲葉　寿)
Institute of Population Problems

1. Introduction

During the past decade, human immunodeficiency virus (HIV) disease has become one of the major public health problems in the world. In many countries AIDS is already a major cause of death, it is predicted that it will soon become so in many others [28]. On the other hand, the HIV/AIDS dynamics provides a large number of new problems to mathematicians, biologists and epidemiologists, since it has many features different from traditional infectious diseases. Hence the study of HIV/AIDS has stimulated the recent developments of mathematical epidemiology. In the following we briefly discuss the characters which should be taken into account in modeling the HIV dynamics.

It is well known that HIV virus has the long incubation and infectious period (its longest estimate is about 8-10 years). Moreover during that period, the infectivity of infected people is varying depending on the time since infection (see [4][25]). Accordingly, the time scale of HIV transmission is so long that demographic change of the host population could affect the transmission process. On the other hand, the death rate caused by AIDS is too high to be neglected, so the present of HIV affects the demographic structure (total size, age-structure, growth rate, etc.) of the host population. In a word, there is true interaction between demography and epidemics.

Next there exist various kind of risk groups for the HIV infection. HIV virus is transmitted by homo- or hetero-sexual intercourses, needle sharing between drug abusers, blood transfusion, etc. Therefore, in the real, the susceptible population is composed of subgroups, each of which has a different susceptibility to the transmission of HIV virus. Even in a subgroup, individuals can be distinguished by the degree of risky behavior (see risk-based models [9][10][16][20]). Moreover the age-structure of the host population would play an important role, since social or sexual behavior of people heavily depend on their age.

Since the whole dynamics of HIV/AIDS is so complex that we could not analyse it all at once. The reader interesting in the recent developments of modeling HIV dynamics may refer to [6][7][16][19]. In this paper, we simply consider an age-structured population model for the HIV infection in a homosexual community. Of our concern here is to study the <u>invasion problem</u> of the HIV infection. That is, the main problem that we are interested in here is to find the <u>basic reproduction number</u> R_0 such that the introduction of some infectives into the susceptible population triggers an epidemic when $R_0>1$, and no epidemic occurs when $R_0<1$. In other words, the disease-free steady state is stable if R_0 is less than one and becomes unstable if R_0 exceeds unity. For this purpose, it is sufficient to deal with the linearized equation around the disease-free steady state. That is, in the initial phase of the epidemic, we can ignore the fact that the density of susceptibles decreases due to the infection process. This type of argument has been systematically developed by Diekmann and his collaborators in order to calculate R_0 (see [11][12][13]).

2. An Age-Structured Model for the HIV infection in a Homosexual Community

In the following, we consider an age-structured population of homosexual men with a constant immigration. For simplicity, individuals are assumed to be homogeneous with respect to their sexual activity. However, note that the following argument can be applied to the risk-based model without any essential modification. Individuals have sexual contacts with each other at random and the duration of a partnership is negligibly short. We divide the homosexual population into three groups: U (uninfected but susceptible), I (HIV infected) and A (fully developed AIDS symptoms). We do not introduce a latent class, since the latent period of AIDS is very short in compare with its long incubation period. Thus all of I-individuals are infectious. A-individuals are assumed to be sexually inactive, because they are too ill to be active.

Let $U(t,a)$ be the age-density of the susceptibles at time t. Let τ be the time since an individual has entered into I-population or A-population. Let $I(t,a,\tau)$ and $A(t,a,\tau)$ be the age-duration-distributions of respectively infected population and AIDS population at time t. Let $\mu(a)$ be the age-specific natural death rate (or the rate of terminating sexual life), $\delta(a,\tau)$ the death rate due to AIDS, $\gamma(a,\tau)$ the rate of developing AIDS, $f(a)$ the age-density of immigrants and let $\lambda(t,a)$ be the infection rate (or the force of infection). Then the dynamics of the population are governed by the following system:

$$(\partial_t+\partial_a)U(t,a)=-(\mu(a)+\lambda(t,a))U(t,a)+f(a), \quad (2.1a)$$

$$(\partial_t+\partial_a+\partial_\tau)I(t,a,\tau)=-(\mu(a)+\gamma(a,\tau))I(t,a,\tau), \quad (2.1b)$$

$$(\partial_t+\partial_a+\partial_\tau)A(t,a,\tau)=-(\mu(a)+\delta(a,\tau))A(t,a,\tau), \quad (2.1c)$$

$$U(t,0)=0, \quad (2.1d)$$

$$I(t,a,0)=\lambda(t,a)U(t,a), \quad (2.1e)$$

$$A(t,a,0)=\int_0^a \gamma(a,\tau)I(t,a,\tau)d\tau, \quad (2.1f)$$

The force of infection $\lambda(t,a)$ is assumed to have the following expression:

$$\lambda(t,a)=\int_0^\omega\int_0^\zeta \beta(a,\zeta,\tau)\chi(a,\zeta,N(t,*))\frac{I(t,\zeta,\tau)}{N(t,\zeta)}d\tau d\zeta, \quad (2.2)$$

where $N(t,a)$ is the age-density of sexually active population at time t:

$$N(t,a)=U(t,a)+\int_0^a I(t,a,\tau)d\tau, \quad (2.3)$$

and $\beta(a,\zeta,\tau)$ is the transmission probability that a susceptible person of age a becomes infected by sexual contact with an infected partner of age ζ and duration τ. The mating function $\chi(a,\zeta,N(t,*))$ depending on the population density $N(t,*)$ denotes the probability that an individual at age a has a partner aged ζ at time t. From its physical meaning, the mating function must satisfy the following condition:

$$N(t,a)\chi(a,\zeta,N(t,*))=N(t,\zeta)\chi(\zeta,a,N(t,*)). \qquad (2.4)$$

Under appropriate conditions, existence and uniqueness of solutions could be shown by using integral equation method [27][29] or semigroup approach [26].

Here we mainly consider the initial invasion process of HIV into the susceptibles. First it is easily observed that system (2.1) has a disease-free steady state

$$U^*(a)=\int_0^a f(\sigma)\frac{\ell(a)}{\ell(\sigma)}d\sigma, \quad I^*(a,\tau)=0, \qquad (2.5)$$

where $\ell(a)$ is the survival function defined by

$$\ell(a):=\exp(-\int_0^a \mu(\sigma)d\sigma).$$

Let y be the age at which an infected individual has entered into the infectious class. Let us define a new function $J(t,\tau,y)$ by $J(t,\tau,y):=I(t,y+\tau,\tau)$. Then J is the density of infecteds at time t and duration τ since infection by age at infection y. Using the function J, we can formulate the linearized equation describing the initial dynamics of infected population:

$$(\partial_t+\partial_\tau)J(t,\tau,y)=-(\mu(y+\tau)+\gamma(y+\tau,\tau))J(t,\tau,y), \qquad (2.6a)$$

$$J(t,0,y)=\int_0^\omega\int_\tau^\omega \beta(y,\zeta,\tau)\chi(\zeta,y,U^*)J(t,\tau,\zeta-\tau)d\zeta d\tau, \qquad (2.6b)$$

$$J(0,\tau,y)=J_0(\tau,y), \qquad (2.6c)$$

where J_0 is the initial data and we have used the relation $U^*(y)\chi(y,\zeta,U^*)=U^*(\zeta)\chi(\zeta,y,U^*)$. From (2.6a), we obtain

$$J(t,\tau,y)=J(t-\tau,0,y)\frac{\ell(y+\tau)}{\ell(y)}\exp\left(-\int_0^\tau \gamma(y+s,s)ds\right) \quad \text{for } t>\tau, \tag{2.7}$$

$$=J_0(\tau-t,y)\frac{\ell(y+\tau-t)}{\ell(y)}\exp\left(-\int_0^t \gamma(y+\tau-t+s,\tau-t+s)ds\right) \quad \text{for } \tau\geq t.$$

Therefore we know that the behavior of $J(t,0,y)$ determine the initial dynamics of the HIV epidemic. From (2.6b) and (2.7), we arrive at the following integral equation for the boundary value $J(t,0,y)$:

$$J(t,0,y)=G(t,y)+\int_0^t\int_\tau^\omega \beta(y,\zeta,\tau)\chi(\zeta,y,U^*)\frac{\ell(\zeta)}{\ell(\zeta-\tau)}\Gamma(\zeta,\tau)J(t-\tau,0,\zeta-\tau)d\zeta d\tau \tag{2.8}$$

where

$$\Gamma(\zeta,\tau):=\exp\left(-\int_0^\tau \gamma(\zeta-\tau+s,s)ds\right),$$

$$G(t,y):=\int_t^\omega\int_\tau^\omega \beta(y,\zeta,\tau)\chi(\zeta,y,U^*)\frac{\ell(\zeta)}{\ell(\zeta-\tau)}\frac{\Gamma(\zeta,\tau)}{\Gamma(\zeta-t,\tau-t)}J_0(\tau-t,\zeta-\tau)d\zeta d\tau.$$

Define a L^1-valued function $B(t)$ by $B(t)(*):=J(t,0,*)$ and let $\Pi(\tau)$ be a linear positive operator from $L^1(0,\omega)$ into $L^1(0,\omega)$ as

$$(\Pi(\tau)\psi)(y):=\int_\tau^\omega \beta(y,\zeta,\tau)\chi(\zeta,y,U^*)\frac{\ell(\zeta)}{\ell(\zeta-\tau)}\Gamma(\zeta,\tau)\psi(\zeta-\tau)d\zeta. \tag{2.9}$$

Then we can rewrite (2.8) as an abstract Volterra integral equation in L^1:

$$B(t)=G(t)+\int_0^t \Pi(\tau)B(t-\tau)d\tau, \quad t>0, \tag{2.10}$$

where we adopt the convention such as $G(t)(*) := G(t,*)$ for $t \le \omega$; $G(t)=0$ for $t>\omega$; $\Pi(\tau)=0$ for $\tau>\omega$. It is easily seen that (2.10) has a unique continuous solution for $t>0$ and the solution is positive with respect to positive initial data.

3. Threshold Condition

The behavior of the solution $B(t)$ can be investigated by the Laplace tranformation technique [15]. The Laplace transformation of a vector-valued function $f(t)$, $0 \le t < \infty$ is defined by

$$\hat{f}(\lambda) = \int_0^\infty e^{-\lambda t} f(t)\,dt,$$

whenever the integral is defined with respect to the norm topology. Using a priori estimate for the growth bound of $B(t)$, we know that Laplace transform of $B(t)$ exists for complex values λ when $\mathrm{Re}\lambda$ is sufficiently large. Since Laplace transforms of $G(t)$ and $\Pi(\tau)$ exist for all complex values λ, we obtain

$$\hat{B}(\lambda) = \hat{G}(\lambda) + \hat{\Pi}(\lambda)\hat{B}(\lambda), \tag{3.1}$$

for complex λ with large real part. Let $\Lambda := \{\lambda \in C:\ (I-\hat{\Pi}(\lambda))^{-1}$ does not exist$\}$. Then it follows that

$$\hat{B}(\lambda) = (I-\hat{\Pi}(\lambda))^{-1}\hat{G}(\lambda) \quad \text{for } \lambda \in C \setminus \Lambda. \tag{3.2}$$

Since $I-\hat{\Pi}(\lambda)$ is invertible for λ with large real part, $B(t)$ can be expressed by the inverse Laplace transform and the behavior of $B(t)$ is determined by the distribution of singular points Λ. In particuler, if there exists a real dominant singuler point λ_0, the solution $B(t)$ would show the exponential growth as time evolves. Heijman [15] has shown that positive operator theory is useful to show the existence of such a dominant singuler point.

In the following we briefly sketch the way how to prove the existence of the dominant singuler point. First observe that $\Lambda \subset \{\lambda \in C: 1 \in \sigma(\hat{\Pi}(\lambda))\}$. In particular, if the operator $\hat{\Pi}(\lambda)$ is compact for all λ, $(I-\hat{\Pi}(\lambda))^{-1}$ is a meromorphic function of λ and Λ is composed of its poles and $\Lambda=\{\lambda \in C: 1 \in P_\sigma(\hat{\Pi}(\lambda))\}$ where $P_\sigma(A)$ denotes the point spectrum of an operator A. By changing the order of integral, we have the following expression for the operator $\hat{\Pi}(\lambda)$:

$$(\hat{\Pi}(\lambda)\psi)(y)=\int_0^\omega \Phi_\lambda(y,z)\psi(z)dz, \tag{3.3a}$$

$$\Phi_\lambda(y,z):=\int_z^\omega e^{-\lambda(\zeta-z)}\beta(y,\zeta,\zeta-z)\chi(\zeta,y,U^*)\frac{\ell(\zeta)}{\ell(z)}\Gamma(\zeta,\zeta-z)d\zeta. \tag{3.3b}$$

On the real axis, $\hat{\Pi}(\lambda)$ is a positive operator and its spectral radius $r(\hat{\Pi}(\lambda))$ is decreasing for real λ. If $\hat{\Pi}(\lambda)$ is compact, its nonzero spectral radius is an eigenvalue and so the roots of the equation $r(\hat{\Pi}(\lambda))=1$ are the singuler points. It is clear that if $r(\hat{\Pi}(\lambda))$, $\lambda \in R$ is strictly decreasing from $+\infty$ to zero, there exists only one real root λ_0. If Perron-Frobenius type theorem holds for $\hat{\Pi}(\lambda)$, $\lambda \in R$, it can be shown that λ_0 is dominant, that is, the element of Λ with the largest real part (see [15] Theorem 6.13 or [18] Lemma 5.6). For example, though we ommit the proof, the following assumption is sufficient to justify the above rough argument:

Assumption 3.1: 1) The operator $\hat{\Pi}(\lambda)$ is compact for all $\lambda \in C$.

2) For $\lambda \in R$, there exist a strictly positive functional F_λ and a quasi-interior point e with respect to natural cone L^1_+ such that

$$\hat{\Pi}(\lambda)\psi \geq \langle F_\lambda, \psi\rangle e, \quad \lim_{\lambda\to-\infty}\langle F_\lambda, e\rangle = +\infty.$$

Using the above condition, according to the lines in [18], the reader may easily give a proof to the following lemma:

Lemma 3.2: Under the assumption 3.1, the following holds:

1) $\Lambda=\{\lambda \in C: 1 \in P_\sigma(\hat{\Pi}(\lambda))\}$.

2) The operator $\hat{\Pi}(\lambda)$ is nonsupporting for all $\lambda \in R$.

3) The spectral radius $r(\hat{\Pi}(\lambda))$, $\lambda \in R$ is strictly decreasing from $+\infty$ to zero.

4) There exists a unique $\lambda_0 \in R \cap \Lambda$ such that $r(\hat{\Pi}(\lambda_0))=1$ and $\lambda_0>0$ if $r(\hat{\Pi}(0))>1$; $\lambda_0=0$ if $r(\hat{\Pi}(0))=1$; $\lambda_0<0$ if $r(\hat{\Pi}(0))<1$.

5) $\lambda_0>\sup\{\mathrm{Re}\lambda: \lambda \in \Lambda-\{\lambda_0\}\}$.

Let E_+ be a cone of a Banach space E. A positive operator T is called <u>nonsupporting</u> if and only if for every pair $\psi \in E_+-\{0\}$, $F \in E^*_+-\{0\}$ there exists a positive integer $p=p(\psi,F)$ such that $\langle F,T^n\psi\rangle>0$ for all $n\geq p$. For the nonsupporting property of a positive operator, the reader may refer to Marek [22] and

Sawashima [24]. Nonsupporting operator on a Banach space with a cone is a natural extension of the idea of primitive matrices to infinite dimensional spaces. In particuler, it can be shown that Perron-Frobenius type theorem holds for the nonsupporting compact operator on a Banach space with a total cone. From the above lemma, it follows immediately that

Proposition 3.3: Under the assumption 3.1, the disease-free steady state is locally stable if $r(\hat{\Pi}(0))<1$ and locally unstable if $r(\hat{\Pi}(0))>1$. That is, the spectral radius $r(\hat{\Pi}(0))$ is the basic reproduction number for the HIV epidemic.

From its biological interpretation, the positive operator $\hat{\Pi}(0)$ is called the next-generation operator [11]. In fact, if Ψ is the age-distribution of newly infected individuals at a moment, $\hat{\Pi}(0)\Psi$ gives exactly the same for the next generation produced by Ψ.

4. Discussion

The characterization of the basic reproduction number by proposition 3.1 is still insufficient. In fact, for many traditional models for infectious diseases (see [18]), we can often prove that there exists a non-trivial (endemic) steady state if and only if the basic reproduction number exceeds unity, otherwise there is only trivial steady state; that is, stationary bifurcation occurs at $R_0=1$. For our model (2.1), though it is possible to show that there is at least one endemic steady state if $r(\hat{\Pi}(0))>1$, we have not yet known what kind of bifurcation can occur as R_0 increases. For the global dynamics of system (2.1), there remains a lot of open problems (number of steady states, their stability, etc.).

Although we so far consider a one-sex model, the transmission of HIV by heterosexual contacts has increasingly become important in the worldwide spread of HIV. As far as we assume random mating and neglect the persistence of couples, it is not difficult to extend our model to a two-sex model. Serious difficulties appear when we intend to take into account the fact that individuals form partnerships for non-negligible periods of time. In this case, even to write down basic nonlinear equations is not easy task (see [6][7][8]) and so little is known for its dynamics. However, if we concentrate to the invasion problem, instead of linearizing a full nonlinear two-sex model, we can again directly start from constructing a linear model that is only used to describe the initial phase for the spread of the HIV infection (see [13][21]).

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