The Exponential Phase of HIV/AIDS Epidemic in Japan

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Abstract
In this paper, our purpose is to develop a method to estimate the number of HIV infecteds in the exponential phase and to apply it to the Japanese AIDS data. First based on the Japanese AIDS surveillance data, we observe that the cumulated AIDS incidence in Japan has been growing exponentially. Using our calculation method, we conclude that the number of infected individuals is about from 10 times to 17 times as much as the size of cumulated AIDS incidence in Japan. Next we briefly sketch relations between the basic reproduction ratio $R_0$ and the Malthusian parameter for HIV infecteds, which are both used to measure the reproductivity of HIV infecteds. The effects of any HIV preventive policy could be estimated by its influences on the reproductivity parameters.

1 Introduction
During the past decade, human immunodeficiency virus (HIV) disease has been slowly but steadily spreading in Japan. At the end of June 1994, the cumulated AIDS incidence reported to the AIDS surveillance committee in Japan is 764 and the cumulated number of HIV infecteds has reached to 3389.

It is well known that HIV has the long incubation and infectious period (the longest estimate for the average incubation period is about from 8 to 10 years), during which infected individuals have little subjective symptom. Since the AIDS surveillance system catches only infected individuals who has taken a serologic test spontaneously, the major part of infecteds could not be reported to the surveillance committee and the gap between the reported HIV/AIDS incidence and the hidden prevalence of HIV could be so large.
In the initial stage of HIV invasion into a host population, the HIV infected population would behave as a Malthusian population, that is, the infection rate (the number of newly infecteds per unit time) grows exponentially, since the supply of susceptibles are sufficient, density-dependent limitations have not yet come to be significant and people have not yet altered their behavior. Such an early phase of the epidemic is called as the exponential phase (Gonzales, et al. 1988). Though the exponential phase of HIV infection would be over in Western European countries, United States and Africa, Asian countries and other areas are now confronting with this phase. In general the exponential phase shows us the intrinsic reproductivity of infected populations under a given socio-environmental situation, which would heavily influence the future course of the epidemic. Hence there are still every reasons for us to pay special attention to the exponential phase not only from practical purpose but also from theoretical point of view.

In this paper, we develop an estimation method for HIV prevalence in the exponential phase and apply it to Japanese data. First we examine the characteristics of HIV/AIDS in Japan based on the surveillance data. Next we develop the estimation procedure under the assumption of exponential growth and use it to estimate the number of HIV infecteds in Japan. Finally we consider relations between the basic reproduction ratio $R_0$ and the Malthusian parameter, which are used to measure the reproductivity of HIV infecteds. The effects of any HIV preventive policy could be estimated by its influences on the reproductivity parameters.

2 Exponential Phase of HIV/AIDS Epidemic in Japan

The first AIDS case in Japan was reported in 1985 and the surveillance system was established in May 1989. Since then the number of AIDS incidence and HIV infection has been reported every two months. The cumulative number of HIV infecteds in Japan is 3389 at the end of June 1994 and it is 0.027 per mill to the total population. The annual average (exponential) growth rate of cumulated number of reported HIV cases (which includes AIDS cases, but excluding cases by the contaminated blood products) is about 47 per cent and so its doubling time is less than 18 months (see Fig.1). Hence the HIV prevalence in Japan estimated from the surveillance report is still about one per cent to the average HIV prevalence in the world calculated based on the estimation by WHO.

Age distribution of HIV infecteds in Japan shows a sharp contrast between male and female. 85 per cent of male infecteds distributes uniformly from 20th to 40th, on the other hand 74 per cent of female infecteds concentrates to 20th (Table 1).

For the reported cases of AIDS, we could assume that the reported number is
Table 1: Age distribution by sex for HIV/AIDS cases reported between May 1989 and the end of June 1994 in Japan

<table>
<thead>
<tr>
<th>age groups</th>
<th>number of cases</th>
<th>percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>male</td>
<td>female</td>
</tr>
<tr>
<td>-20</td>
<td>10</td>
<td>83</td>
</tr>
<tr>
<td>20-29</td>
<td>215</td>
<td>514</td>
</tr>
<tr>
<td>30-39</td>
<td>260</td>
<td>64</td>
</tr>
<tr>
<td>40-49</td>
<td>196</td>
<td>17</td>
</tr>
<tr>
<td>50+</td>
<td>104</td>
<td>9</td>
</tr>
<tr>
<td>unknown</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>total</td>
<td>786</td>
<td>692</td>
</tr>
</tbody>
</table>

near equal to the actual number of AIDS cases, because nowadays the definition and diagnosis of AIDS has been established in Japan. Of course, it would be reasonable to assume that there would be underreporting for AIDS cases, we have not yet had any clear studies for underreporting. Since our purpose is to establish a calculation method, here we simply assume the completeness of AIDS reporting. If we exclude the cases infected by the contaminated blood products (which cases are excluded from the surveillance report, because the contaminated blood products no longer becomes a route of infection), since May 1989 the reported cumulative number of AIDS cases in Japan clearly shows the exponential growth. If we apply a log-linear model for the cumulative AIDS incidence as

\[
\log_e[\text{cumulated AIDS incidence at time } t] = y + xt,
\]

(2.1)

where \( t \) is the time (years) since May 1989, then its annual (exponential) growth rate given by \( x \) is 36 per cent \( (R^2 = 0.998) \) and so the doubling time is 23 months (Fig.2). This annual growth rate is stable in the last three years.

Even if we see the growth trends by cause of infection, we can again observe the clear trends of exponential growth. For example, the reported cumulative AIDS cases by heterosexual contact is growing exponentially with 41 per cent per year and the reported cumulative AIDS cases by male homosexual contact is growing exponentially with 22 per cent per year (Table 2). So the ratio of the cases by heterosexual contact to the total HIV/AIDS cases is growing continuously, it has reached 46 per cent of the cumulative number of HIV cases and 33 per cent of the cumulative number of AIDS cases. That is, heterosexual contact would be the main route of infection in the HIV/AIDS epidemic of Japan.
Table 2: The regression equation to $\log_e$[cumulated AIDS incidence] in Japan: 
$t$ denotes years passed since May 1989.

<table>
<thead>
<tr>
<th>infection route</th>
<th>the regression equation</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>total</td>
<td>$3.893 + 0.359t$</td>
<td>0.998</td>
</tr>
<tr>
<td>heterosexual contact</td>
<td>$2.463 + 0.412t$</td>
<td>0.989</td>
</tr>
<tr>
<td>male homosexual contact</td>
<td>$3.420 + 0.223t$</td>
<td>0.988</td>
</tr>
<tr>
<td>unknown</td>
<td>$1.400 + 0.621t$</td>
<td>0.977</td>
</tr>
</tbody>
</table>

3 The estimation of the number of HIV infecteds

In this section we first formulate a model for HIV/AIDS epidemic in the early stage of the epidemic in a closed entirely susceptible population. In this early phase, we assume that the epidemic is in the exponential phase, that is, the infection rate is growing exponentially and as a result the number of virus carriers and cumulative AIDS incidence also show exponential growth. Among the Western European countries, the exponential phase was observed in the late 80th. The typical extent of the exponential phase is thought to be the first 3-6 years of the visible AIDS epidemic (Gonzalez, et al. 1988).

In the following, we consider a closed entirely susceptible population and assume that a few HIV infecteds have invaded into the population. Let $i(t, \tau)$ be the density of infected population at time $t$ and disease-age (duration since infection) $\tau$. Let $I(t)$ be the number of HIV infecteds at time $t$. Then it follows that

$$I(t) = \int_0^\infty i(t, \tau) d\tau. \quad (3.1)$$

Let $\gamma^*(\tau)$ be the force of developing AIDS (or instantaneous incidence rate) at disease-age $\tau$ and let $B(t)$ be the number of newly infected individuals per unit time (infection rate) at time $t$. If we disregard the natural death rate, we obtain that

$$i(t, \tau) = (\alpha\ell^*(\tau) + (1 - \alpha))B(t - \tau), \quad (3.2)$$

where $\alpha$ denotes the proportion that newly infected individual will eventually develop AIDS and $\ell^*(\tau)$ is the probability that an infected individual who eventually develops AIDS stays in the infectious status at disease-age $\tau$ given by

$$\ell^*(\tau) = \exp \left( - \int_0^\tau \gamma^*(\sigma) d\sigma \right). \quad (3.3)$$
Let $D(t)$ be the cumulative AIDS incidence to time $t$, let $A(t)$ be the number of AIDS incidence at time $t$ and let $F(\tau)$ be the incubation period distribution given by

$$F(\tau) = \alpha(1 - \ell^*(\tau)).$$  \hspace{1cm} (3.4)

Then it is easily seen that the following relations hold:

$$D(t) = \int_0^\infty F(\tau)B(t - \tau)d\tau, \hspace{1cm} (3.5)$$

$$A(t) = \frac{dD(t)}{dt} = \int_0^\infty F'(\tau)B(t - \tau)d\tau. \hspace{1cm} (3.6)$$

The famous back-calculation is the method to estimate unknown $B(t)$ based on the knowledge of $F(\tau)$ and $D(t)$ by using relation (3.5). However in general the estimate for the infection rate by the back calculation method is very sensitive to changes in the incubation period distribution $F(\tau)$ (Brookmeyer and Gail 1994). In fact it is clear that from (3.5) the most recent infection rate could not affect $D(t)$ because $F(0) = 0$ and $F(\tau)$ is very small near to $\tau = 0$. Moreover to identify $F(\tau)$ itself is not easy task, because it could be different among risk groups and could vary with any progress of medical treatment. Since the observed $D(t)$ always cannot avoid stochastic or statistical uncertainty, several kind of estimates for the infection rate $B(t)$ could be consistent with the observed $D(t)$. That is, the back calculation is an ill-posed problem.

Here we a priori assume that the epidemic is in the exponential phase, that is, the infection rate is given by the exponential law as

$$B(t) = B(0)e^{rt}. \hspace{1cm} (3.7)$$

As far as we focus on the early stage of the epidemic, to assume the exponential law for the infection rate is most reasonable, because it is consistent with the exponential growth of observed cumulative AIDS incidence, it is also consistent with the prediction by theoretical epidemic models and it makes calculations much easier.

Under the assumption (3.7), it is easy to verify the following relations:

$$a := \frac{A(t)}{I(t)} = \frac{r\alpha \kappa}{r + (1 - \alpha)\kappa}, \hspace{1cm} (3.8)$$

$$b := \frac{B(t)}{I(t)} = \frac{r(r + \kappa)}{r + (1 - \alpha)\kappa}, \hspace{1cm} (3.9)$$

$$c := \frac{D(t)}{I(t)} = \frac{\alpha \kappa}{r + (1 - \alpha)\kappa}, \hspace{1cm} (3.10)$$

5
where $\kappa$ is the crude incidence rate of AIDS in HIV infecteds who eventually develop AIDS given by

$$
\kappa := \frac{\int_0^\infty e^{-r\sigma} \ell^*(\sigma) \gamma^*(\sigma) d\sigma}{\int_0^\infty e^{-r\sigma} \ell^*(\sigma) d\sigma}.
$$
(3.11)

The parameter $b$ denotes the crude birth rate of newly infecteds and $a$ is the crude rate of developing AIDS. Hence if $\alpha = 1$, we have $a = \kappa$ and $r = b - a$.

Under the exponential growth, the disease-age distribution of HIV infecteds is time invariant and given by

$$
\frac{i(t, \tau)}{I(t)} = be^{-r\tau} (1 - F(\tau)).
$$
(3.12)

From (3.10), we obtain that

$$
I(t) = \frac{D(t)}{c} = \left[ \frac{1}{\alpha} \left( \frac{r}{\kappa} + 1 \right) - 1 \right] D(t),
$$
(3.13)

Hence if we can estimate $\kappa$ and $\alpha$, the size of HIV infecteds $I(t)$ could be estimated from (3.13) based on the knowledge of $D(t)$. The ratio $I/D$ grows rapidly with the Malthusian parameter $r$. Fig.3 shows the response of the ratio $I/D$ to the Malthusian parameter $r$.

Moreover it should be noted that the incidence rate $\kappa$ is sensitive to the choice of the survival rate $\ell^*(\tau)$. For example, if we could assume that the probability density $\ell^*(\tau) \gamma^*(\tau)$ concentrates around the average incubation period, a useful approximation formula for $\kappa$ can be derived as follows (Inaba 1994).

$$
\frac{r}{\kappa} \approx \frac{e^{r e_0^*}}{1 + \frac{r e_0^*}{2}} - 1,
$$
(3.14)

where $e_0^*$ is the average incubation period given by

$$
e_0^* := \int_0^\infty \ell^*(\tau) d\tau,
$$
(3.15)

and $\sigma^2$ denotes the dispersion of the probability density of developing AIDS given by

$$
\sigma^2 := \int_0^\infty (\tau - e_0^*)^2 \ell^*(\tau) \gamma^*(\tau) d\tau.
$$
(3.16)

From (3.14), it is clear that the incidence rate $\kappa$ is smaller (i.e., the ratio $r/\kappa$ is larger) if the average incubation period is longer and the dispersion of the incubation period distribution is smaller. In particular, the ratio $r/\kappa$ is very sensitive to the average incubation period $e_0^*$, hence the estimate of incubation period is most crucial point that influences the estimation result for the size of infecteds.
Table 3: Basic parameters: \( r = 0.359, \alpha = 0.9 \).

<table>
<thead>
<tr>
<th>model type</th>
<th>survival function</th>
<th>( e^*_0 )</th>
<th>( \kappa )</th>
<th>( a )</th>
<th>( b )</th>
<th>( c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>( \ell(\tau) = \exp(-0.004\tau^2 + 0.359) )</td>
<td>8.5</td>
<td>0.03895</td>
<td>0.03468</td>
<td>0.39368</td>
<td>0.09660</td>
</tr>
<tr>
<td>II</td>
<td>( \ell(\tau) = \exp(-0.0021\tau^2 + 0.65) )</td>
<td>9</td>
<td>0.03151</td>
<td>0.02811</td>
<td>0.38711</td>
<td>0.07831</td>
</tr>
<tr>
<td>III</td>
<td>( \ell(\tau) = \exp(-0.0021\tau^2 + 0.516) )</td>
<td>10</td>
<td>0.02592</td>
<td>0.02316</td>
<td>0.38216</td>
<td>0.06453</td>
</tr>
<tr>
<td>IV</td>
<td>( \ell(\tau) = \frac{1}{1 + (0.1\tau)^3} )</td>
<td>11</td>
<td>0.02423</td>
<td>0.02166</td>
<td>0.38066</td>
<td>0.06033</td>
</tr>
</tbody>
</table>

4 Applications to the Japanese exponential phase

As is shown in Table 2, excluding AIDS incidence caused by contaminated blood products, the cumulative AIDS incidence from May 1989 to the end of June 1994 in Japan is well approximated by the exponential function, that is, the natural logarithm of \( D(t) \) has a linear pattern as

\[
\log_e D(t) \approx 3.89 + 0.359t, \quad (4.1)
\]

where \( t \) denotes years passed since May 1989 and \( R^2 = 0.998 \). Fig.4 shows the regression coefficient calculated by the cumulated AIDS incidence data from May 1989 to the time \( t \) (years passed since May 1989) in Japan. We can observe that the regression coefficient converges to about 0.36 during the last three years. Hence the extrapolation for several years of future by the exponential law could be reliable.

If we assume that the percentage of long-term survivor is 10 per cent (\( \alpha = 0.9 \)), the total number of HIV infecteds at time \( t \) (=years passed since May 1989) in Japan can be estimated as

\[
I(t) \approx \left( \frac{3.59}{9\kappa} + \frac{1}{9} \right) \exp(3.893 + 0.359t). \quad (4.2)
\]

To calculate the parameter \( \kappa \), we have to know the survival rate \( \ell^*(\tau) \). We have not yet known what kind of incubation distribution most fits to Japanese AIDS cases, hence we use some typical survival functions used by Brookmeyer and Gail (Gail and Brookmeyer 1988; Brookmeyer and Gail 1994). Results are shown in Table 3. Since the cumulated AIDS cases at the end of June 1994 is 314, the estimated number of HIV infecteds of Japan (excluding about 1800 cases by contaminated blood products) is about from 3200 (model I) to 5200 (model IV). Then we could say that the surveillance system catches from 30 percent to 50 per cent of the HIV infecteds.

Here we do not take into account migration effect, so it is important to note that our estimate is an estimate not for the unknown actual size of infecteds in Japan but for the size needed to produce the observed AIDS incidence in
the exponential phase. In fact, it is difficult to count the number of infected individuals who stay in Japan temporarily and emigrate before developing AIDS. Hence our estimate would be a lower bound on the size of the AIDS epidemic in Japan.

5 Reproductivity of HIV Infecteds

The basic model for the exponential phase in the previous section could be seen as a kind of *Euler-Malthus* population model, because it *a priori* assumes the exponential growth of newborns. The essential step to extend the descriptive model to a dynamical model is to introduce a *reproduction mechanism*. In the following we introduce the reproduction structure that can produce the exponential growth, that is, we formulate the basic model as a *Lotka’s stable population model* (Pollard 1973; Keyfitz 1977; Brouard 1987; Inaba 1994).

For simplicity, suppose that HIV infecteds do not terminate their risky behavior until they develop AIDS and AIDS patients do no longer infect susceptibles. Then newly infected population is produced by transmission of HIV from infected individuals. Let \( \beta(\tau) \) be the expected number of secondary cases produced by an infected individual at disease-age \( \tau \). For sexual transmission in a homogeneous population, \( \beta \) could be given by the product of the transmission probability per contact and the number of sexual contact with susceptible per unit time at disease-age \( \tau \). For vertical transmission, it would be the product of the transmission probability from mother to newborn per birth and the expected number of childbearing per individual per unit time at disease-age \( \tau \). In the following we assume that there exists an upper bound \( \omega > 0 \) of the infectious period, that is, \( \beta(\tau) = 0 \) for \( \tau > \omega \). Then we have

\[
B(t) = \int_0^\omega \beta(\tau)i(t, \tau)d\tau. \tag{5.1}
\]

Hence we arrive at the following *renewal equation* (Lotka’s integral equation)

\[
B(t) = \int_0^\omega \phi(\tau)B(t - \tau)d\tau, \tag{5.2}
\]

where \( \phi(\tau) := \beta(\tau)(1 - F(\tau)) \) is the net reproduction function. From (5.2) if the infection rate grows exponentially with Malthusian parameter \( r \), it must satisfy the *Lotka’s characteristic equation*:

\[
1 = \int_0^\omega e^{-r\tau}\phi(\tau)d\tau. \tag{5.3}
\]

Then the *basic reproduction ratio* (i.e., net reproduction rate in demographic literature) \( R_0 \) is given by

\[
R_0 = \int_0^\omega \phi(\tau)d\tau. \tag{5.4}
\]
In general, $R_0$ is defined as the expected number of secondary cases produced, in a completely susceptible population, by a typical infected individual during its entire period of infectiousness. From (5.3)-(5.4), we know immediately that the infected population will grow exponentially (with Malthusian parameter $r$ given by the unique real root of (5.3)) if $R_0 > 1$, whereas it will decay exponentially if $R_0 < 1$. That is, the disease can invade if $R_0 > 1$, whereas it cannot if $R_0 < 1$, which is the famous threshold condition for infectious diseases. Therefore the HIV control strategy should be planned as it can attain the subcritical condition $R_0 < 1$.

We should note that the reproductivity of HIV infecteds given by its Malthusian parameter depends not only on the basic reproduction ratio but also on the reproduction pattern. In fact, it is well known that the Malthusian parameter is roughly approximated as

$$r \approx \frac{\log_e R_0}{\mu},$$

(5.5)

where $\mu$ is the average disease-age at secondary infection given by

$$\mu := \int_0^{\omega} \tau \frac{\phi(\tau)}{R_0} d\tau.$$  (5.6)

Hence a longer mean interval between primary case to secondary cases would lead to a lower growth rate even if the basic reproduction ratio is not changed.

If we could determine the reproduction schedule by route of infection, it would provide very useful information in order to judge whether any HIV preventive policy is effective to attain the subcritical condition $R_0 < 1$ and to lead a lower growth rate of the epidemic.

The dynamical model (5.2) can be used to calculate the future course of HIV epidemic based on possible scenarios for $\beta(\tau)$. For Japanese HIV/AIDS epidemic, even under the most optimistic, hence unrealistic, assumption that $R_0 = 0$ from now on, it can be predicted that the infection rate will grow within this century and the increase of the number of living AIDS patients will not cease for about ten years from now.

Once the initial invasion phase of the epidemic is over, we have to take into account the nonlinear interaction between infecteds and susceptibles. Even in such a case, the basic reproduction ratio would play an important role, because the supercritical condition $R_0 > 1$ would imply the existence and stability of the endemic steady state.

6 Discussion

Using the estimation method developed above, the number of infected individuals in Japan is estimated to be about from 5000 to 7000 (including about 1800 cases infected by contaminated blood products) at the end of June 1994. Our
estimate would be a lower bound for the actual size of HIV infected population in Japan, since we can not take into account infecteds whose AIDS incidence is not reported in Japan. However as far as the reproduction schedule is not altered, the effect of migration flow is transient and it would not change the long-term trend of the HIV epidemic. For example, even if we have a constant number of infected immigrants every year, the size of infected population will be bounded as long as the subcritical condition \( R_0 < 1 \) holds (Inaba 1988). That is, the most important point to control the epidemic is to attain the subcritical condition.

From this point of view, much more important observation is the stability of the initial growth rate of HIV infecteds, because it would reflect the intrinsic reproductivity of HIV infected population during the period when the saturation effect or the effect of behavioral changes have not yet come to be significant. As far as we observe the initial phase of the epidemic, until now the growth rate of Japanese HIV infection is much lower than that of Western countries at the 80th. One of interpretations for the low growth rate would be that the size of high risk groups (homosexual men with high sexual activity or drug abusers), in which the epidemic can spread very rapidly, has been much smaller in Japan and the heterosexual transmission has been the major route for HIV infection in Japan.

Even though the initial spread speed of HIV in heterosexual populations is slow, we could not be optimistic for the future trend of HIV infection in Japan, because we have already observed that the serious HIV/AIDS epidemic could be caused by heterosexual transmission in Asian and African countries. To develop effective preventive policies, we must improve our understanding for the reproduction mechanism of HIV infecteds in heterosexual populations. In particular, since pair formation phenomena would play an important role in the spread of HIV in heterosexual populations, we would have to develop two-sex population models.

References


