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BioSystems 35 (1995) 75–81

Bio Systems

Community treatment of HIV-1: initial stage and asymptotic dynamics

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Received 24 January 1994; revision received 27 September 1994; accepted 29 September 1994

Abstract

Treatment with antiviral drugs (zidovudine and ddI) has been reported to delay progression to AIDS, and may even possibly lower the infectiousness of the infectives. However, its effect on the community level is still uncertain. The latter is important since a successful community treatment program must meet both public health and individual health goals. Our study will focus on the effect of a community-wide treatment program initiated at the early stages of the disease as well as the long-term effect of the program. Using a simple mathematical model, we demonstrate that a community-wide treatment program could be instrumental in decreasing HIV incidence rate and eradicating the disease in the future if certain conditions on the parameters are met. On the other hand, when the above mentioned conditions on the parameters are not satisfied, we show that even if the treatment does improve survival in AIDS patients and decrease the rate at which HIV infection spreads in the community, it is still possible for the treatment program to have an adverse effect on the spread of AIDS in the population in the long run. Hence, a public health policy maker must exercise caution in order to design an effective treatment program for HIV/AIDS.

Keywords: HIV/AIDS; Mathematical models; Mathematical epidemiology; Basic reproductive ratio; Treatment and behavioral change

1. Introduction

Treatment of HIV-positive patients with antiviral drugs such as AZT (zidovudine) and ddI has been shown to prolong the survival time of AIDS patients and symptomatic carriers in some studies (Fischl et al., 1987, 1989; Volberding et al., 1990). However, whether such treatment will reduce infectiousness of the patients is hard to determine. Despite many reports that AZT therapy does have some effect on HIV prevalence in the patients' body (Fischl et al., 1987; Richman et al., 1987; Larder et al., 1989; Ho et al., 1989; Volberding et al., 1990; O'Brien et al., 1991), there are also reports to the contrary (Krieger et al., 1991) and one study which reports the level of virus and antigen in the patients' body returning to the pretreatment level within a year (Jackson et al., 1988).

The effect of a treatment program on reducing the net transmission rate (the product of mean contact rate and infectiousness) of HIV infectives

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SSDI 0303-2647(94)01482-M

is important since a truly successful community-wide treatment program must not only improve and prolong the life of infectives, but also be able to reduce the overall spread of the disease by reducing, roughly, the product of the number of infectives and the effective infectiousness.

Anderson et al. (1991) first raised the question of the concomitant implications of a community-wide treatment program on the overall transmission of HIV-1 within the community. Using a simple mathematical model of the male homosexual population, they showed that community-wide treatment of HIV infectives with antiviral drugs or immunotherapies that prolong the incubation period of AIDS without significantly reducing the infectiousness of the treated individuals can possibly increase AIDS-related deaths in the community. Hence it is important to be able to determine the effect of the treatment on the infectiousness of patients, if any. Gupta et al. (1993) also proposed a model to provide a framework for assessing various treatment strategies for a community-wide program, under certain assumptions on the efficacy of the treatment. Their model also contains an extension to heterogeneous population. Discussion on study of effect of behaviour change on HIV transmission using mathematical models can also be found in Anderson and May (1991).

In Velasco-Hernandez and Hsieh (1994), we propose a mathematical model for community treatment where we assume a fixed number of random screenings being carried out each year in a male homesexual population with the detected infectives being taken into treatment. By dividing the population into three groups, namely, S (susceptibles), U (untreated infectives), and I (treated infectives), we have the following model:

$$S'(t) = \Lambda \rightleftharpoons - B(t) - \mu S + \delta I \tag{1}$$

$$U'(t) = B(t)S - (\mu + \nu)U - \sigma U/T \tag{2}$$

$$I'(t) = \sigma U/T - (\mu + \nu' + \delta)I \tag{3}$$

with $T(t) = S(t) + U(t) + I(t)$ being the total population size, and

$$B(t)S = S(t)[c\beta U/T + c'\beta' I/T]$$

being the HIV incidence rate. Note that in Velasco-Hernandez and Hsieh (1994) we used β and, β' instead of $c\beta$ and $c'\beta'$, respectively.

We let Λ be the constant recruitment rate of susceptibles into the population; $1/\mu$ is the average length of the sexually active life of an uninfected individual; σ is the fixed number of random screening carried out each year; $c\beta$ and $c'\beta'$ are the net transmission rates (mean contact rate times transmission probability) of the untreated and treated infectives, respectively; $1/(\mu + \nu)$ and $1/(\mu + \nu')$ are the infectious periods of the untreated and treated infectives, respectively; and δ is the cure rate of the treated infectives returning to susceptible class.

The main mathematical analysis of this model was given in Velasco-Hernandez and Hsieh (1994). In this article we focus on how a community-wide treatment program can sometimes adversely effect the population under certain assumptions on the efficacy of the treatment to prolong survival and reduce infectiousness. In Section 2 we explore the effect of the treatment program implemented in the early stage of the spread of the disease. We give simple conditions which determines whether the disease will grow exponentially. Section 3 is devoted to describing the circumstances under which a treatment program can possibly decrease HIV incidence rate while having a perverse effect on the population level in the long run. We conclude with remarks on the biological implication of our result.

2. Initial stage analysis

At the early stage of the spread of the disease, we assume the population is at the disease-free equilibrium (DFE) $(\Lambda/\mu,0,0)$ when the infectives are first introduced into the population. Hence $\sigma/T \approx \sigma\mu/\Lambda = \sigma'$. Moreover, $U + I$ is small compared with S so that $S/T \approx 1$. We also assume $\delta I \approx 0$ initially since it would take some time before an infective is treated and then cured. It follows that $B(t)S \approx c\beta U + c'\beta' I$ and Eqs. 1 and 2 become asymptotically:

$$U'(t) = (c\beta - \mu - \nu - \sigma')U + c'\beta' I \tag{4}$$

$$I't = \sigma' U - (\mu + \nu')I \tag{5}$$

Suppose the initial value for (U,I) is $(U(0),I(0)) = (U_0,0)$; then the solution to Eqs. 4 and 5 is

$$U(t) = \frac{U_0}{\lambda_+ - \lambda_-}[(\lambda_+ + \mu + \nu')e^{\lambda_+ t} - (\lambda_- + \mu + \nu')e^{\lambda_- t}] \quad (6)$$

$$I(t) = \frac{\sigma U_0}{\lambda_+ - \lambda_-}[e^{\lambda_+ t} - e^{\lambda_- t}] \quad (7)$$

where $\lambda_\pm = 1/2\{c\beta - 2\mu - \nu - \nu' - \sigma' \pm [(c\beta - \nu - \sigma' + \nu')^2 + 4c'\beta'\sigma']^{1/2}\}$ with λ_+ being the eigenvalue with plus sign.

In other words, the linear approximations of $U(t)$ and $I(t)$ for small t are obtained and it is clear from Eqs. 6 and 7 that the necessary and sufficient condition for the epidemic to grow initially (or, equivalently, for the initial growth to be exponential) is $\lambda_+ > 0$. More simply put, the epidemic grows initially if and only if

$$(\mu + \nu')(c\beta - \mu - \nu) + \sigma'(c'\beta' - \mu - \nu') > 0 \quad (8)$$

When $c\beta > \mu + \nu$, the epidemic will grow in the early stage without any treatment program ($\sigma = 0$). However, if a community-wide treatment program is implemented in the population which: (a) decreases the infectiousness and sexual contact of the treated infectives significantly so that $c'\beta' < \mu + \nu'$, (b) is comprehensive enough so that $\sigma' > (\mu + \nu')(c\beta - \mu - \nu)/(\mu + \nu' - c'\beta')$; it will force the left-hand-side of the inequality in Eq. 8 to become negative and thus the epidemic will not grow initially.

Perhaps the more interesting feature of condition in Eq. 8 is the 'worst case scenario' it presents. That is the case when $c\beta < \mu + \nu$, i.e. when the net transmission rate $c\beta$ is small so that there would be no epidemic at all even without any treatment program. However, if an ill-conceived treatment program is initiated at the first appearance of the disease in the community which satisfies the following conditions: (i) $c'\beta' > \mu + \nu'$, (ii) $\sigma' > (\mu + \nu')(\mu + \nu - c\beta)/(c'\beta' - \mu - \nu')$; the left-hand-side of the inequality in Eq. 8 will become positive; hence the treatment program could actually cause the disease to spread, at least initially, when it would not have spread otherwise.

Taking a closer look at the above-mentioned conditions (i) and (ii) which could cause a treatment program to effect the population adversely, we assume that the treatment program does indeed lower the net transmission rate of the treated infectives, $c'\beta'$, so that $c'\beta' < c\beta$. If we assume further that the treatment is also effective in prolonging the incubation period of the treated infectives significantly so that

$$\frac{1}{(\mu + \nu')} >> \frac{1}{(\mu + \nu)}$$

it is then possible that

$$\mu + \nu > c\beta > c'\beta' > \mu + \nu'$$

which is consistent with all restrictions we have given so far. The last inequality, $c'\beta' > \mu + \nu'$, is exactly condition (i) in the last paragraph. In this case the more comprehensive the program is, the worse the situation gets. If σ is large enough so that condition (ii) is also satisfied, the course for the spread of disease will be altered for the worse.

3. Asymptotic analysis

In Velasco-Hernandez and Hsieh (1994), we derived a threshold for screening term σ^*. If the number of yearly random screening exceeds σ^*, the treatment program can successfully eradicate the disease provided $c'\beta' < \mu + \nu' + \delta$. We also showed that the community-wide treatment program with random screening will decrease the HIV incidence rate if and only if $c'\beta' < c\beta$. On the other hand, if the treatment results in an increase in net transmission rate ($c'\beta' > c\beta$) through, say, an increase in the mean contact rate, the HIV incidence rate may increase (as also pointed out by Anderson et al., 1991).

Furthermore, the condition for spread of disease, $\sigma < \sigma^*$, is equivalent to the well-known epidemiological condition for spread of a disease, $R_0 > 1$, where R_0 is the basic reproductive num-

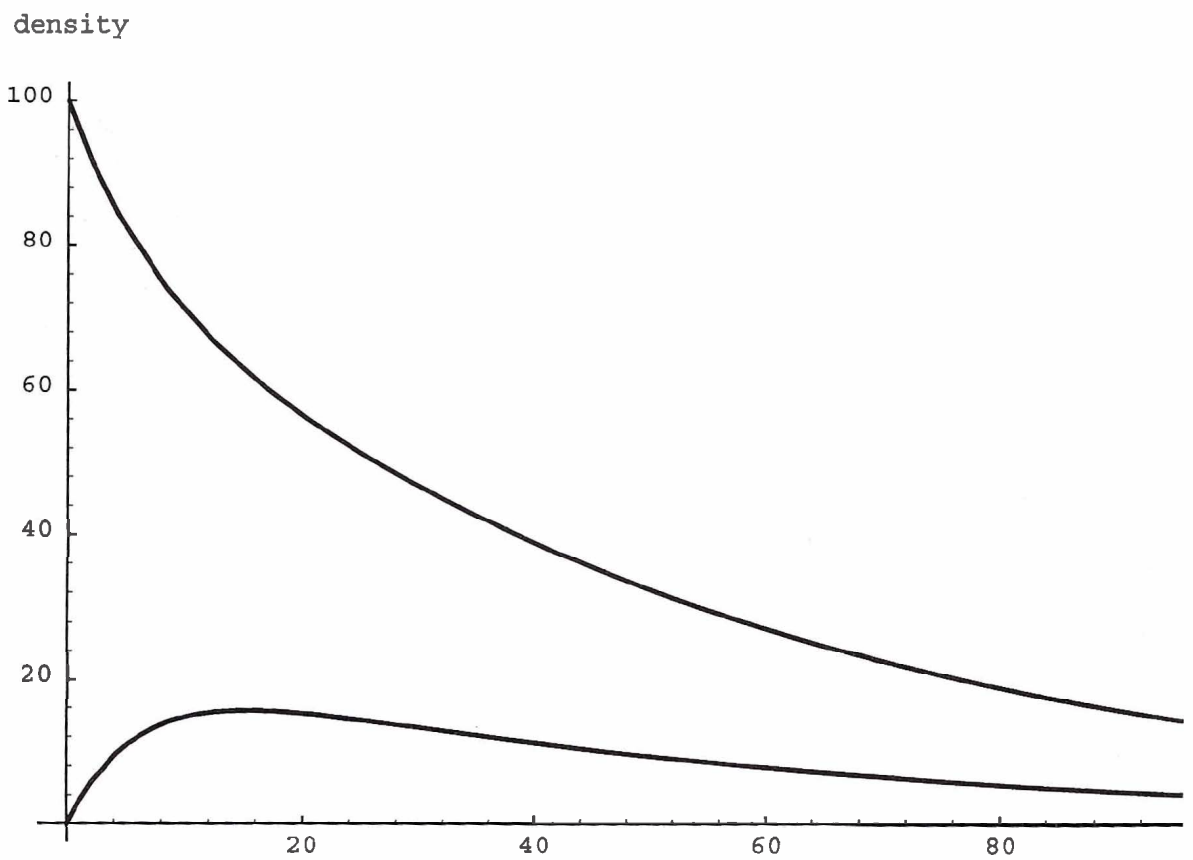

Fig. 1. Simulation of 100 years of the model of Eqs. 1–3 with the following initial conditions and parameter values: $S(0) = 30\,000$, $U(0) = 100$ and $I(0) = 0$ (number of individuals). Only the graphs of $U(t)$ and $I(t)$ are shown. The parameter values are $c\beta = 0.12$/year, $c'\beta' = 0.1$/year, $\Lambda = 1000$/year, $\mu = 1/30$ year, $\nu = 1/10$ year, $\nu' = 1/10$ year, $\delta = 0$, $\sigma = 1000$ ind/year.

ber. From Eq. 3.1 in Velasco-Hernandez and Hsieh (1994), $R_0 > 1$ can be rewritten as:

$$\left[\frac{c\beta}{\mu + \nu} - 1\right] + \frac{\sigma\mu/\Lambda}{\mu + \nu} \times \left[\frac{c'\beta'}{\mu + \nu' + \delta} - 1\right] > 0 \quad (9)$$

Note that Eq. 9 is the same as Eq. 8 if we let $\delta = 0$. It is clear that if $c\beta > \mu + \nu$, the disease will spread in the absence of a treatment program ($\sigma = 0$). However, if community treatment is carried out with the net transmission rate of the treated infectives, $c'\beta'$, sufficiently small (i.e., $c'\beta' < \mu + \nu' + \delta$), it will halt the spread of the disease by making the left-hand-side of Eq. 9 negative provided the number of random screenings done each year, σ, is large enough.

An important observation one can make is the case when $c\beta < \mu + \nu$. In this case the net transmission rate is sufficiently small so that the disease will not spread, even without any treatment program. However, if a community treatment program is launched where the net transmission is not lowered to a sufficient level, i.e. $c'\beta' > \mu + \nu + \delta$, it could contribute to the spread of the disease by making the left-hand-side of Eq. 9 positive. In this

instance, the larger σ is the worse the situation gets.

The most striking case is the one where $c\beta < \mu + \nu$ but $c\beta > c'\beta' > \mu + \nu' + \delta$. Here the disease will not spread in absence of a community-wide treatment program. However, suppose we have a treatment program which (i) prolongs the incubation period too much without attaining a high cure rate $\mu + \nu > \mu + \nu' + \delta$, (ii) lowers the net transmission rate but not sufficiently so that (iii) $c\beta > c'\beta' > \mu + \nu' + \delta$ is too large, i.e.

$$\sigma > \frac{\Lambda(\mu + \nu - c\beta)}{\mu[c'\beta'/(\mu + \nu' + \delta) - 1]}$$

The net transmission rate is lowered so that it decreases the rate at which HIV infection spreads, but not sufficiently low so that it will actually have an adverse effect in contributing to the disease persisting in the population. It is an unlikely but not impossible situation, especially if the treatment program is implemented at the early stage of the spread of disease when data on the net transmission rate $c\beta$ is unavailable. Hence it would be prudent not to launch community-wide treatment program prematurely which are not only unnecessary but may be detrimental to any effort to combat the epidemic.

In Figs. 1–3 we show a series of graphs for different parameter values illustrating the situation

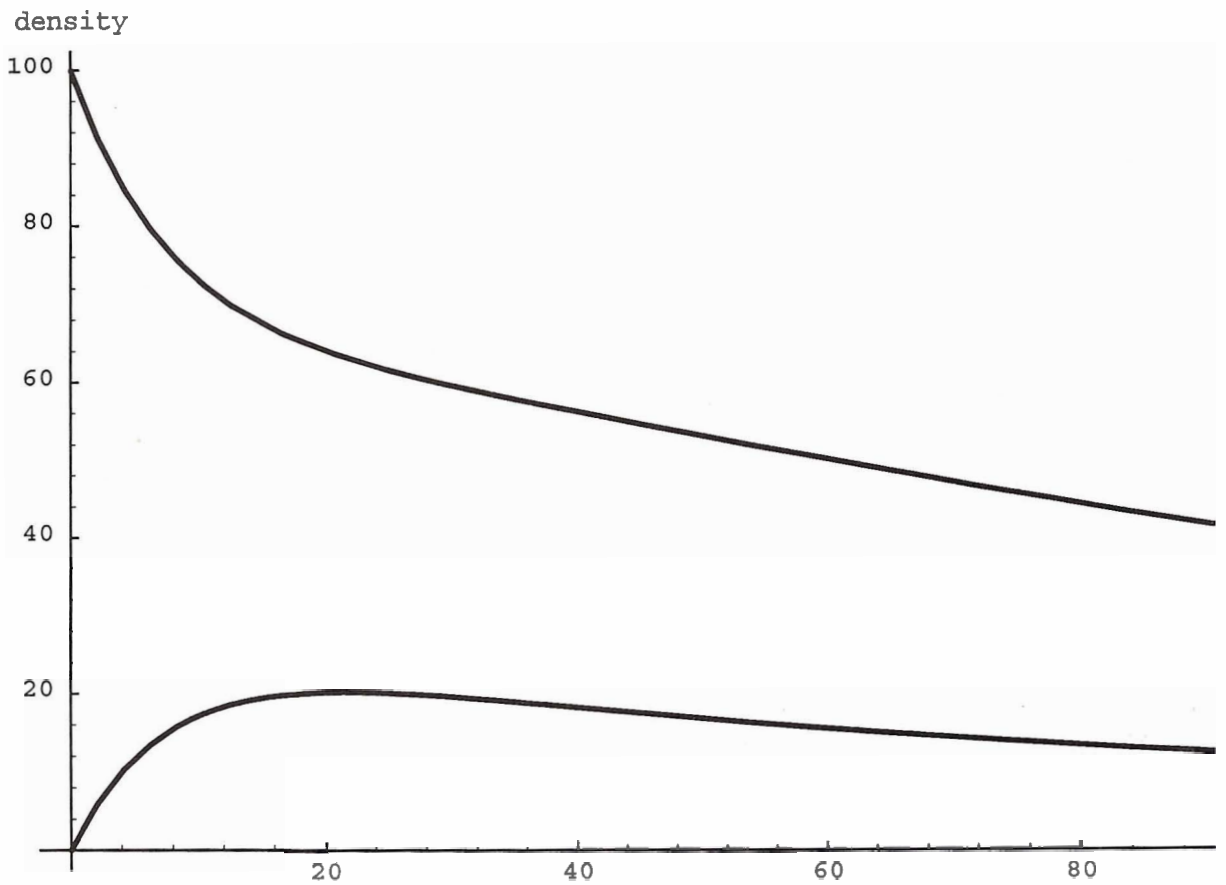

Fig. 2. Simulation of 100 years of the model of Eqs. 1–3 with the following initial conditions and parameter values: $S(0) = 30\,000$, $U(0) = 100$ and $I(0) = 0$. Only the graphs of $U(t)$ and $I(t)$ are shown. The parameter values are $c\beta = 1.0$, $c'\beta' = 1.0$, $\Lambda = 1500$, $\mu = 1/30$, $n = 1/10$, $\nu' = 1/20$, $\delta = 0$, $\sigma = 1000$ (units as in Fig. 1).

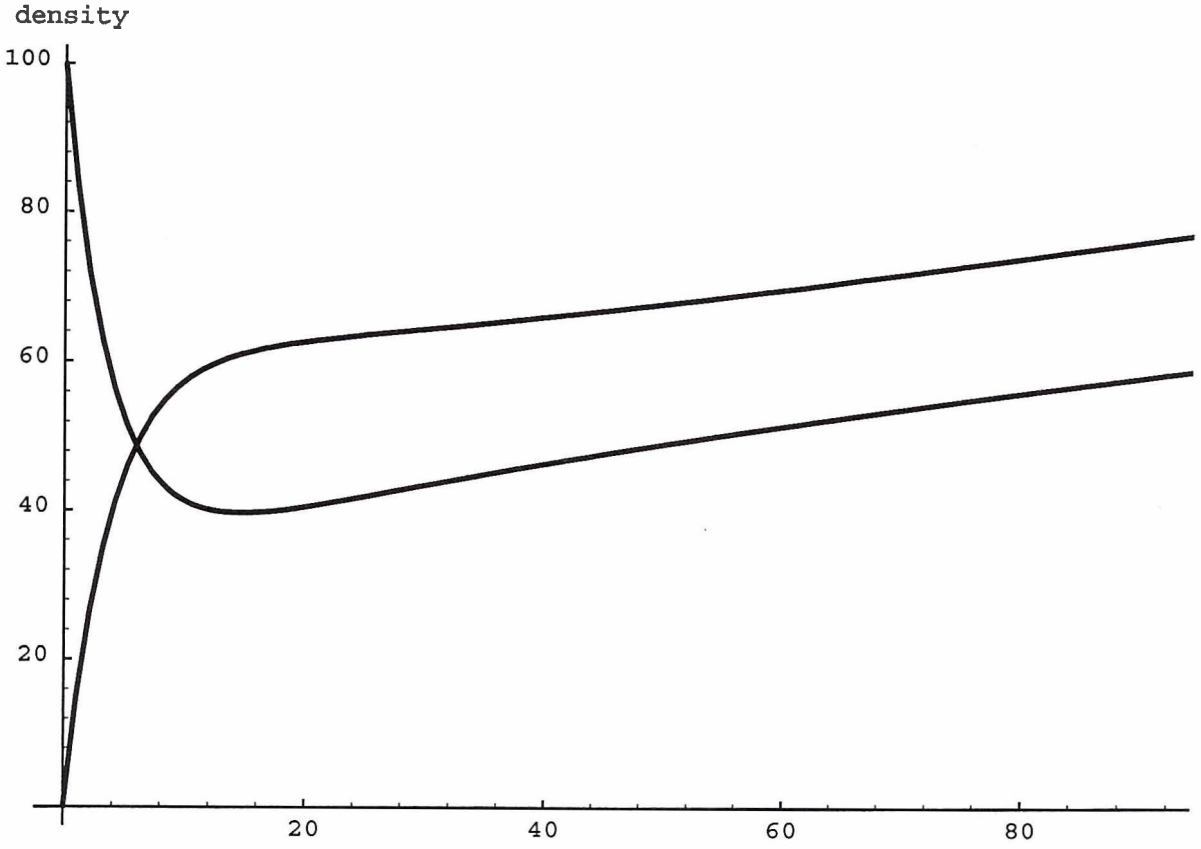

Fig. 3. Simulation of 100 years of the model of Eqs. 1–3 with the following initial conditions and parameter values: $S(0) = 30\,000$, $U(0) = 100$ and $I(0) = 0$. Only the graphs of $U(t)$ and $I(t)$ are shown. The parameter values are $c\beta = 1.0$, $c'\beta' = 1.0$, $\Lambda = 1500$, $\mu = 1/30$ $\nu = 1/10$, $\nu' = 1/20$, $\delta = 0$, $\sigma = 5000$ (units as in Fig. 1).

described above. In Fig. 1 the typical behavior for $R_0 < 1$ is shown: the disease is eventually eradicated. However, when the condition $c\beta > c'\beta' > \mu + \nu' + \delta$ holds, we obtain Figs. 2 and 3. Fig. 2 has a lower value of σ than that of the simulation in Fig. 3 and, therefore, the impact on disease dynamics is that of slowing down the decay to zero. However, for higher σ, R_0 is already greater than one: higher treatment with prolongation of the incubation period might contribute to the spread of the disease rather than to eradication.

4. Concluding remarks

The initial stage analysis in Section 2 shows that it is possible for an ill-planned treatment program to enable the disease to spread in the population initially, when it would not otherwise have spread at all. Furthermore, such a program, while possibly effective in reducing the HIV incidence rate, could still be harmful to the population by helping the epidemic to persist in the community in the long run, as the result in Section 3 indicates.

In heterosexual communities where the overall contact rate may be low, the implementation of treatment programs must be especially cautioned if there is insufficient prior information on the relative size of $c\beta$ and $\mu + \nu$. On the other hand, treatment programs carried out in high-risk groups (e.g. the male homosexual population or i.v. drug users), where the contact rate c or transmission probability β may be much higher, would most likely be successful both on community and

individual levels. Thus we re-emphasize the need of treatment programs directed at high-risk groups. Sections 2 and 3 demonstrate the possible risk of an ill-planned treatment program. More importantly, it also echoes the observation made by Anderson et al. (1991) and Gupta et al. (1993) on the importance of studies regarding reduction of infectiousness resulted from treatments and the accompanying change in sexual behaviour

Although the model discussed in this article is rather simple, it does point out the possible adverse effect of community-wide treatment without careful planning. It also raises the possibility that even when the treatment might be beneficial both to the individual and to the community in decreasing HIV incidence rate, it still could have a perverse effect on the population in the long run. There exists the moral imperative of providing care and treatment to everyone suffering from HIV/AIDS. This duty is however not incompatible with a carefully planned treatment and prevention policy designed to eliminate the plausible scenarios where individual benefits are translated into deleterious effects at the community level. Our work highlights and warns about this latter possibility.

Acknowledgements

This work stems from a discussion with Professor R.M. May for which the authors are grateful. Y.-H. Hseih is supported by grant NSC82-0208-M-005-027 from National Science Council of ROC; J.X. Velasco-Hernandez is supported by a post-doctoral fellowship from the Ricardo J. Zevada Foundation, by CONACYT grant 400200-5-3551E (Mexico) and partially supported by the U.S. Army Research Office through the Mathematical Sciences Institute of Cornell University.

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