Journal of Biological Dynamics
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t744398444

Global dynamics of a staged-progression model with amelioration for infectious diseases

Hongbin Guo; Michael Y. Li

Online Publication Date: 01 April 2008

To cite this Article Guo, Hongbin and Li, Michael Y.(2008)'Global dynamics of a staged-progression model with amelioration for infectious diseases',Journal of Biological Dynamics,2:2,154 — 168

To link to this Article: DOI: 10.1080/17513750802120877

URL: http://dx.doi.org/10.1080/17513750802120877

Journal of Biological Dynamics
Vol. 2, No. 2, April 2008, 154–168

Taylor & Francis
Taylor & Francis Group

Global dynamics of a staged-progression model with amelioration for infectious diseases†

Hongbin Guo and Michael Y. Li*

Department of Mathematical and Statistical Sciences, University of Alberta, Edmonton, Alberta, Canada T6G 2G1

(*Received 01 September 2007; final version received 14 March 2008*)

We analyze the global dynamics of a mathematical model for infectious diseases that progress through distinct stages within infected hosts with possibility of amelioration. An example of such diseases is HIV/AIDS that progresses through several stages with varying degrees of infectivity; amelioration can result from a host's immune action or more commonly from antiretroviral therapies, such as highly active antiretroviral therapy. For a general n-stage model with constant recruitment and bilinear incidence that incorporates amelioration, we prove that the global dynamics are completely determined by the basic reproduction number R_0. If $R_0 \leq 1$, then the disease-free equilibrium P_0 is globally asymptotically stable, and the disease always dies out. If $R_0 > 1$, P_0 is unstable, a unique endemic equilibrium P^* is globally asymptotically stable, and the disease persists at the endemic equilibrium. Impacts of amelioration on the basic reproduction number are also investigated.

Keywords: staged disease progression; disease amelioration; HIV/AIDS; basic reproduction number; global stability; Lyapunov functions

1. Introduction

For infectious diseases that progress through a long infectious period, infectivity or infectiousness can vary greatly in time. The progression of a typical HIV infection can take 8–10 years before the clinical syndrome (AIDS) occurs, and the progression goes through several distinct stages, marked by drastically different $CD4^+$ T-cell counts and viral RNA levels. HIV-infected individuals are highly infectious in the first few weeks after infection, then remain in an asymptotic stage of low infectiousness for many years, and become gradually more infectious as their immune system becomes compromised and they progress to AIDS. With antiretroviral drug treatment such as highly active antiretroviral therapy (HARRT), progression of HIV infection can be reverted so that a patient may ameliorate to higher $CD4^+$ counts. Although antiretoviral therapies have greatly improved the survival rates of HIV patients, there is a concern that ameliorated patients may resume to be active in sexual or drug activities while being infectious,

*Corresponding author. Email: mli@math.cealberat.ca
†Dedicated to Professor Hal Smith on the occasion of his 60th birthday.

ISSN 1751-3758 print/ISSN 1751-3766 online

DOI: 10.1080/17513750802120877
http://www.informaworld.com

especially after an incomplete course of treatment. Such patients may have a much greater degree of infectivity because of risky behaviours and pose a greater threat to the general public. To fully evaluate the effectiveness of the antiretroviral therapies in the global war against HIV/AIDS, it is important to investigate the effects of amelioration on the population dynamics of the HIV transmission.

Staged-progression (SP) models have been formulated in the literature to investigate variability of infectivity during the progression of HIV infection [1,4,6,8,9,11,12,18,19,20,21]. In [11], SP models using ordinary differential equations were derived. In [4], SP models with general distribution functions were formulated, and the models are described by systems of differential–integral equations. In [20], amelioration was first incorporated into an SP model for HIV/AIDS with standard incidence and exponential recruitment. The basic reproduction number in the presence of amelioration was derived in [20], and global analysis was carried out for the special case of three infectious stages. In [6], effects of vaccine and amelioration on the progression of HIV were investigated using an SP model.

In this paper, we consider a general n-stage SP model that incorporates disease amelioration, with constant recruitment and density-dependent incidence. Our goals are to establish the global dynamics of the general n-stage model and to investigate the effects of amelioration on the global dynamics. Our results show that amelioration does not alter the qualitative behaviours of the SP model; its impacts are quantitative and achieved by changing the basic reproduction number. More specifically, we prove that, for a general class of density-dependent incidence forms, the dynamics of the model are completely determined by the basic reproduction number R_0: if $R_0 \leq 1$, the disease-free equilibrium P_0 is globally asymptotically stable; if $R_0 > 1$, then P_0 is unstable and a unique endemic equilibrium exists. For the case of bilinear incidence, we established the global stability of the endemic equilibrium when $R_0 > 1$. A similar threshold result has been established for an SP model without amelioration in [7]. Our global stability result also generalizes those in [20].

With regard to the effects of amelioration on the basic reproduction number R_0, our results show that introducing amelioration at stage k may change R_0 in both directions; whether it increases or decreases R_0 is determined by a quantity,

$$\Delta_k = R_{0,(k-1)} - R_{0,k},$$

where $R_{0,k}$ represents the average number of secondary infections produced by a single infective from stage k and onwards, when amelioration is not present (see Section 5). This direct relation allows us to conclude that amelioration tends to increase R_0 in the following situations: (1) if the overall death rates are small; (2) if the amelioration is from a stage of high fatality rate to one with a much smaller fatality rate; and (3) if amelioration is from a stage of low infectivity to one with much higher infectivity. These findings have important implications on the HIV-infection dynamics. Since amelioration due to antiretroviral therapies usually comes with a reduction in fatality rates in HIV patients, if it is also accompanied by higher average infectivity because of risky behaviours, then the overall impact on the population level of antiretroviral therapies can be a net increase of the basic reproduction number, making the disease control in the whole population more difficult to achieve. Thus, it is crucial that antiretroviral therapies be administered with an education campaign to increase the awareness on danger of risky behaviours.

In the next section, we derive our model and present some preliminary analysis. Existence and uniqueness of the endemic equilibrium when $R_0 > 1$ are proved in Section 3. Global stability of the disease-free equilibrium is given in Section 4. Impacts of amelioration on the basic reproduction number R_0 are investigated in Section 5. In Section 6, we prove the global stability of the endemic equilibrium for the case of bilinear incidence using a global Lyapunov function. We end the paper with a brief summary in Section 6.

2. An SP model with amelioration

To formulate an n-stage model with both disease progression and amelioration, the total host population is partitioned into the following compartments: the susceptible compartment S, the infectious compartment I_i for individuals in the ith stage, where $i = 1, 2, \ldots, n$, and the removed compartment R for individuals in the terminal stage of the disease who are removed from the infection process. For $1 \leq i \leq n-1$, let δ_i denote the mean progression rate from the ith stage to the $(i+1)$th stage, γ_{i+1} the mean amelioration rate from the $(i+1)$th stage to the ith stage, and δ_n the mean progression rate from the nth stage to the terminal stage of the disease. It is also assumed that there is no recovery from the disease, and thus the only exit from the compartment R is death. Let $\lambda_i \geq 0$ be the transmission coefficient for the infection of a susceptible individual by an individual in the compartment I_i. Then the total incidence is given by $\sum_{i=1}^{n} \lambda_i I_i S f(N)$, where $N = S + I_1 + \cdots + I_n$ is the total number of individuals who are active in the infection process. Here, we assume that the density dependence of the incidence is described by a function $f(N)$, which will be specified later. A function class of special interest is $f(N) = N^{-\alpha},\ 0 \leq \alpha \leq 1$, as the resulting incidence term includes two of the most common forms: the standard incidence ($\alpha = 1$) and the bilinear incidence ($\alpha = 0$). The mean death rate for compartment S is d_0, for the compartment I_i is d_i, which may include death due to infection, and for compartment R is d_R. We assume the inflow of susceptibles is a constant Λ. The population transfer among compartments are schematically depicted in the transfer diagram in Figure 1. All parameters in the model are assumed to be non-negative. We remark that if $\lambda_i = 0$ for some i, then the compartment I_i will be regarded as a latent compartment. Thus, our model includes, as a special case, models of $SE_1 \cdots E_m I_1 \cdots I_n R$ type, for any finite m and n. When all the amelioration rates are zero, our model reduces to the staged progression model in [7].

Based on our assumptions and the transfer diagram, the following system of differential equations can be derived for the n-stage model,

$$\begin{aligned} S' &= \Lambda - d_0 S - \lambda S, \\ I_1' &= \lambda S - (d_1 + \delta_1) I_1 + \gamma_2 I_2, \\ I_i' &= \delta_{i-1} I_{i-1} - (d_i + \delta_i + \gamma_i) I_i + \gamma_{i+1} I_{i+1}, \quad i = 2, \ldots, n-1, \\ I_n' &= \delta_{n-1} I_{n-1} - (d_n + \delta_n + \gamma_n) I_n, \end{aligned} \tag{1}$$

and $R' = \delta_n I_n - d_R R$. The incidence term is λS, where the force of infection,

$$\lambda = f(N) \sum_{i=1}^{n} \lambda_i I_i, \tag{2}$$

is density-dependent. We assume that the function $f(N)$ is C^1 for $N > 0$ and satisfies the following assumptions.

$$(\mathbf{H})\ f(N) > 0, \qquad f'(N) \leq 0, \qquad \text{and} \qquad |N f'(N)| \leq f(N), \quad \text{for} \quad N > 0.$$

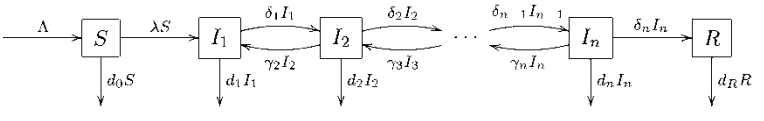

Figure 1. The transfer diagram for model (1).

The assumptions that $f(N) > 0$ and $f'(N) \leq 0$ are biologically motivated; as the total population N increases, the probability of a contact with a susceptible decreases, and thus the force of infection is expected to be a decreasing function of N. The third condition is imposed to ensure uniqueness of the endemic equilibrium when $R_0 > 1$ and global stability of the disease-free equilibrium when $R_0 \leq 1$. These conditions imply that $Nf(N)$ is monotonically non-decreasing, as $(Nf(N))' = f(N) + Nf'(N) \geq 0$. It can be verified that the class $f(N) = N^{-\alpha},\ 0 \leq \alpha \leq 1$, satisfies (**H**), including the standard incidence ($\alpha = 1$) and the bilinear incidence ($\alpha = 0$).

Adding the Equations in (1), we obtain

$$N' = \Lambda - d_0 S - d_1 I_1 - \cdots - d_n I_n - \delta_n I_n \leq \Lambda - dN,$$

where $d = \min\{d_0, d_1, \ldots, d_n\}$. It follows that $\lim_{t\to\infty} \sup N(t) \leq \Lambda/d$. Here, we assume that $d > 0$ so that the total active population N remains bounded. Similarly, from the first part of Equation (1), we obtain $S' \leq \Lambda - d_0 S$, and thus $\lim_{t\to\infty} \sup S(t) \leq \Lambda/d_0$. The global attractor of system (1) in $\mathbb{R}^{n+1}_+$ is contained in the bounded closed set,

$$\Gamma = \left\{(S, I_1, \ldots, I_n) \in \mathbb{R}^{n+1}_+ : 0 \leq S \leq \frac{\Lambda}{d_0}, \quad 0 \leq S + I_1 + \cdots + I_n \leq \frac{\Lambda}{d}\right\}.$$

It can be verified that Γ is positively invariant.

3. Existence and uniqueness of the endemic equilibrium

An equilibrium $(S, I_1, \ldots, I_n)$ of Equation (1) satisfies,

$$\begin{aligned}
0 &= \Lambda - d_0 S - \lambda S, \\
0 &= \lambda S - (d_1 + \delta_1) I_1 + \gamma_2 I_2, \\
0 &= \delta_{i-1} I_{i-1} - (d_i + \delta_i + \gamma_i) I_i + \gamma_{i+1} I_{i+1}, \quad i = 2, \ldots, n-1, \\
0 &= \delta_{n-1} I_{n-1} - (d_n + \delta_n + \gamma_n) I_n.
\end{aligned} \tag{3}$$

The disease-free equilibrium $P_0 = (\Lambda/d_0, 0, \ldots, 0)$ exists for all non-negative parameter values. An endemic equilibrium $P^* = (S^*, I_1^*, \ldots, I_n^*)$ satisfies $S^* > 0$, $I_i^* > 0$, $i = 1, \ldots, n$. Let

$$A = \begin{bmatrix}
-d_1 - \delta_1 & \gamma_2 & & & & \\
\delta_1 & -d_2 - \delta_2 - \gamma_2 & \gamma_3 & & & \\
 & \delta_2 & -d_3 - \delta_3 - \gamma_3 & \ddots & & \\
 & & \ddots & \ddots & \gamma_n & \\
 & & & \delta_{n-1} & -d_n - \delta_n - \gamma_n
\end{bmatrix}. \tag{4}$$

Then $-A$ is an M-matrix. As a consequence, $-A^{-1}$ exists and is non-negative. Furthermore, there exists $\alpha > 0$ such that $-A^{-1}x \geq \alpha x$ for $x \geq 0$ (see Appendix). It follows that

$$\beta = -(\lambda_1, \ldots, \lambda_n) A^{-1} (1, 0, \ldots, 0)^{\mathrm{t}} > 0, \tag{5}$$

and that

$$p = -(1, \ldots, 1) A^{-1} (1, 0, \ldots, 0)^{\mathrm{t}} > 0, \tag{6}$$

where the superscript t denotes the transposition. The basic reproduction number of equation (1) is

$$R_0 = \beta \frac{\Lambda}{d_0} f\left(\frac{\Lambda}{d_0}\right). \tag{7}$$

It can be derived using the method of next generation matrix as given in [16]. In Section 4, we derive expressions of R_0 in terms of model parameter for some special cases.

THEOREM 3.1 *Assume that f satisfies* (**H**). *If $R_0 \leq 1$, then P_0 is the only equilibrium in Γ. If $R_0 > 1$, then a unique endemic equilibrium P^* exists in the interior of Γ.*

Proof It suffices to prove that the unique endemic equilibrium P^* exists if and only if $R_0 > 1$. To show this, we write the last n equations of Equation (3) in the form,

$$(I_1, \ldots, I_n)^{\mathrm{t}} = -\lambda S A^{-1}(1, 0, \ldots, 0)^{\mathrm{t}}. \tag{8}$$

Multiplying the row vector $(\lambda_1, \ldots, \lambda_n)$ with Equation (8) and using Equations (2) and (5), we obtain,

$$\begin{aligned}\sum_{i=1}^{n} \lambda_i I_i &= (\lambda_1, \ldots, \lambda_n)(I_1, \ldots, I_n)^{\mathrm{t}} = -(\lambda_1, \ldots, \lambda_n) A^{-1}(1, 0, \ldots, 0)^{\mathrm{t}} \lambda S \\ &= \beta \lambda S = \beta f(N) S \sum_{i=1}^{n} \lambda_i I_i.\end{aligned}$$

Since $\sum_{i=1}^{n} \lambda_i I_i \neq 0$, it follows that

$$\beta\, S\, f(N) = 1. \tag{9}$$

Similarly, multiplying row vector $(1, \ldots, 1)$ with Equation (8), and applying Equation (2), we have,

$$\sum_{i=1}^{n} I_i = (1, \ldots, 1)(I_1, \ldots, I_n)^{\mathrm{t}} = p f(N) S \sum_{i=1}^{n} \lambda_i I_i, \tag{10}$$

where $p > 0$ is defined in Equation (6). From the first equation of Equation (3), we get $f(N) S \sum_{i=1}^{n} \lambda_i I_i = \Lambda - d_0 S$, which, together with Equation (10), implies $\sum_{i=1}^{n} I_i = p(\Lambda - d_0 S)$, and thus

$$N = S + \sum_{i=1}^{n} I_i = S + p(\Lambda - d_0 S) = p\Lambda + (1 - p d_0) S. \tag{11}$$

Substituting Equation (11) into Equation (9), we obtain the following equation for endemic equilibria

$$S f(p\Lambda + (1 - p d_0) S) = \frac{1}{\beta}. \tag{12}$$

We will show that Equation (12) has a unique positive solution in the interval $(0,\ \Lambda/d_0)$ when $R_0 > 1$ using the standard graphical method. Let,

$$g(S) = S\, f(p\Lambda + (1 - p d_0) S).$$

Then $g(0) = 0$, and $g(\Lambda/d_0) = \Lambda/d_0 f(p\Lambda + (1 - pd_0)\Lambda/d_0) = \Lambda/d_0 f(\Lambda/d_0) = R_0/\beta$. Furthermore, by our assumption (**H**),

$$\begin{aligned} g'(S) &= f(p\Lambda + (1 - pd_0)S) + (1 - pd_0)Sf'(p\Lambda + (1 - pd_0)S) \\ &= f(N) + N\, f'(N) - p\,\Lambda\, f'(N) > 0, \end{aligned}$$

where $N = p\Lambda + (1 - pd_0)S$. It follows that $y = g(S)$ is strictly monotonically increasing, and its graph has at most one intersection with the line $y = 1/\beta$. Such an intersection exists for $S \in (0,\ \Lambda/d_0)$ if and only if $g(\Lambda/d_0) > 1/\beta$, namely, $R_0 > 1$. Using Equation (8), we know that $(I_1, \ldots, I_n)$ is uniquely determined from S. This completes the proof of Theorem 3.1. ■

4. Global stability of the disease-free equilibrium

THEOREM 4.1 *Assume that f satisfies* (**H**). *If $R_0 \le 1$, then P_0 is globally asymptotically stable in Γ. If $R_0 > 1$, then P_0 is unstable, and system* (1) *is uniformly persistent.*

Proof Define a Lyapunov function $L = \sum_{k=1}^{n} c_k I_k$, with

$$(c_1, c_2, \ldots, c_n) = -(\lambda_1, \lambda_2, \ldots, \lambda_n)A^{-1}.$$

Note that $c_k \ge 0, k = 1, \ldots, n$, since $-A^{-1}$ is non-negative. In particular,

$$c_1 = -(\lambda_1, \lambda_2, \ldots, \lambda_n)A^{-1}(1, 0, \ldots, 0)^{\mathrm{t}} = \beta > 0.$$

Rewriting the last n equations in Equation (1) as $(I_1', \ldots, I_n')^{\mathrm{t}} = (\lambda S, 0, \ldots, 0)^{\mathrm{t}} + A\,(I_1, \ldots, I_n)^{\mathrm{t}}$, and using assumption (**H**) and the fact that $Nf(N)$ is non-decreasing, we obtain that, along a solution of Equation (1),

$$\begin{aligned} L' &= c_1 f(N)S \sum_{i=1}^{n} \lambda_i I_i - \sum_{i=1}^{n} \lambda_i I_i \;=\; (\beta f(N)S - 1) \sum_{i=1}^{n} \lambda_i I_i \le (\beta f(S)S - 1) \sum_{i=1}^{n} \lambda_i I_i \\ &\le \left[\beta f\Big(\frac{\Lambda}{d_0}\Big)\frac{\Lambda}{d_0} - 1\right] \sum_{i=1}^{n} \lambda_i I_i = (R_0 - 1) \sum_{i=1}^{n} \lambda_i I_i \;\le\; 0, \quad \text{if } R_0 \le 1. \end{aligned}$$

Furthermore, $L' = 0$ only if $\sum_{i=1}^{n} \lambda_i I_i = 0$ or $S = \Lambda/d_0$. It can be verified that the largest compact invariant subset of the set $G = \{(S, I_1, \ldots, I_n) \in \Gamma : L' = 0\}$ is the singleton $\{P_0\}$. Therefore, all solutions in Γ converge to P_0, by the LaSalle Invariance Principle [16]. The global attractivity of P_0 and the Lyapunov function L imply that P_0 is also locally stable, since otherwise P_0 will have a homoclinic orbit that is entirely contained in G, contradicting that the largest compact invariant set in G is $\{P_0\}$. This establishes the global stability of P_0 when $R_0 \le 1$.

If $R_0 > 1$, then $L' > 0$ for $\sum_{i=1}^{n} \lambda_i I_i > 0$ and S sufficiently close to Λ/d_0. Solutions in $\mathbb{R}_+^{n+1}$ sufficiently close to P_0 move away from P_0, except those on the invariant S-axis, along which solutions converge to P_0. Therefore, this implies that P_0 is unstable. The maximal invariant set on the boundary of $\mathbb{R}_+^{n+1}$ is the singleton $\{P_0\}$ and is isolated. By a uniform persistence result (Theorem 4.3) in [5], the instability of P_0 implies that system (1) is uniformly persistent [3]. This completes the proof of Theorem 4.1. ■

5. Impacts of amelioration on the basic reproduction number

Theorems 3.1 and 4.1 establish R_0 as a sharp threshold parameter. If $R_0 \leq 1$, the disease dies out irrespective of the initial number of cases. If $R_0 > 1$, then the disease persists in the feasible region, and there is a unique endemic equilibrium.

For the special case of bilinear incidence ($f(N) = 1$) and when all death rates are the same as Λ, namely, $d_i = \Lambda$, $i = 1, \ldots, n$, the R_0 in Equation (7) gives the basic reproduction number in [20] for the system of fractional variables. For the special case when there is no amelioration, explicit expressions of β in Equation (5) and R_0 in Equation (7) can be derived. In this case, the matrix A in Equation (4) is lower triangular, and

$$-A^{-1} = \begin{bmatrix} c_{11} & & & 0 \\ c_{21} & c_{22} & & \\ \vdots & \vdots & \ddots & \\ c_{n1} & c_{n2} & \cdots & c_{nn} \end{bmatrix}, \tag{13}$$

where c_{ij}'s are determined by the following iterative relations

$$c_{ii} = \frac{1}{d_i + \delta_i}, \quad c_{ki} = \frac{\delta_{k-1}}{d_k + \delta_k} c_{(k-1)i}, \quad i = 1, \ldots, n, \ \ k = 2, \ldots, n, \ \ k \neq i.$$

Therefore, when $\gamma_i = 0, \ i = 1, \ldots, n$,

$$R_0 = \left[\frac{\lambda_1}{d_1 + \delta_1} + \frac{\lambda_2}{d_2 + \delta_2} \frac{\delta_1}{d_1 + \delta_1} + \ldots + \frac{\lambda_n}{d_n + \delta_n} \frac{\delta_1}{d_1 + \delta_1} \cdots \frac{\delta_{n-1}}{d_{n-1} + \delta_{n-1}} \right] \frac{\Lambda}{d_0} f\left(\frac{\Lambda}{d_0}\right). \tag{14}$$

If $f(N) = N^{-1}$, then R_0 gives the basic reproduction number for the standard incidence as in [11,20,22], while if $\alpha = 0$, R_0 gives the basic reproduction number for the bilinear incidence. We note that the basic reproduction number for a class of finite-stage SP models with a general distribution function for the infectious periods was derived in [4].

To investigate the impacts of amelioration on the basic reproduction number, we introduce, for $k = 1, \ldots, n$,

$$R_{0,k} = \left[\frac{\lambda_k}{d_k + \delta_k} + \frac{\lambda_{k+1}}{d_{k+1} + \delta_{k+1}} \frac{\delta_k}{d_k + \delta_k} + \cdots + \frac{\lambda_n}{d_n + \delta_n} \frac{\delta_k}{d_k + \delta_k} \cdots \frac{\delta_{n-1}}{d_{n-1} + \delta_{n-1}} \right] \frac{\Lambda}{d_0} f\left(\frac{\Lambda}{d_0}\right), \tag{15}$$

which represents the average number of secondary infections produced by an infective from the kth stage of the disease progression onwards when no amelioration is present. If $k = 1$, then $R_{0,1}$ gives the basic reproduction number R_0 in Equation (14). The following relation is immediate from Equation (15).

$$R_{0,(k-1)} = \frac{\lambda_{k-1}}{d_{k-1} + \delta_{k-1}} \frac{\Lambda}{d_0} f\left(\frac{\Lambda}{d_0}\right) + R_{0,k} \frac{\delta_{k-1}}{d_{k-1} + \delta_{k-1}}, \quad k = 2, \ldots, n. \tag{16}$$

Recall that γ_k is the rate of amelioration from stage k to stage $k - 1$. Let $\gamma = (\gamma_2, \gamma_3, \ldots, \gamma_n)$.

THEOREM 5.1 *Let $R_{0,k}$ be defined in Equation* (15). *Then*

$$\left.\frac{\partial R_0}{\partial \gamma_k}\right|_{\gamma=0} > 0 \quad \Longleftrightarrow \quad \Delta_k = R_{0,(k-1)} - R_{0,k} > 0. \tag{17}$$

Proof *Using relation* (5) *and expression* (7) *for* R_0 *and differentiating the identity* $AA^{-1} = I$ *with respect to* γ_k, *we obtain*,

$$\frac{\partial R_0}{\partial \gamma_k} = (\lambda_1, \ldots, \lambda_n)(-A^{-1})\frac{\partial A}{\partial \gamma_k}(-A^{-1})(1, 0, \ldots, 0)^{\mathrm{t}}\frac{\Lambda}{d_0} f\left(\frac{\Lambda}{d_0}\right).$$

Using the definition of A in Equation (4) to calculate the partial derivative $\partial A/\partial \gamma_k$ in the relation above, then setting $\gamma = 0$ and using the expression for $-A^{-1}$ in Equation (13), we obtain relation (17). ■

Intuitively, Theorem 5.1 describes the effects on the basic reproduction number in a forward progression model when amelioration is introduced at the kth stage of the disease. In this case, when an infective ameliorates from stage k to stage $k-1$, the average number of secondary infections is increased by $R_{0,(k-1)}$ and is decreased by $R_{0,k}$, with the net gain $\Delta_k = R_{0,(k-1)} - R_{0,k}$. Therefore, amelioration at stage k increases R_0 if $\Delta_k > 0$, and it decreases R_0 if $\Delta_k < 0$.

Several conclusions can be drawn based on Theorem 5.1. We first observe from Equation (15) that if the overall death rate d_{k-1}, including the disease-caused death and natural death, is small, then

$$R_{0,(k-1)} \approx \frac{\lambda_{k-1}}{d_{k-1} + \delta_{k-1}}\frac{\Lambda}{d_0} f\left(\frac{\Lambda}{d_0}\right) + R_{0,k} > R_{0,k},$$

and amelioration at stage k increases R_0. We thus have the following conclusions.

(1) *Amelioration tends to increase* R_0 *for non-fatal diseases. This is also the case if amelioration is from a stage with high fatality rate to a stage with much lower fatality rate.*

We also observe from Equation (16) that $\Delta_k > 0$ if $\lambda_{k-1}/(d_{k-1} + \delta_{k-1})$ is sufficiently large. This can happen if either λ_{k-1} is large or $d_{k-1} + \delta_{k-1}$ is small. We thus arrive at the following conclusion.

(2) *Amelioration increases* R_0 *if it is into a disease stage with much higher infectivity or of much longer duration.*

Observation (2) has important implications for antiviral therapy of HIV/AIDS. It is known that HIV infection has several distinctive stages according to the level of $CD4^+$ count. HIV-infected individuals are highly infectious in the first few weeks after infection, then remain in an asymptotic stage of low infectiousness for many years, and become gradually more infectious as they progress to AIDS. However, HIV-positive patients may be sexually much more active during the long asymptotic stage than during the later stage when they become more aware of the infection or when they are more limited by their physical conditions. As a consequence, the transmission coefficient λ_k may be greater during the asymptotic phase because of more sexual contacts or more needle sharing, the so-called risky behaviours, than during the later stages. If antiviral therapies only lead to partial amelioration to the asymptotic phase, then a net effect can be an increase of the basic reproduction number R_0, making the infection control at the population level more difficult to achieve. It is important that antiviral therapies are administered with an education campaign to reduce risky behaviours.

If a treatment measure only results in partial amelioration, then it is most effective at a population level if applied at the disease stage with the highest infectivity, namely the largest transmission coefficient, λ_k. We thus have the following conclusion.

(3) *Treatment of the disease is best applied at a stage of the highest infectivity.*

6. Global stability of the endemic equilibrium for the bilinear incidence

THEOREM 6.1 *Assume that $f(N) \equiv 1$ and $R_0 > 1$. Then the endemic equilibrium P^* is globally asymptotically stable in the interior of Γ.*

The equilibrium Equations (3) for $P^* = (S^*, I_1^*, \ldots, I_n^*)$ are

$$\begin{aligned} \Lambda &= d_0 S^* + \sum_{i=1}^{n} \lambda_i I_i^* S^*, \\ \sum_{i=1}^{n} \lambda_i I_i^* S^* + \gamma_2 I_2^* &= (d_1 + \delta_1) I_1^*, \\ \delta_{i-1} I_{i-1}^* + \gamma_{i+1} I_{i+1}^* &= (d_i + \delta_i + \gamma_i) I_i^*, \quad i = 2, \ldots, n-1, \\ \delta_{n-1} I_{n-1}^* &= (d_n + \delta_n + \gamma_n) I_n^*. \end{aligned} \tag{18}$$

Set $x = (S, I_1, I_2, \ldots, I_n) \in \Gamma \subset \mathbb{R}_+^{n+1}$. The proof of Theorem 6.1 utilizes a global Lyapunov function

$$W(x) = \left(S - S^* - S^* \ln \frac{S}{S^*} \right) + \sum_{i=1}^{n} B_i \left(I_i - I_i^* - I_i^* \ln \frac{I_i}{I_i^*} \right), \tag{19}$$

where $x^* = P^* = (S^*, I_1^*, \ldots, I_n^*)$, and constants B_i are defined inductively as follows:

$$\begin{aligned} B_1 &= 1, \qquad B_2 = \frac{B_1(d_1 + \delta_1) - \lambda_1 S^*}{\delta_1}, \\ B_{i+1} &= \frac{B_i(d_i + \delta_i + \gamma_i) - (\lambda_i S^* + B_{i-1}\gamma_i)}{\delta_i}, \quad i = 2, \ldots, n-1. \end{aligned} \tag{20}$$

It follows from these definitions that B_i satisfies a linear system,

$$\begin{aligned} \lambda_1 S^* + B_2 \delta_1 - B_1(d_1 + \delta_1) &= 0, \\ \lambda_i S^* + B_{i+1}\delta_i + B_{i-1}\gamma_i - B_i(d_i + \delta_i + \gamma_i) &= 0, \quad i = 2, \ldots, n-1, \\ \lambda_n S^* + B_{n-1}\gamma_n - B_n(d_n + \delta_n + \gamma_n) &= 0. \end{aligned} \tag{21}$$

Solving this system, we obtain,

$$(B_1, \ldots, B_n) = (\lambda_1 S^*, \ldots, \lambda_n S^*)(-A)^{-1} \geq 0,$$

where matrix A is given in Equation (4). We first establish the following properties of B_i.

PROPOSITION 6.2 *The constants B_i, as defined in Equation* (20)*, satisfy the following relations.*

(a) $B_k(d_k + \delta_k + \gamma_k) I_k^* = \sum_{i=k}^{n} \lambda_i I_i^* S^* + B_{k-1}\gamma_k I_k^* + B_k \gamma_{k+1} I_{k+1}^*, \quad 2 \leq k \leq n-1.$

(b) $B_i \delta_{i-1} I_{i-1}^* = \sum_{k=i}^{n} \lambda_k I_k^* S^* + B_{i-1}\gamma_i I_i^*, \quad 2 \leq i \leq n-1.$

Proof To see the relations in Equation (1), we multiply the ith equation in Equation (21) by I_i^* and obtain

$$\begin{aligned} B_1(d_1+\delta_1)I_1^* &= \lambda_1 I_1^* S^* + B_2\delta_1 I_1^*, \\ B_i(d_i+\delta_i+\gamma_i)I_i^* &= \lambda_i I_i^* S^* + B_{i+1}\delta_i I_i^* + B_{i-1}\gamma_i I_i^*, \quad i=2,\ldots,n-1, \\ B_n(d_n+\delta_n+\gamma_n)I_n^* &= \lambda_n I_n^* S^* + B_{n-1}\gamma_n I_n^*. \end{aligned} \tag{22}$$

For $i=2,\ldots,n$, multiplying the ith equation in (18) by B_i, we get,

$$\begin{aligned} B_1(d_1+\delta_1)I_1^* &= \sum_{i=1}^{n}\lambda_i I_i^* S^* + B_1\gamma_2 I_2^*, \\ B_i(d_i+\delta_i+\gamma_i)I_i^* &= B_i\delta_{i-1}I_{i-1}^* + B_i\gamma_{i+1}I_{i+1}^*, \quad i=2,\ldots,n-1, \\ B_n(d_n+\delta_n+\gamma_n)I_n^* &= B_n\delta_{n-1}I_{n-1}^*. \end{aligned} \tag{23}$$

For $2\le k\le n-1$, adding the last $(n-k+1)$ equations in (22), we obtain,

$$\sum_{i=k}^{n} B_i(d_i+\delta_i+\gamma_i)I_i^* = \sum_{i=k}^{n}\lambda_i I_i^* S^* + \sum_{i=k}^{n-1} B_{i+1}\delta_i I_i^* + \sum_{i=k-1}^{n-1} B_i\gamma_{i+1}I_{i+1}^*. \tag{24}$$

Similarly, adding the last $(n-k)$ equations in (23), we arrive at

$$\sum_{i=k+1}^{n} B_i(d_i+\delta_i+\gamma_i)I_i^* = \sum_{i=k}^{n-1} B_{i+1}\delta_i I_i^* + \sum_{i=k+1}^{n-1} B_i\gamma_{i+1}I_{i+1}^*. \tag{25}$$

The identities in (a) follow from relations (24) and (25).

To derive the relations in (b), we equate the left-hand sides of the ith equations in Equations (22) and (23), for $i=1,\ldots,n$, and obtain

$$\begin{aligned} \sum_{i=1}^{n}\lambda_i I_i^* S^* + B_1\gamma_2 I_2^* &= \lambda_1 I_1^* S^* + B_2\delta_1 I_1^*, \\ B_i\delta_{i-1}I_{i-1}^* + B_i\gamma_{i+1}I_{i+1}^* &= \lambda_i I_i^* S^* + B_{i+1}\delta_i I_i^* + B_{i-1}\gamma_i I_i^*, \quad i=2,\ldots,n-1, \\ B_n\delta_{n-1}I_{n-1}^* &= \lambda_n I_n^* S^* + B_{n-1}\gamma_n I_n^*. \end{aligned} \tag{26}$$

From the first identity in Equation (26), we have $B_2\delta_1 I_1^* = \sum_{i=2}^{n}\lambda_i I_i^* S^* + B_1\gamma_2 I_2^*$. For $2\le i\le n-1$, adding the first $(i-1)$ equations in Equation (26) and cancelling common terms, we arrive at the relations in (b). This completes the proof of Proposition 6.2. ■

Relations in (b) of Proposition 6.2 imply the following result.

COROLLARY 6.3 *For each* $2\le i\le n$, *let*

$$a_k^{(i)} = \frac{\lambda_{k+1}I_{k+1}^* S^*}{B_i\delta_{i-1}I_{i-1}^*}, \quad i-1\le k\le n-1, \quad \textit{and} \quad a_n^{(i)} = \frac{B_{i-1}\gamma_i I_i^*}{B_i\delta_{i-1}I_{i-1}^*}. \tag{27}$$

Then $a_k^{(i)}>0$, *and* $\sum_{k=i-1}^{n} a_k^{(i)} = 1$.

Continuing the proof of Theorem 6.1, we compute the derivative of the Lyapunov function W and obtain,

$$\frac{\mathrm{d}W}{\mathrm{d}t} = \left(1 - \frac{S^*}{S}\right) S' + \sum_{i=1}^{n} B_i \left(1 - \frac{I_i^*}{I_i}\right) I_i'. \tag{28}$$

Using system (1) we have,

$$\begin{aligned}
&\left(1 - \frac{S^*}{S}\right) S' = \Lambda - d_0 S - \sum_{i=1}^{n} \lambda_i I_i S - \frac{\Lambda S^*}{S} + d_0 S^* + \sum_{i=1}^{n} \lambda_i I_i S^* \\
&= d_0 S^* + \sum_{i=1}^{n} \lambda_i I_i^* S^* - d_0 S - \sum_{i=1}^{n} \lambda_i I_i S - \frac{d_0 S^{*2}}{S} - \sum_{i=1}^{n} \lambda_i I_i^* \frac{S^{*2}}{S} + d_0 S^* \\
&\quad + \sum_{i=1}^{n} \lambda_i I_i S^* = \left(2 d_0 S^* - d_0 S - \frac{d_0 S^{*2}}{S}\right) - \sum_{i=1}^{n} \lambda_i I_i S + \sum_{i=1}^{n} \lambda_i I_i S^* + \sum_{i=1}^{n} \lambda_i I_i^* S^* \\
&\quad - \sum_{i=1}^{n} \lambda_i I_i^* \frac{S^{*2}}{S} \leq - \sum_{i=1}^{n} \lambda_i I_i S + \sum_{i=1}^{n} \lambda_i I_i S^* + \sum_{i=1}^{n} \lambda_i I_i^* S^* - \sum_{i=1}^{n} \lambda_i I_i^* \frac{S^{*2}}{S},
\end{aligned} \tag{29}$$

since

$$\left(2 d_0 S^* - d_0 S - \frac{d_0 S^{*2}}{S}\right) = d_0 S^* \left(2 - \frac{S}{S^*} - \frac{S^*}{S}\right) \leq 0. \tag{30}$$

In the second step of the above derivation, we substituted Λ by the right-hand side of the first part of Equation (18). Similarly, using Equations (1) and (18), we obtain,

$$\left(1 - \frac{I_1^*}{I_1}\right) I_1' = \sum_{i=1}^{n} \lambda_i I_i S - (d_1 + \delta_1) I_1 + \gamma_2 I_2 - \sum_{i=1}^{n} \lambda_i I_i S \frac{I_1^*}{I_1} + (d_1 + \delta_1) I_1^* - \frac{\gamma_2 I_2 I_1^*}{I_1}. \tag{31}$$

For $i = 2, \ldots, n-1$, using Equation (1), we have,

$$\begin{aligned}
\left(1 - \frac{I_i^*}{I_i}\right) I_i' &= \delta_{i-1} I_{i-1} - (d_i + \delta_i + \gamma_i) I_i + \gamma_{i+1} I_{i+1} - \frac{\delta_{i-1} I_{i-1} I_i^*}{I_i} + \\
&\quad (d_i + \delta_i + \gamma_i) I_i^* - \frac{\gamma_{i+1} I_{i+1} I_i^*}{I_i},
\end{aligned} \tag{32}$$

and

$$\left(1 - \frac{I_n^*}{I_n}\right) I_n' = \delta_{n-1} I_{n-1} - (d_n + \delta_n + \gamma_n) I_n - \frac{\delta_{n-1} I_{n-1} I_n^*}{I_n} + (d_n + \delta_n + \gamma_n) I_n^*. \tag{33}$$

Substituting Equations (29)–(33) into Equation (28), using $B_1 = 1$ and rearranging terms, we obtain,

$$\begin{aligned}
\frac{\mathrm{d}W}{\mathrm{d}t} \leq \Bigg\{ &[\lambda_1 S^* + B_2 \delta_2 - B_1 (d_1 + \delta_1)] I_1 + \sum_{i=2}^{n-1} [\lambda_i S^* + B_{i+1} \delta_i + B_{i-1} \gamma_i \\
&- B_i (d_i + \delta_i + \gamma_i)] I_i + [\lambda_n S^* + B_{n-1} \gamma_n - B_n (d_n + \delta_n + \gamma_n)] I_n \Bigg\}
\end{aligned}$$

$$+\left\{\sum_{i=1}^{n}\lambda_i I_i^* S^* + B_1(d_1+\delta_1)I_1^* + \sum_{i=2}^{n} B_i(d_i+\delta_i+\gamma_i)I_i^*\right\} \tag{34}$$

$$-\left\{\sum_{i=1}^{n}\lambda_i I_i^* \frac{S^{*2}}{S} + \sum_{i=1}^{n}\lambda_i I_i S\frac{I_1^*}{I_1} + \sum_{i=1}^{n-1} B_i\frac{\gamma_{i+1}I_{i+1}I_i^*}{I_i} + \sum_{i=2}^{n} B_i\frac{\delta_{i-1}I_{i-1}I_i^*}{I_i}\right\}$$

$$\doteq W_1 + W_2 + W_3.$$

From relations (21), we see that $W_1 \equiv 0$ for all $I_1, I_2, \ldots, I_n$. Substituting the first equilibrium equation in (23) into W_2, we have,

$$W_2 = 2\sum_{i=1}^{n}\lambda_i I_i^* S^* + B_1\gamma_2 I_2^* + \sum_{i=2}^{n} B_i(d_i+\delta_i+\gamma_i)I_i^*.$$

Substituting the identities in (a) of Proposition 6.2 into the above relation, we obtain,

$$\begin{aligned} W_2 &= \left[2\sum_{i=1}^{n}\lambda_i I_i^* S^* + \sum_{k=2}^{n}\sum_{i=k}^{n}\lambda_i I_i^* S^*\right] + 2\sum_{i=1}^{n-1} B_i\gamma_{i+1}I_{i+1}^* \\ &= \sum_{i=1}^{n}(i+1)\lambda_i I_i^* S^* + 2\sum_{i=1}^{n-1} B_i\gamma_{i+1}I_{i+1}^*. \end{aligned} \tag{35}$$

For each $i = 2, \ldots, n$, we have the following relation from Corollary 6.3,

$$B_i = B_i\sum_{k=i-1}^{n-1} a_k^{(i)} + B_i a_n^{(i)} = \sum_{k=i-1}^{n-1}\frac{\lambda_{k+1}I_{k+1}^* S^*}{\delta_{i-1}I_{i-1}^*} + \frac{B_{i-1}\gamma_i I_i^*}{\delta_{i-1}I_{i-1}^*}.$$

Therefore,

$$\begin{aligned} \sum_{i=2}^{n} B_i\frac{\delta_{i-1}I_{i-1}I_i^*}{I_i} &= \sum_{i=2}^{n}\left(\sum_{k=i-1}^{n-1}\frac{\lambda_{k+1}I_{k+1}^* S^*}{\delta_{i-1}I_{i-1}^*} + \frac{B_{i-1}\gamma_i I_i^*}{\delta_{i-1}I_{i-1}^*}\right)\frac{\delta_{i-1}I_{i-1}I_i^*}{I_i} \\ &= \sum_{i=2}^{n}\lambda_i I_i^* S^*\sum_{k=1}^{i-1}\frac{I_k I_{k+1}^*}{I_k^* I_{k+1}} + \sum_{i=1}^{n-1} B_i\gamma_{i+1}I_{i+1}^*\cdot\frac{I_i I_{i+1}^*}{I_i^* I_{i+1}}. \end{aligned} \tag{36}$$

Substituting Equation (36) into W_3, we get,

$$\begin{aligned} W_3 &= -\left[\sum_{i=1}^{n}\lambda_i I_i^*\frac{S^{*2}}{S} + \sum_{i=1}^{n}\lambda_i I_i S\frac{I_1^*}{I_1} + \sum_{i=2}^{n}\lambda_i I_i^* S^*\sum_{k=1}^{i-1}\cdot\frac{I_k I_{k+1}^*}{I_k^* I_{k+1}}\right] \\ &\quad -\left[\sum_{i=1}^{n-1} B_i\gamma_{i+1}I_{i+1}^*\frac{I_i I_{i+1}^*}{I_i^* I_{i+1}} + \sum_{i=1}^{n-1} B_i\gamma_{i+1}I_{i+1}^*\cdot\frac{I_{i+1}I_i^*}{I_{i+1}^* I_i}\right] \\ &= \sum_{i=1}^{n}\lambda_i I_i^* S^*\left(-\frac{S^*}{S} - \frac{I_i S I_1^*}{I_i^* S^* I_1} - \sum_{k=1}^{i-1}\frac{I_k I_{k+1}^*}{I_k^* I_{k+1}}\right) + \sum_{i=1}^{n-1} B_i\gamma_{i+1}I_{i+1}^*\left(-\frac{I_i I_{i+1}^*}{I_i^* I_{i+1}} - \frac{I_{i+1}I_i^*}{I_{i+1}^* I_i}\right). \end{aligned} \tag{37}$$

From Equations (34), (35), and (37), we obtain,

$$\frac{\mathrm{d}W}{\mathrm{d}t} \le \sum_{i=1}^{n} \lambda_i I_i^* S^* \left[(i+1) - \frac{S^*}{S} - \frac{I_i S I_1^*}{I_i^* S^* I_1} - \sum_{k=1}^{i-1} \frac{I_k I_{k+1}^*}{I_k^* I_{k+1}} \right] + \sum_{i=1}^{n-1} B_i \gamma_{i+1} I_{i+1}^* \left[2 - \frac{I_i I_{i+1}^*}{I_i^* I_{i+1}} - \frac{I_{i+1} I_i^*}{I_{i+1}^* I_i} \right] \le 0,$$

for all $(S, I_1, \ldots, I_n) \in \overset{\circ}{\Gamma}$, since, for $1 \le i \le n$,

$$\frac{S^*}{S} + \frac{I_i S I_1^*}{I_i^* S^* I_1} + \sum_{k=1}^{i-1} \frac{I_k I_{k+1}^*}{I_k^* I_{k+1}} \ge i+1 \quad \text{and} \quad \frac{I_i I_{i+1}^*}{I_i^* I_{i+1}} + \frac{I_{i+1} I_i^*}{I_{i+1}^* I_i} \ge 2, \tag{38}$$

by the inequality

$$\frac{a_1 + a_2 + \cdots + a_m}{m} \ge \sqrt[m]{a_1 \cdot a_2 \cdots a_m}, \quad \text{for } a_i \ge 0, \ \ i = 1, \ldots, m.$$

Furthermore, from inequalities (30) and (38), we know that $\mathrm{d}W/\mathrm{d}t = 0$ if and only if $S = S^*$ and $I_i = qI_i^*$, $i = 1, 2, \ldots, n$, for some constant $q > 0$. Substituting $S = S^*$ and $I_i = qI_i^*$ into the first equation of system (1), we obtain,

$$0 = \Lambda - d_0 S^* - q \sum_{i=1}^{n} \lambda_i I_i^* S^*. \tag{39}$$

Since the right-hand side of Equation 39 is strictly decreasing in q, we know by Equation (18) that Equation (39) holds if and only if $q = 1$, namely at P^*. Therefore, the only compact invariant subset of the set where $\mathrm{d}W/\mathrm{d}t = 0$ is the singleton $\{P^*\}$. By the LaSalle Invariance Principle, P^* is globally asymptotically stable in the interior of Γ. This completes the proof of Theorem 6.1.

When a transmission coefficient $\lambda_i = 0$, the compartment I_i can be regarded as a latent compartment. Theorem 6.1 thus contains earlier global stability results for SEIR (Succeptible Exposed Infectious Recovered) models with bilinear incidence form [13,17]. In the case of no amelioration, namely, $\gamma_i = 0$ for all i, Theorem 6.1 gives Theorem 5.1 of [7], in which a similar global Lyapunov function to $W(x)$ in Equation (19) is used. We remark that this form of global Lyapunov function has been previously applied to epidemic models [2,13–15].

7. Summary

Antiretroviral therapies such as HARRT have been successful in suppressing the viral activities in HIV patients and reverting the progression of HIV, albeit temporarily, so that patients may ameliorate to a stage with low infectiousness. If some ameliorated HIV patients resume risky behaviours in sexual contacts or drug activities, their infectivity may be greater after amelioration because of a larger number of contacts, and hence pose a greater threat to the general public. As drug treatments allow more and more people with HIV to live longer, the trade-off between benefits to personal health brought by drug treatments and potential threat to the general population of risky behaviours accompanying amelioration needs to be carefully evaluated.

In this paper, we address this issue by investigating the impacts of amelioration on the global dynamics in a general SP model with constant recruitment and bilinear incidence. We prove in

Theorems 4.1 and 6.1 that the global dynamics of the model is completely determined by the basic reproduction number R_0: if $R_0 \leq 1$, then the disease-free equilibrium is globally asymptotically stable and the disease dies out; if $R_0 > 1$, then the unique endemic equilibrium P^* is globally asymptotically stable and the disease persists at the level of P^*. Our global stability result for P^* generalizes earlier results in [7,20]. The proof utilizes a global Lyapunov function motivated by the work in [13–15].

We have shown that introducing amelioration at stage k of the disease progression indeed may increase the basic reproduction number, and hence may have a negative effect on the disease control in the population. We have introduced in Equation (15) a quantity $R_{0,k}$ that measures the average number of secondary infections produced by an infective from the kth stage of the disease progression onwards when no amelioration is present. We show in Theorem 5.1 that the introduction of amelioration at stage k will increase R_0 if and only if $R_{0,(k-1)} > R_{0,k}$. Based on this result and relation (16), we conclude that amelioration tends to increase R_0 if it is into a stage that has either (1) a much lower fatality rate, or (2) much higher infectivity, or (3) a much longer duration. In the case of HIV, this implies that if risky behaviours result in higher infectivity on average after antiretroviral therapies, then the basic reproduction number may increase.

Acknowledgements

This research was supported in part by grants from the Natural Science and Engineering Research Council of Canada (NSERC) and Canada Foundation for Innovation (CFI). H. Guo acknowledges the support of a PIMS Graduate Scholarship at the University of Alberta. We thank two anonymous referees whose comments and suggestions helped to improve the exposition of the paper.

References

[1] R.M. Anderson et al., *A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV), the causative agent of AIDS*, IMA J. Math. Med. Biol. 3 (1986), pp. 229–263.
[2] E. Beretta and V. Capasso, *Global stability results for a multigroup SIR epidemic model*, in: Mathematical Ecology, T.G. Hallam, L.J. Gross, and S.A. Levin, eds., Singapore World Scientific, Teaneck, NJ, 1986, pp. 317–342.
[3] G.J. Butler and P. Waltman, *Persistence in dynamical systems*, Proc. Amer. Math. Soc. 96 (1986), pp. 425–430.
[4] Z. Feng and H.R. Thieme, *Endemic model with arbitrarily distributed periods of infection I. General theory*, SIAM J. Appl. Math. 61 (2000), pp. 803–833.
[5] H.I. Freedman, M.X. Tang, and S.G. Ruan, *Uniform persistence and flows near a closed positively invariant set*, J. Dynam. Diff. Equat. 6 (1994), pp. 583–600.
[6] A.B. Gumel, C.C. McCluskey, and P. van den Driessche, *Mathematical study of a staged-progression HIV model with imperfect vaccine*, Bull. Math. Bio. 68 (2006), pp. 2105–2128.
[7] H. Guo and M.Y. Li, *Global dynamics of a staged progression model for infectious diseases*, Math. Biosci. Eng. 3 (2006), pp. 513–525.
[8] J.C. Hendriks et al., *Use of immunological markers and continuous-time Markov models to estimate progression of HIV infection in homosexual men*, AIDS 10 (1996), pp. 649–656.
[9] H.W. Hethcote, J.W. Van Ark, and I.M. Longini Jr., *A simulation model of AIDS in San Francisco: I. Model formulation and parameter estimation*, Math. Biosci. 106 (1991), pp. 203–222.
[10] R.A. Horn and C.R. Johnson, *Topics in Matrix Analysis*, Cambridge University Press, Cambridge, 1991.
[11] J.M. Hyman, J. Li, and E.A. Stanley, *The differential infectivity and staged progression models for the transmission of HIV*, Math. Biosci. 155 (1999), pp. 77–109.
[12] J.A. Jacquez et al., *Modelling and analyzing HIV transmission: The effect of contact patterns*, Math. Biosci. 92 (1988), pp. 119–199.
[13] A. Korobeinikov, *Lyapunov functions and global properties for SEIR and SEIS epidemic models*, Math. Med. Bio. 21 (2004), pp. 75–83.
[14] A. Korobeinikov and P.K. Maini, *A Lyapunov function and global properties for SIR and SEIR epidemiological models with nonlinear incidence*, Math. Biosci. Eng. 1 (2004), pp. 57–60.
[15] A. Korobeinikov and G.C. Wake, *Lyapunov functions and global stability for SIR, SIRS, SIS epidemiological models*, Appl. Math. Lett. 15 (2002), pp. 955–961.
[16] J.P. LaSalle, *The Stability of Dynamical Systems*, SIAM, Philadelphia, 1976.
[17] M.Y. Li and J.S. Muldowney, *Global stability for the SEIR model in epidemiology*, Math. Biosci. 125 (1995), pp. 155–164.

[18] X. Lin, H.W. Hethcote, and P. van den Driessche, *An epidemiological model for HIV/AIDS with proportional recruitment*, Math. Biosci. 118 (1993), pp. 181–195.
[19] I.M. Longini et al., *The dynamics of CD4+ T-lymphocyte decline in HIV-infected individuals: A Markov modeling approach*, J. AIDS 4 (1991), pp. 1141–1147.
[20] C.C. McCluskey, *A model of HIV/AIDS with staged progression and amelioration*, Math. Biosci. 181 (2003), pp. 1–16.
[21] A. Perelson and P. Nelson, *Mathematical analysis of HIV-1 dynamics in vivo*, SIAM Rev. 41 (1999), p. 344.
[22] P. van den Driessche and J. Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Math. Biosci. 180 (2002), pp. 29–48.

Appendix

The following definition and properties of M-matrices are used in our analysis. They can be found in most of the texts on matrix theory, see e.g. [10].

DEFINITION *$B_{n\times n}$ is a M-matrix if*

(1) *Off-diagonal entries of B are non-positive, and*
(2) *B is positively stable, namely, all eigenvalues of B have positive real parts.*

PROPOSITION *Properties of M-matrices*

(1) $B = \alpha I - P,\ P \geq 0,\ \alpha > \rho(P)$, *the spectral radius of P.*
(2) *B is non-singular and $B^{-1} \geq 0$.*
(3) *There exists $\beta > 0$ such that $B^{-1}x \geq \beta\, x$ for $x \geq 0$.*