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A NECESSARY CONDITON ON THE FUNCTIONAL CURABILITY OF HIV INFECTION

Jeng-Huei Chen

Department of Mathematical Sciences
National Chengchi University
Taipei, 11605, TAIWAN

Abstract: Let the Human Immunodeficiency Virus (HIV) infection be modeled by a dynamical system. A classical result shows that if the basic reproduction number is less than one, the system eventually reaches the virus eradication state. If it is greater than one, the virus population sustains within hosts. In the latter case, treatments are required for patients with persistent high viral load. However, in the treatment of this infection, it is usually difficult to completely eliminate the within-host viruses for infected patients. Recently, a treatment goal set up by the medical society is to achieve a functional cure for patients. A functional cure in the treatment of HIV infection is to permanently suppress the virus replication or to lead to patients' long-term remission state without completely eliminating the within-host viruses. In our previous study, we extend the classical result and show that a functional cure is possible only if the capability of patients' immune stimulation starts to attenuate when the density of infected cells is below a threshold. In this study, we show that the conclusion is still valid in a more accurate model proposed by Adams, Banks et al. This finding implies that the reached conclusion is robust under different accuracy in modeling HIV infection and suggests that it is the fundamental principle in governing the the phenomenon of a functional cure.

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1. Introduction

The Human Immunodeficiency Virus (HIV) is a lentivirus that attacks vital immune cells such as helper T cells, macrophages, and follicular dendritic cells. The infection of HIV may cause progressive failure of the immune system and leads to Acquired Immune Deficiency Syndrome (AIDS). Patients frequently die because of the resulting opportunistic infections or cancer. Currently, no vaccines are available. Highly Active Anti-Retroviral Therapy (HARRT), which combines multiple antiviral drugs to suppress the within-host viruses, is typically recommended to treat this infection.

Since the discovery of HIV, significant scientific effort has led to its further understanding. For instances, its genome, replication cycle, genetic variability as well therapy have been researched extensively. In addition, important sight to the virus-host intersection has been considered based on experimental data and mathematical models. One important contribution with this type of approach is made by Ho, Perelson [9], Shaw, Nowak [16] and their colleagues. They realize that they may perturb the within-host equilibrium between immune clearance and virus production by initiating antiviral treatment to collect data for dynamical information of virus production and clearance. With their experimental data and mathematical models, the life-span of infected cells, virus production rate and virus clearance rate can be estimated. Their success stimulates massive follow-up researches. For examples, the complicated viral decay profile under treatment is studied with this approach by Arnaout et al. [4], Althaus and De Boer [2], and Hlavacek et al. [8]. The modeling approach in drug resistance problems is considered by Nowak et al. [10] and Ribeiro et al. [13]. Nowak and May [11], and Wodarz [17] also consider immune response stimulated HIV infection with mathematical modeling. The early treatment to avoid the establishment of latent cells is analyzed by Archin et al. [3]. The possibility to activate late cells for followed-up therapy is examined with the same method by Rong and Perelson [14]. A more detailed review of mathematical modeling in HIV infection can be referred to the recent survey paper by Perelson [12].

Despite the great advances in understanding the HIV infection and in its treatment, it is still difficult to completely eliminate the within-host viruses for infected patients. Furthermore, current therapy with antiviral drugs has serious side effects and drug resistance problems. This motivates researchers to explore more effective treatment methods. Particularly, researchers are interested in methods such as immune therapy that may avoid the serious disadvantage of lifelong usage of antiviral drugs. A treatment goal to achieve a functional

cure for patients therefore recently set up by the medical society. A functional cure in the treatment of the human immunodeficiency virus (HIV) infection is to permanently suppress the virus replication or to lead to patients' long-term remission state without completely eliminating the within-host viruses, [18]. Consider the HIV infection modeled by the following dynamical system in Adams et al. [1]:

$$\frac{dT(t)}{dt} = s_T - d_T \cdot T(t) - \beta \cdot T(t) \cdot V(t), \tag{1}$$

$$\frac{dI(t)}{dt} = \beta \cdot T(t) \cdot V(t) - d_I \cdot I(t) - p \cdot E(t) \cdot I(t), \tag{2}$$

$$\frac{dV(t)}{dt} = k \cdot I(t) - d_V \cdot V(t) - \beta \cdot T(t) \cdot V(t), \tag{3}$$

$$\frac{dE(t)}{dt} = c_E + g(I) \cdot E(t), \tag{4}$$

where $g(I) = (\frac{b_1 \cdot I}{I+M_1} - \frac{b_2 \cdot I}{I+M_2} - d_E)$ is coined as the immune induction function. In this system, T, I, V and E represent the density of susceptible target cells, infected target cells, viruses, and immune effector cells, respectively, and the rest of symbols are system parameters. To make this system meaningful in biological sense, it is assumed that all these system parameters are positive. In Eq. (1), s_T is the production rate of target cell T, and $-d_T T(t)$ represents the death of cell T with death rate $-d_T$. The term $-\beta \cdot T(t) \cdot V(t)$ models the reduction of the density of the target cell T caused by target cells being infected by viruses with an infection rate β. In Eq. (2), $\beta \cdot T(t) \cdot V(t)$ represents the increase of the density of cell I caused by target cell T being infected by virus V. The term $-d_I I(t)$ represents the death of cell I with death rate d_I. In the same equation, $-p \cdot E(t) \cdot I(t)$ represents the clearance of cell I by immune response E with clearance rate p. In Eq. (3), $k \cdot I(t)$ represents the production of free viruses generated by the infected cells I. The term $-d_V \cdot V(t)$ models the death of virus with death rate d_V. The term $-\beta T(t) V(t)$ is the reduction of free viruses caused by their infecting target cells. The final equation describes the immune response stimulated by the infected cells with the immune induction function $g_0(I)$. Because T, I, V and E represent the density of cells and should be nonnegative, an equilibrium state of the system is called biologically meaningful if all these variables are nonnegative. A functional cure corresponds to drive the system from a stable high-viral-load biologically meaningful state to a stable low-viral-load biologically meaningful state with an appropriate treatment method.

In the literature, different patients' clinical outcomes such as a stable low-viral-load state, a persistent high-viral-load state, and a functional cure have

been reported in Vanham and Van Gulck [15], and Autran et al. [5]. To well model these reported cases, the system should possess either one or multiple stable equilibrium states. Eq. (1) to Eq. (4) (will be called the Adams system) is proposed in the work of Adams et al. [1] except that two types of target cells are considered therein. The major contribution of the work in Adams et al. [1] is to show that a functional cure is possible with optimal control theory when two stable biologically meaningful states coexist in the system. However, little on how system parameters determine the number of stable biologically meaningful states is discussed. Because this number is related to clinical outcomes, it is of fundamental importance and will be analyzed in details. The analysis explains how patents' different characteristics of immune response, representing with various system parameters, lead to various clinical outcomes with focus on conditions of functional curability.

It can be noted that Eq. (1) to Eq. (3) in the Adams system are the same as equations of the well-known basic model of virus dynamics in Nowak and May [11] except that the term $-\beta \cdot T(t) \cdot V(t)$ in Eq. (3) is usually neglected in the basic model. The functional curability problem of the basic model has been investigated in Chen [7]. Because the Adams system reflects the realistic situation more accurately and is also much more difficult to analyze, it is considered in details in this study. In the following, a system is called functional curable if it possesses at least two stable biologically meaningful equilibrium states and none of these two states represent virus eradication (i.e. $T > 0$, $E \geq 0$ and $I = V = 0$).

2. The Equilibrium States of the System

To consider the number of biologically meaningful equilibrium states of the Adams system, first focus on the immune induction function $g(I)$. Because I represents the density of infected cells, $g(I)$ is of interest only within the region $I \geq 0$. Depending on various parameters, the behavior of $g(I)$ with $I \geq 0$ has been classified into four types of functions in Chen [7]. Type I and type II functions are defined by the following definitions. Their graphs are presented in Fig. 1.

Definition 1. An immune induction function $g(I)$ is a type I function, if it is increasing and concave within $[0, \infty)$ and has a upper limit as $I \to \infty$.

Definition 2. An immune induction function $g(I)$ is a type II function,

if it possesses a local maximum I^* and an inflection point I^{**} with $I^* < I^{**}$. Mover, the function is increasing and decreasing over the intervals $[0, I^*)$ and (I^*, ∞), respectively. It is concave and convex over the intervals $[0, I^{**})$ and (I^{**}, ∞), respectively. As $I \to \infty$, the function approaches a lower limit.

Denote $D_1 = [2M_1M_2(b_1 - b_2)]^2 - 4M_1M_2(b_1M_1 - b_2M_2)(b_1M_2 - b_2M_1)$. By Definition 2, it can be computed that

$$I^* = \frac{-2M_1M_2(b_1 - b_2) + \sqrt[2]{D_1}}{2(b_1M_1 - b_2M_2)}, \tag{5}$$

or

$$I^* = \frac{-2M_1M_2(b_1 - b_2) - \sqrt[2]{D_1}}{2(b_1M_1 - b_2M_2)}, \tag{6}$$

depending which one is a positive number. The inflection point I^{**} can be computed to be $\frac{M_2 - mM_1}{m-1}$ with $m = \sqrt[3]{\frac{b_2M_2}{b_1M_1}}$. Type III and type IV functions are defined based on type I and type II functions as follows: A function $g(I)$ belongs to the category of type III functions if $-g(I)$ satisfies the definition of type I functions. Similarly, a function $g(I)$ belongs to the category of type IV functions if $-g(I)$ satisfies the definition of type II functions.

System parameters leading to different types of functions are summarized in Table 1 and had been reported in Chen [7]. The derivations of results in Table 1 are based on standard techniques in calculus through tedious calculation and therefore not provided here. In Adams et al. [1], realistic parameters satisfying conditions of case 6 and leading to a functional cure have been reported. Therefore, the following study only focuses on type II functions. Other types of functions can be similarly considered if further evidence indicates that they are significant in the functional curability problem.

The biologically equilibrium states of this system can be obtained by letting the derivatives in Eq. (1) to Eq. (4) be zeros. For notational convenience, denote $D_1 = (d_V d_T - \beta k I + \beta s_T)$, $D_2 = (d_V d_T + \beta k I - \beta s_T)$, and $U_2 = \beta d_T d_V s_T$. The equilibrium states can be equivalently considered from the following system

Type I and conditions
(case 1) $M_1 = M_2$, $b_1 > b_2$
(case 2) $M_1 > M_2, b_1 > b_2, b_2 M_1 \leq b_1 M_2$
(case 3) $M_1 < M_2, b_1 > b_2$, $b_2 M_2 \leq b_1 M_1$
Type II and conditions
(case 4) $M_1 < M_2, b_1 < b_2$, $b_1 M_2 > b_2 M_1$
(case 5) $M_1 < M_2$, $b_1 = b_2$
(case 6) $M_1 < M_2, b_1 > b_2$, $b_2 M_2 > b_1 M_1$
Type III and conditions
(case 7) $M_1 = M_2$, $b_1 < b_2$
(case 8) $M_1 > M_2, b_1 < b_2$, $b_1 M_1 \leq b_2 M_2$
(case 9) $M_1 < M_2, b_1 < b_2$, $b_1 M_2 \leq b_2 M_1$
Type IV and conditions
(case 10) $M_1 > M_2, b_1 > b_2$, $b_2 M_1 > b_1 M_2$
(case 11) $M_1 > M_2$, $b_1 = b_2$
(case 12) $M_1 > M_2, b_1 < b_2$, $b_1 M_1 > b_2 M_2$

Table 1: The behavior of $g(I)$ with respective to system parameters in Chen [7].

of equations:

$$T = \frac{-D_2 + \sqrt{D_2^2 + 4U_2}}{2\beta d_T}, \tag{7}$$

$$V = \frac{d_T}{d_V}[\frac{-D_1 + \sqrt{D_2^2 + 4U_2}}{2\beta d_T}], \tag{8}$$

$$E = \frac{-c_E}{g(I)}, \tag{9}$$

$$I \cdot H_1(I) = 0, \tag{10}$$

where $H_1(I) = [\frac{2\beta s_T}{2\beta k s_T + D_2 + \sqrt{D_2^2+4U_2}} - d_I + \frac{pc_E}{g(I)}]$. It can be noted that T, V, E are expressed in terms of I in Eq. (7) to Eq. (9), respectively. The values of I can be obtained by solving the Eq. (10). One root of this equation is $I = 0$. This root leads to one equilibrium state $Q_1 = (\frac{s_T}{d_T}, 0, 0, \frac{c_E}{d_E})$. Other roots of this equation are the roots of $H_1(I) = 0$. To obtain the explicit expressions of these roots and henceforth other equilibrium states, it requires to solve a fifth order polynomial equation and this is generally difficult. Denote $H(I) =$

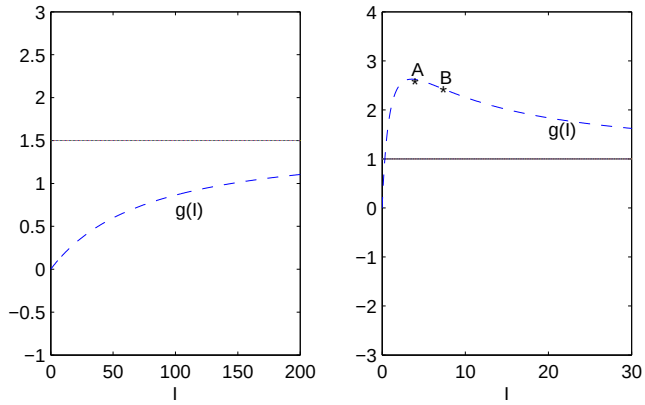

Figure 1: Graphs of type I (left hand side) and type II functions (right hand side). The system parameters for the graph on the left hand side are $b_1 = 4$, $M_1 = 100$, $b_2 = 2.5$, $M_2 = 120$ and $d_E = 0$. The parameters for the graph on the right hand side are $b_1 = 6$, $M_1 = 1.25$, $b_2 = 5$, $M_2 = 6.25$ and $d_E = 0$. The local maximum is located at $I^* = 3.55$ (point A) and the inflection point is located at $I^{**} = 6.96$. These parameters are chosen for better visual presentation and might not be meaningful in biological sense. Chen [7]

$(I + \frac{d_T d_V}{\beta k} - \frac{s_T}{k})^2 + 4\frac{d_T d_V s_T}{\beta k^2}$. To analyze these roots, the equation $H_1(I) = 0$ is reformed as

$$g(I) = \frac{pc_E}{d_I}\left[\frac{I + \sqrt{H(I)} + \frac{d_T d_V + \beta s_T}{\beta k}}{I + \sqrt{H(I)} + \frac{d_T d_V + \beta s_T}{\beta k} - 2\frac{s_T}{d_I}}\right]. \tag{11}$$

Denote $H_2(I)$ the function of the right hand side of Eq. (11). The solutions to Eq. (11) may be considered from the intersection points of the graphs of $g(I)$ and $H_2(I)$. The graph of $g(I)$ has been fully characterized. The graph of $H_2(I)$ can be analyzed with the following lemma and its proof is provided in the Appendix.

Lemma 3. *Let $y(I)$ be a function defined as*

$$y(I) = \frac{I + \sqrt{(I + a - b)^2 + 4ab} + (a + b)}{I + \sqrt{(I + a - b)^2 + 4ab} + (a + b) - c} \tag{12}$$

with $a, b, c > 0$. *Let* $\overline{I} = \frac{c[c-2(a+b)]}{2(c-2b)}$. *Depending on the parameters* a, b *and* c, *the graph of* $y(I)$ *can be classified into one of the following three cases:*

(i) $(c > 2(b+a))$ *The function* $y(I)$ *has horizontal asymptotes* $y = 1$, $y = \frac{-2b}{(c-2b)}$ *and a vertical asymptote* $I = \overline{I}$ *with* $\overline{I} > 0$. *The function* $y(I)$ *is decreasing and greater than one when* $I \in (\overline{I}, \infty)$ *and it is decreasing and less than* $\frac{-2b}{(c-2b)}$ *when* $I \in (-\infty, \overline{I})$. *Furthermore, as* $I \to (\overline{I})^+$, *the function* $y(I)$ *goes to* ∞ *and as* $I \to \infty$, *it approaches one. When* $I \to (\overline{I})^-$, $y(I)$ *goes to* $-\infty$ *and as* I *goes to* $-\infty$, *it approaches* $\frac{-2b}{(c-2b)}$.

(ii) $(c > 2b$ *but* $c \leq 2(a+b))$ *The function* $y(I)$ *has the same properties as (i) except that* $\overline{I} \leq 0$.

(iii) $(c < 2b$ *or* $c = 2b)$ *The function* $y(I)$ *is decreasing and greater than one within the interval* $[0, \infty)$.

Proof. See Appendix. The graphs of $y(I)$ are presented in Fig. 2.

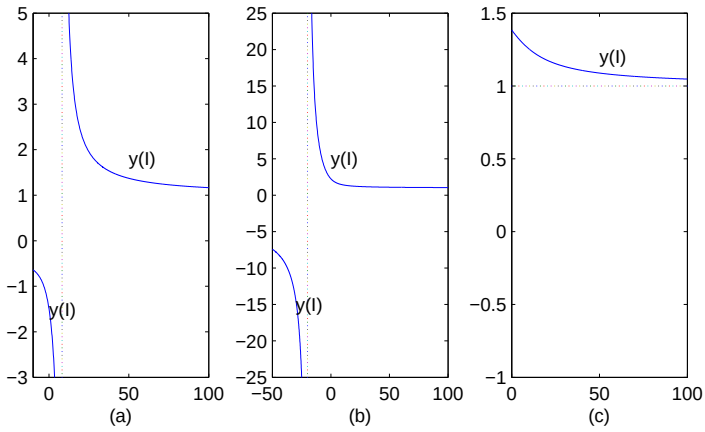

Figure 2: The graphs of $y(I)$. The graphs of case (i), (ii) and (iii) in Lemma 3 are shown in graph (a), (b) and (c), respectively. For case (i), the parameters are $a = 5$, $b = 4$ and $c = 30$. For case (ii), the parameters are $a = 5$, $b = 4$ and $c = 10$. For case (iii), the parameters are $a = 10$, $b = 8$ and $c = 10$. Only case (i) can lead to biologically meaningful equilibrium states.

Based on Lemma 3, it can be shown that the intersection of $g(I)$ and $H_2(I)$ may lead to biologically meaningful equilibrium states other than Q_1 (virus eradication state) only when case (i) is valid. In addition, the stability of

Q_1 can be investigated. They are stated in the following two theorems and are essential in deriving a necessary condition for functional curability in the discussion section. In the following theorems, R_0, defined as $\frac{s_T \beta k}{d_V d_I d_T}$, is the basic reproduction number. It represents the number of newly infected cells caused by one infected cell when all other cells are kept uninfected in the basic model of virus dynamics in Nowak and May [11].

Theorem 4. *The equilibrium state Q_1 is biologically meaningful. It is stable if the following inequality*

$$(\frac{p}{k}\frac{c_E}{d_E} + \frac{d_I}{k} + \frac{d_V}{\beta}\frac{p}{k}\frac{c_E}{d_E}\frac{d_T}{s_T} + \frac{1}{R_0} > 1)$$

holds. On the other hands, if

$$(\frac{p}{k}\frac{c_E}{d_E} + \frac{d_I}{k} + \frac{d_V}{\beta}\frac{p}{k}\frac{c_E}{d_E}\frac{d_T}{s_T} + \frac{1}{R_0} < 1),$$

it is not stable.

Proof. Since $\frac{s_T}{d_T} > 0$ and $\frac{c_E}{d_E} > 0$, the equilibrium state Q_1 is biologically meaningful. The stability can be considered from the eigenvalues of the characteristic equation of Eq. (1) to Eq. (4). The four eigenvalues are

$$x_1 = \frac{-(d_I + d_V + p\frac{c_E}{d_E} + \beta\frac{s_T}{d_T}) + \sqrt{(d_I - d_V + p\frac{c_E}{d_E} - \beta\frac{s_T}{d_T})^2 + 4k\beta\frac{s_T}{d_T}}}{2},$$

$$x_2 = \frac{-(d_I + d_V + p\frac{c_E}{d_E} + \beta\frac{s_T}{d_T}) - \sqrt{(d_I - d_V + p\frac{c_E}{d_E} - \beta\frac{s_T}{d_T})^2 + 4k\beta\frac{s_T}{d_T}}}{2},$$

$x_3 = -d_E$, and $x_4 = -d_T$, respectively. Since k, β, s_T and d_T are all positive numbers, four eigenvalues are all real numbers with x_2, x_3 and $x_4 < 0$. Therefore, the equilibrium state Q_1 is stable if $x_1 < 0$ and this directly leads to the stated condition.

Theorem 5. *Suppose that the immune induction function $g(I)$ is a type II function. It possesses a positive local maximum at $I = I^*$ and a horizontal asymptote $y = y_h$. Denote*

$$h_H = H_2(0) = \left(\frac{pc_E}{d_I} + \frac{pc_E}{d_I}\frac{\beta k s_T}{d_I d_V d_T + \beta d_I s_T - \beta k s_T}\right).$$

Also, denote $\overline{I} = \frac{c[c-2(a+b)]}{2(c-2b)}$ *with* $a = \frac{d_T d_V}{\beta k}$, $b = \frac{s_T}{k}$ *and* $c = \frac{2s_T}{d_I}$. *Then, the following statements hold:*

(i) *If the conditions* $d_E \leq -h_H$ *and* $h_H \leq y_h$ *hold, there exists no biologically meaningful equilibrium state other than* Q_1.

(ii) *If the conditions* $\frac{s_T}{d_I} > (\frac{d_V d_T}{\beta k} + \frac{s_T}{k})$ *and* $d_E > -h_H$ *hold, there exists at least one biologically meaningful equilibrium state other than* Q_1.

(iii) *If the conditions* $\frac{s_T}{d_I} > (\frac{d_V d_T}{\beta k} + \frac{s_T}{k})$, $d_E > -h_H$ *and* $I^* \geq \overline{I}$ *hold, there exists exactly one biologically meaningful equilibrium state other than* Q_1.

Proof. From Eq. (7) and Eq. (8), if $I > 0$, T and V are all nonnegative. Therefore, from Eq. (9), if there exists an $I_e > 0$ such that $H_2(I_e) = g(I_e)$ and $g(I_e) < 0$, then I_e leads to a biologically meaningful equilibrium state other than Q_1. This may occur only if case (i) in Lemma 3 holds and this case leads to the condition $\frac{s_T}{d_I} > (\frac{d_V d_T}{\beta k} + \frac{s_T}{k})$. The rest of the theorem can be observed from the graphs of $g(I)$ and $H_2(I)$ in Fig. 1 and Fig. 2. Case (i) is obtained from the conditions $g(0) \geq H_2(0)$ and $y_h \geq H_2(0)$. Case (ii) is obtained from the condition $g(0) < H_2(0)$, which leads to $d_E > -h_H$. When $I^* \geq \overline{I}$, $g(I)$ and $H_2(I)$ can intersect exactly once within $[0, \overline{I})$ and case (iii) follows directly.

3. Numerical Examples

In this section, several numerical examples are presented to justify the theoretical analysis. In the literature, the values of system parameters have be estimated based on experimental data and reported on different articles. These values are adopted in the work by Adams, Banks et al. [1] and summarized in Table 2. In the following numerical studies, some of the values of these parameters are modified for demonstrating the correctness of the presented theorems.

(a) Choose $\beta = 1.6 \times 10^{-7}(\frac{ml}{virions \cdot day})$ and $k = 20(\frac{virions}{day})$. The values of the rest parameters are kept unchanged. The equilibrium states of the system and their corresponding eigenvalues of the characteristic equations are shown in Table 3.

With the selected values of system parameters, it can be computed that $R_0 = 0.35$ and $\frac{p}{k}\frac{c_E}{d_E} + \frac{d_I}{k} + \frac{d_V}{\beta}\frac{p}{k}\frac{c_E}{d_E}\frac{d_T}{s_T} + \frac{1}{R_0} = 2.8792$. Moreover, the immune induction function $g(I)$ is a type II function. According to Theorem 4, the equilibrium state Q_1 is biologically meaningful and stable. This can be confirmed by the computed eigenvalues. All of its eigenvalues are negative. Furthermore, it can be computed that $s_T/d_I = 1.4286 \times 10^4$ and $(\frac{d_V d_T}{\beta k} + \frac{s_T}{k}) = 4.1125 \times 10^4$.

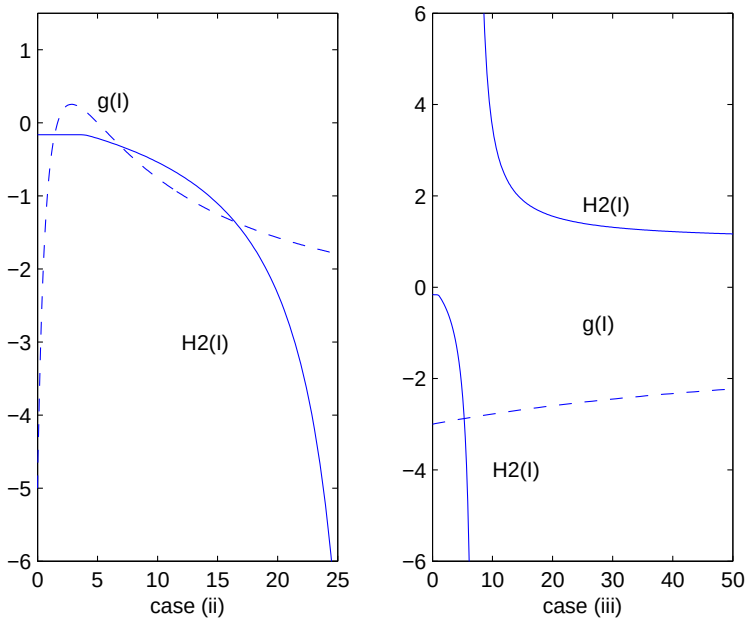

Figure 3: The graphs of the intersection of $H_2(I)$ and $g(I)$. The graphs of case (ii) and case (iii) in Theorem 5 are shown on the left hand side and right hand side, respectively. The parameters of graph on the right hand side are $s_T = 20$, $d_T = 0.01$, $\beta = 8$, $d_I = 0.7$, $p = 0.7$, $k = 5$, $d_V = 13$, $c_E = 1$, $b_1 = 12$, $M_1 = 1$, $b_2 = 10$, $M_2 = 5$ and $d_E = 5$. The parameters of this graph on the right hand side are $s_T = 5$, $d_T = 0.01$, $\beta = 8$, $d_I = 0.7$, $p = 0.7$, $k = 5$, $d_V = 13$, $c_E = 1$, $b_1 = 3$, $M_1 = 100$, $b_2 = 2.5$, $M_2 = 500$ and $d_E = 0.9999$.

According to Theorem 5, the equilibrium states Q_2, Q_3 and Q_4 are not biologically meaningful. The computed result is consistent with the prediction of the theorem. Based on the obtained information, this system achieves the state of virus eradication.

(b) The values of the system parameters are chosen to be the same as the values summarized in Table 2. The equilibrium states of the system and their corresponding eigenvalues of the characteristic equations are shown in Table 4.

With the selected values of parameters, it can be computed that $R_0 =$

	Value		Value
s_T	$10^4(\frac{cells}{ml\cdot day})$	c_E	$1(\frac{cells}{ml\cdot day})$
d_T	$0.01(\frac{1}{day}$	b_1	$0.3(\frac{1}{day})$
β	$8\times 10^{-7}(\frac{ml}{virions\cdot day})$	M_1	$100(\frac{cells}{ml})$
d_I	$0.7(\frac{1}{day})$	b_2	$0.25(\frac{1}{day})$
p	$10^{-5}(\frac{ml}{cells\cdot day})$	M_2	$500(\frac{cells}{ml})$
k	$100(\frac{virions}{day})$	d_E	$0.1(\frac{1}{day})$
d_V	$13(\frac{1}{day})$		

Table 2: The values of system parameters in Adams et al. [1].

Eq.	T	I	V	E
Q_1	1.0×10^6	0	0	10
Q_2	2.95×10^6	-2.78×10^4	-4.13×10^4	18
Q_3	9.71×10^5	1217	1850	-4.64×10^4
Q_4	9.98×10^5	82	125	-4.57×10^4
Eq.	e. value1	e. value2	e. value3	e. value4
Q_1	-0.01	-0.10	-13.41	-0.45
Q_2	-14.17	0.06	-0.07	-0.054
Q_3	-13.39	-0.00 + 0.12i	-0.00 - 0.12i	-0.01
Q_4	-13.40	0.14	-0.14	-0.01

Table 3: Equilibrium states and their eigenvalues.

8.7912 and $\frac{p}{k}\frac{c_E}{d_E}+\frac{d_I}{k}+\frac{d_V}{\beta}\frac{p}{k}\frac{c_E}{d_E}\frac{d_T}{s_T}+\frac{1}{R_0}=0.1208$. Moreover, the immune induction function $g(I)$ is a type II function with a local maximum at $I^*=284$. From Theorem 4, the equilibrium state Q_1 is biologically meaningful but is not stable. This can be confirmed by the computed eigenvalues. Not all its eigenvalues are negative and henceforth it is not stable. Furthermore, it can be computed that $s_T/d_I=1.4286\times 10^4$ and $(\frac{d_V d_T}{\beta k}+\frac{s_T}{k})=1725$. The terms $H_2(0)$ and $\overline{I}$ defined in Theorem 5 are -1.9619×10^{-6} and 1.2649×10^4, respectively. According to parts (ii) of Theorem 5, there exists at least one biologically meaningful equilibrium state other than Q_1. In this case, the equilibrium states Q_2, Q_3 and Q_4 are all biologically meaningful. From the computed eigenvalues, Q_2 and Q_4 are stable but Q_3 is not stable. In this system, two stable biologically meaningful equilibrium states Q_2 and Q_4 coexist. Therefore, it is

Eq.	T	I	V	E
Q_1	1.0×10^6	0	0	10
Q_2	1.15×10^5	1.26×10^4	9.66×10^4	23
Q_3	5.80×10^5	1218	9046	2.75×10^5
Q_4	9.54×10^5	82	596	4.85×10^5
Eq.	e. value1	e. value2	e. value3	e. value4
Q_1	-0.01	-0.10	-18.34	3.84
Q_2	-13.80	-0.042 + 0.22i	-0.042 - 0.22i	-0.042
Q_3	-16.91	0.22	-0.21	-0.024
Q_4	-19.31	-0.0016 + 0.39i	-0.0016 - 0.39i	-0.0103

Table 4: Equilibrium states and their eigenvalues.

functional curable with a high-viral-load state Q_2 and a low-viral-load state Q_4.

(c) Choose $M_1 = 1 \times 10^4(\frac{cells}{ml})$ and $M_2 = 5 \times 10^4(\frac{cells}{ml})$. The values of the rest parameters are kept unchanged. The equilibrium states of the system and their corresponding eigenvalues of the characteristic equations are shown in Table 5.

Eq.	T	I	V	E
Q_1	1.0×10^6	0	0	10
Q_2	1.32×10^4	1.22×10^5	9.36×10^5	-6.19×10^4
Q_3	1.15×10^5	1.27×10^4	9.67×10^4	-58
Q_4	1.67×10^5	8205	6.25×10^4	3.16×10^4
Eq.	e. value1	e. value2	e. value3	e. value4
Q_1	-0.01	-0.10	-18.34	3.84
Q_2	-13.10	-0.67	-0.04 + 0.14i	-0.04 - 0.14i
Q_3	-13.80	-0.042 + 0.22i	-0.042 - 0.22i	0.017
Q_4	-14.15	-0.022 + 0.24i	-0.022 - 0.24i	-0.013

Table 5: Equilibrium states and their eigenvalues.

With the selected values of system parameters, it can be computed that $R_0 = 8.7912$ and $\frac{p}{k}\frac{c_E}{d_E} + \frac{d_I}{k} + \frac{d_V}{\beta}\frac{p}{k}\frac{c_E}{d_E}\frac{d_T}{s_T} + \frac{1}{R_0} = 0.1208$. Moreover, the immune induction function $g(I)$ is a type II function with a local maximum at $I^* = 2.8416 \times 10^4$. According to Theorem 4, the equilibrium state Q_1

is biologically meaningful but is not stable. This can be confirmed by the computed eigenvalues. Not all its eigenvalues are negative and henceforth it is not stable. Furthermore, it can be computed that $s_T/d_I = 1.4286 \times 10^4$ and $(\frac{d_V d_T}{\beta k} + \frac{s_T}{k}) = 1725$. The terms $H_2(0)$ and $\overline{I}$ defined in Theorem 5 are -1.9619×10^{-6} and 1.2649×10^4, respectively. According to part (iii) of Theorem 5, there exists exactly one biologically meaningful equilibrium state other than Q_1. In this case, except Q_1, the only biologically meaningful equilibrium state is Q_4. From the computed eigenvalues, it is stable because all its eigenvalues have negative real parts. Based on the obtained information, this system possesses only one stable biologically meaningful equilibrium state Q_4. Because the viral load at the state Q_4 is relatively high, this system can be recognized as the case of persistent infection.

4. Discussion

Based on the obtained theoretical results, some important biological insights are concluded as follows.

(1) Consider the basic model of virus dynamics:

$$\frac{dT(t)}{dt} = s_T - d_T \cdot T(t) - \beta \cdot T(t) \cdot V(t), \tag{13}$$

$$\frac{dI(t)}{dt} = \beta \cdot T(t) \cdot V(t) - d_I \cdot I(t), \tag{14}$$

$$\frac{dV(t)}{dt} = k \cdot I(t) - d_V \cdot V(t). \tag{15}$$

The classical result in Nowak and May [11] indicates that virus eradication state is stable if the basic reproduction number $R_0 < 1$. If $R_0 > 1$, it is not stable. Define the modified basic reproduction number $R_0^{'}$ as $\frac{1}{R_0^{'}} = \frac{pc_E}{kd_E} + \frac{d_I}{k} + \frac{d_V pc_E d_T}{\beta k d_E s_T} + \frac{1}{R_0}$. In the Adams system, the immune response is taken into account. From Theorem 4, virus eradication state is stable only when $R_0^{'} < 1$. Because $R_0^{'} < R_0$, this implies that due to the effect of immune clearance, the virus population becomes extinct within hosts easier.

(2) The number of biologically meaningful equilibrium states can be further discussed when $R_0^{'} < 1$. From the proof of Theorem 5, if $\frac{s_T}{d_I} < (\frac{d_V d_T}{\beta k} + \frac{s_T}{k})$, no biologically meaningful equilibrium states other than Q_1 exist. Furthermore, by assuming $\frac{s_T}{d_I} > (\frac{d_V d_T}{\beta k} + \frac{s_T}{k})$ to be valid, the condition $d_E < -h_H$ in part (i)

of Theorem 5 is equivalent to the condition $R_0^{'} < 1$. Therefore, from part (i) of Theorem 5, unless $h_H > y_h$, it may be concluded that Q_1 is the only stable and biologically meaningful equilibrium state when $R_0^{'} < 1$. In other words, the virus population eventually becomes extinct under this condition. Because $0 > h_H$, in biological viewpoints, $0 > h_H > y_h$ implies that stable equilibrium states other than Q_1 could exist only if the immune response deeply attenuates at high viral load. However, whether this does occur cannot be concluded based on this study.

(3) In part (ii) and part (iii) of Theorem 5, by assuming $\frac{s_T}{d_I} > (\frac{d_V d_T}{\beta k} + \frac{s_T}{k})$ to be valid, it can be shown that the condition $d_E > -h_H$ is equivalent to the condition $R_0^{'} > 1$. That is, conditions of part (ii) and part (iii) are valid only when Q_1 is unstable. Furthermore, a functional cure may occur only if at least two stable equilibrium states other than Q_1 coexist in the system due to the proper intersection of $g(I)$ and $H_2(I)$. It can be noted that this cannot be possible when the local maximum I^* of $g(I)$ is on the right hand side of the vertical asymptote of $H_2(I)$ as shown in Fig. 3. This condition implies a criterion that a functional cure is possible only under the circumstance that the capability of immune stimulation starts to attenuate when the density of infected cells is below a threshold $\overline{I} = \frac{c[c-2(a+b)]}{2(c-2b)}$ with $a = \frac{d_T d_V}{\beta k}$, $b = \frac{s_T}{k}$ and $c = \frac{2s_T}{d_I}$. As it was pointed out in Adams et al. [1] and Bonhoeffer et al. [6], such attenuation is caused by immune impairment at high viral load. In our previous study by Chen [7], we consider a system similar to the Adams system except that the Adams system includes an additional term $-\beta T(t)V(t)$ in Eq. (3). We reach the same conclusion that a functional cure is possible only if the capability of immune stimulation starts to attenuate when the density of infected cells is below a threshold (the thresholds of two systems are different due to the additional term in the Adams system). The finding in this study suggests that our conclusion is robust under different accuracy in modeling HIV infection and the reached conclusion is a fundamental principle in governing the phenomenon of a functional cure.

(4) From the numerical examples, realistic system parameters exist such that the system may possesses one or multiple stable equilibrium states in modeling various reported clinical outcomes. Therefore, it reconfirms that the Adams system is a suitable model in studying the functional curability problems.

Appendix

Proof of Lemma 3

For notational convenience, denote $A(I) = \sqrt{(I+a-b)^2 + 4ab}$, $B(I) = (I+a+b)$ and $C(I) = I+a-b$. Moreover, let $p_1(I) = A(I)+B(I)$, $p_1{}^*(I) = A(I)-B(I)$, $p_2(I) = A(I) + C(I)$, $p_2{}^*(I) = A(I) - C(I)$, $p_3(I) = A(I) + B(I) - c$, and $p_3{}^*(I) = A(I) - B(I) + c$. The derivative of $y(I)$ is

$$y'(I) = \frac{-c[A(I) + C(I)]}{A(I)[A(I) + B(I) - c]^2}.$$

To prove this lemma, we consider the properties of the numerators and the denumerators of $y(I)$ and $y'(I)$, respectively.

We first show that the numerator of $y(I)$ is always positive. Consider the product $p_1(I)p_1^*(I) = -4bI$. When $I > 0$, the product is negative. The functions $p_1(I)$ and $p_1^*(I)$ are of opposite signs. Because $a, b, c > 0$, it is easy to check that $p_1(I) > 0$ when $I > 0$. Therefore, the function $p_1^*(I) < 0$ when $I > 0$. When $I = 0$, it can be observed that $p_1(I) > 0$ and $p_1^*(I) = 0$. When $I < 0$, the product of $p_1(I)$ and $p_1^*(I)$ is positive. These two functions are of the same sign. Furthermore, notice that the term $-4bI$ can be zero only when $I = 0$. This indicates that the function $p_1(I)$ can never be zero. By continuity of $p_1(I)$ and intermediate value theorem, if $p_1(I) < 0$ when $I < 0$, there exists some constant w such that $p_1(I) = 0$ at $I = w$. This contradicts to the fact that $p_1(I)$ can never be zero. From the discussion of all cases $I > 0$, $I = 0$ and $I < 0$, it can be concluded that $p_1(I)$ is always positive.

Similarly, it can be shown that the numerator of $y'(I)$ is negative. Consider the product $p_2(I)p_2^*(I) = 4ab$. Because $a, b > 0$, this implies that $p_2(I)$ and $p_2^*(I)$ are of the same sign and they can never be zero. By continuity, both functions do not change their signs. When $I > 0$, it is easy to observe that $p_2(I)$ is positive. Therefore, both functions $p_2(I)$ and $p_2^*(I)$ are positive and the numerator of $y'(I)$, $-cp_2(I)$, is always negative.

We next analyze the denumerator of $y(I)$. Consider the product $p_3(I)p_3^*(I) = 2I(c-2b) + c[2(a+b) - c]$. To study the properties of $p_3(I)$, it requires to consider three cases: (1) $c = 2b$,(2) $c > 2b$, and (3) $c < 2b$. When $c = 2b$, the function $p_3(I)$ is equivalent to $p_2(I)$ and henceforth it is always positive. The case $c > 2b$ can be divided into two subcases: $c > 2(a + b)$ and $c \leq 2(a + b)$. We first consider the first subcase. Rewrite the product as $p_3(I)p_3^*(I) = 2(c-2b)(I-\overline{I})$. It indicates that $p_3(I)$ and $p_3^*(I)$ can only be zero

at $I = \overline{I}$. It can be computed that $p_3(\overline{I}) = \sqrt{\left[\frac{(c-2b)^2+4ab}{2(c-2b)}\right]^2} + \left[\frac{-(c-2b)^2-4ab}{2(c-2b)}\right]$ and $p_3^*(\overline{I}) = \sqrt{\left[\frac{(c-2b)^2+4ab}{2(c-2b)}\right]^2} - \left[\frac{-(c-2b)^2-4ab}{2(c-2b)}\right]$. Clearly, because $c > 2b$, it can be observed that $p_3(\overline{I}) = 0$ but $p_3^*(\overline{I}) \neq 0$. By continuity of $p_3^*(I)$ and intermediate value theorem, it may be argued that the function $p_3^*(I)$ does not change sign. Since $p_3^*(I)$ is positive as I goes to minus infinity, it is always positive. Therefore, the sign of $p_3(I)$ follows the sign of $2(c-2b)(I-\overline{I})$. It can be concluded that the function $p_3(I)$ is greater than, equals to and is less than zero when $I > \overline{I}$, $I = \overline{I}$, and $I < \overline{I}$, respectively. By the same arguments, in the subcase $c \leq 2(a+b)$, the function $p_3(I)$ is also greater than, equals to and is less than zero when $I > \overline{I}$, $I = \overline{I}$, and $I < \overline{I}$, respectively. We now consider the case $c < 2b$. From $p_3(\overline{I}) = \sqrt{\left[\frac{(c-2b)^2+4ab}{2(c-2b)}\right]^2} + \left[\frac{-(c-2b)^2-4ab}{2(c-2b)}\right]$, it is easy to see that $p_3(\overline{I}) \neq 0$ and therefore it does not achieve zero. By continuity of $p_3(I)$ and intermediate value theorem, the function $p_3(I)$ does not change sign. Since $p_3(I)$ is positive as I goes to infinity, it is always positive.

With the properties of the numerators and denumerators of $y(I)$ and $y'(I)$, we now prove (i), (ii), and (iii). For part (i), we first consider the asymptotes of $y(I)$. As I goes to infinity, the function $y(I)$ approaches one. As I goes to $\overline{I}$, the denumerator of function $y(I)$ approaches zero. Furthermore, consider

$$y(I) = \frac{p_1(I)}{p_3(I)} = \frac{p_1(I)p_1^*(I)p_3^*(I)}{p_3(I)p_3^*(I)p_1^*(I)} = \frac{-4bIp_3^*(I)}{2(c-2b)(I-\overline{I})p_1^*(I)}. \tag{16}$$

From the definitions of $p_1(I), p_1{}^*(I), p_3(I)$ and $p_3{}^*(I)$, it can be seen that as I goes to minus infinity, the function $y(I)$ approaches $\frac{-2b}{(c-2b)}$. Therefore, the function $y(I)$ has horizontal asymptotes $y = 1$, $y = \frac{-2b}{(c-2b)}$ and a vertical asymptote $I = \overline{I}$. The behavior of $y(I)$ as I approaches $\overline{I}$, infinity and minus infinity, respectively, can also be easily observed. From the analysis of $p_2(I)$, the function $y'(I)$ is always negative except that it does not exist at $I = \overline{I}$. This indicates that $y(I)$ is decreasing over the intervals $(\overline{I}, \infty)$ and $(-\infty, \overline{I})$, respectively. It remains to show that $y(I) > 1$ when $I > \overline{I}$ and $y(I) < \frac{-2b}{(c-2b)}$ when $I < \overline{I}$. They may be observed from the numerator and the denumerator of $y(I)$. From Eq. (12), as I goes to infinity, the absolute value of the numerator is strictly greater than the absolute value of the denumerator. Moreover, the function $y(I)$ is decreasing over the interval $(\overline{I}, \infty)$. Therefore, the function $y(I) > 1$ when $I > \overline{I}$. It can be similarly proved that $y(I) < \frac{-2b}{(c-2b)}$ when $I < \overline{I}$.

The proof of the statement in part (ii) is exactly the same as that of part (i). We next prove (iii). First, consider $c < 2b$. From the property of $p_2(I)$,

the function $y'(I)$ is always negative. This indicates that $y(I)$ is decreasing. Furthermore, from the properties of $p_1(I)$ and $p_3(I)$, the function $y(I)$ is always positive and is greater than one. The function $y(I)$ evaluated at $I = 0$ is $\frac{2(a+b)}{2(a+b)-c}$. As I goes to infinity, $y(I)$ approaches its horizontal asymptote $y = 1$ and henceforth it is greater than one. The proof for case $c = 2b$ is the same as that of case $c < 2b$ except that $y(0) = \frac{a+b}{a}$ in this case.

References

[1] B.M. Adams, H.T. Banks, H. Kwon and H.T. Tran, Dynamic multidrug therapies for HIV: optimal and STI control apporahces, *Math. Biosci. Eng.*, **2** (2004), 223-241.

[2] C.L. Althaus and R.J. De Boer, Intracellular transactivation of HIV can account for the decelerating decay of virus load during drug therapy, *Mol. Syst. Biol.*, **6** (2010), 348.

[3] N.M. Archin, N.K. Vaidya, J.D. Kuruc, A.L. Liberty, A. Wiegand, M.F. Kearney, M.S. Cohen, J.M. Coffin, R.J. Bosch, C.L. Gay, J.J. Eron, D.M. Margolis and A.S. Perelson, Immediate antiviral therapy appears to restrict resting CD4+ cell HIV-1 infection without accelerating the decay of latent infection, *Proc. Natl. Acad. Sci. U.S.A.*, **109** (2012), 9523-9528.

[4] R.A. Arnaout, M.A. Nowak and D. Wodarz, HIV-1 dynamics revisited: biphasic decay by cytotoxic T lymphocyte killing? *Proc. Biol. Sci.*, **267** (2000), 1347-1354.

[5] B. Autran, B. Descours, V. Avettand-Fenoel and C. Rouzioux, Elite controllers as a model of functional cure, *Curr. Opin. HIV AIDS*, **6** (2011), 181-187.

[6] S. Bonhoeffer, M. Rembiszewski et al., Risks and benefits of structured antiretroviral drug therapy interruptions in HIV-1 infection, *AIDS*, **14** (2000), 2313-2322.

[7] J.H. Chen, An analysis of functional curability on HIV infection models with Michaelis-Menten-type immune response and its generalization, Submitted to: *Discrete and Continuous Dynam. Systems - Series B.*

[8] W.S. Hlavacek, C. Wofsy and A.S. Perelson, Dissociation of HIV-1 from follicular dendritic cells during HAART: mathematical analysis, *Proc. Natl. Acad. Sci. U.S.A.*, **96** (1999), 14681-14686.

[9] D.D. Ho, A.U. Neuman, A.S. Perelson, W. Chen, J.M. Leonard and M. Markowitz, Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection, *Nature*, **373** (1995), 123-126.

[10] M.A. Nowak, S. Bonhoeffer, G.M. Shaw and R.M. May, Anti-viral drug treatment: dynamics of resistance in free virus and infected cell populations, *J. Theor. Biol.*, **184** (1997), 203-217.

[11] M.A. Nowak and R.M. May, *Virus Dynamics*, Oxford University Press, New York (2000).

[12] A.S. Perelson, Modeling the within-host dynamics of HIV infection, *BMC Biology*, **11** (2013), 1-10.

[13] R.M. Ribeiro, S. Bonhoeffer and M.A. Nowak, The frequency of resistant mutant virus before antiviral therapy, *AIDS*, **12** (1998), 461-465.

[14] L. Rong and A.S. Perelson, Modeling HIV persistence, the latent reservoir, and viral blips, *J. Theor. Biol.*, **260** (2009), 308-331.

[15] G. Vanham and E. Van Gulck, Can immunotherapy be useful as a "functional cure" for infection with Human Immunodeficiency Virus-1? *Retrovirology*, **9** (2012), 1-21.

[16] X. Wei, S.K. Ghosh, M.E. Taylor, J.A. Johnson, E.A. Emini, P. Deutsch, J.D. Lifson, S. Bonhoeffer, N.A. Nowak, B.H. Hahn, et al., Viral dynamics in human immunodeficiency virus type 1 infection, *Nature*, **373** (1995), 117-122.

[17] D. Wodarz, *Killer Cell Dynamics: Mathematical and Computational Approaches to Immunology*, Springer, New York (2007).

[18] http://www.iasociety.org/What-we-do/Towards-an-HIV-Cure/Activities/The-Rome-Statement, Accessed 22 January 2016.