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**EPIDEMIOLOGY OF HIV IN CUBA, 1986-2008:
MODELING DETECTION WITH TEMPORALLY VARYING PARAMETERS.**

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Abstract

A nonlinear compartmental model is developed for the HIV detection system in Cuba with different types of detections, some random and others non-random. We analyze the dynamics of this system, compute the reproduction numbers, and use the data from the Cuban HIV/AIDS epidemic between 1986-2008 to fit the model. We obtain estimates for the detection-related parameters during two separate time periods to reflect the timeline of the implementation of various types of searches. We also estimate the magnitude of Cuban HIV epidemic and the mean time for detecting a person infected with HIV. The reproduction numbers for each time period are also computed from the sets of values of the parameters. We found that random screening is most important as a mean of surveillance, since there will always be an epidemic if the averaged total number of infections by an infective detected through random screening exceeds one. Moreover, local asymptotic stability for DFE can be achieved if (i) random screening is sufficiently effective and (ii) infection by detected HIV-positive individuals is minimal. Our results highlight the importance of education for the known infectious for the purpose of preventing further infection. If the average number of infections by a known infective exceeds unity (due to inefficient detection by random screening or lack of behavior change by the known infectious), the endemic equilibrium is always unstable and it is possible for the total number of infectious would increase without bound, if the initial infective population sizes are large and outside the domain of attraction of the disease-free equilibrium (DFE). On the other hand, if it is less than one, then either the DFE or the endemic equilibrium is globally asymptotically stable, leading to a more manageable epidemic for public health purposes, even if the disease is not eradicated. Fitting the 1986-2008 HIV data to obtain the model parameter estimates indicates that the HIV epidemic in Cuba is currently approaching an endemic equilibrium.

1 Introduction

The Cuban HIV/AIDS program was established in 1983 and the detection of the first HIV-positive person in Cuba, a heterosexual male returning from travel abroad, took place in December 1985. The first AIDS case was diagnosed in Cuba in April 1986 and passed away later that month, which signaled the official start of the AIDS epidemic in the country.

The Cuban HIV/AIDS epidemic has the lowest prevalence rate in the Caribbean region, which has the second highest prevalence rate of HIV/AIDS in the world after Sub-Saharan Africa [14]. Cuba, an archipelago in the Caribbean Basin, is formed by the island of Cuba and several smaller islands, with 11.2 million inhabitants and 6.1 million of age 15-49. Life expectancy is 75 years and 80 years for men and women, respectively [17], the highest in Latin America. The UNAIDS Epidemiological Fact Sheet on HIV and AIDS for Cuba (2008 update) reports, for Cuba, an HIV prevalence of less than 0.1 % for adults.

The Cuban HIV/AIDS program includes a detection system that allows for detection of HIV-positive cases from several sources. Some of these sources were initiated at the beginning of the program, while others were introduced later and some have been discontinued in time. Since 1993, this detection system is composed of 6 major sources. These were random screenings of blood donors, persons that were treated for other sexually transmitted infections, persons admitted to a hospital with a suspicion of HIV infection or subject to specific procedures like dialysis, and persons volunteered to be tested. In addition, detection also came from persons having received a recommendation for HIV testing from his/her general practitioner (family doctor) and through sexual partner tracing. Other minor sources include testing of all pregnant women and prison inmates that were implemented for some time intervals during this period [5].

From 1986 up to 2008 more than 34 million tests were performed, in recent years since 2002, the total number of tests performed has stabilized to 1.6-1.7 million test every year [18]. Since 1990, each time a person is tested for HIV, she/he is informed that such a test is going to be performed. From 1986, in keeping with the "partner notification program", a person tested to be HIV-positive is invited to give names and contact details of his/her sexual partners during the past two years. These partners are then traced and a recommendation for voluntary HIV testing is made. The detection system has changed over the years. For example, during the period 1986-1999, the partner notification and contact tracing detected 30.7% of the new HIV infections while the Family Doctors Program detected only 8.9% of new infections reported. From 2000 and up to September 2008, the family doctors were responsible for the detection of 31.7% of the new cases while contact tracing detected 20.4% of the new cases. From this information we can deduce that the detection system is not static in terms of the contribution to the detection of new HIV cases. Before 1999 the most important contribution was from the contact tracing and partner notification program, while after 1999 the family doctors play a dominant role in the detection system.

In a 2006 paper by Rapatski et al. [16] the authors propose that the coefficients in the model presented by two of the present authors in 2002 [4] should be considered as nonconstant. With the data up to the year 2008 now available to us, we will now focus on modeling this change in the detection system by dividing the course of Cuban HIV/AIDS epidemic into two periods of 1986-1999 and 1999-2008 (with the model-generated values for 1999 using 1986-1999 data are used as initial values for the second period), and introducing model parameters that will differentiate the detection by the family doctors from contact tracing and other (random) searches. In this sense the present paper updates its predecessor by taking into account the significant changes that have occurred during the period 1986-2008 in the detection system for HIV/AIDS in Cuba.

2 The model

As noted earlier, the primary objective of the Cuban Program to control the HIV/AIDS epidemic is the active search of persons infected with HIV long before they show any signs of AIDS. Our focus is not to model how new infections by HIV are generated, but how the HIV-infected persons are detected. We will consider the following variables and parameters.

Model Variables:

1. $X(t)$ the number of HIV infected persons that do not know they are infected at time t ,
2. $Y(t)$ the number of HIV infected persons that know they are infected at time t ,
3. $Z(t)$ the number of persons with AIDS at time t .

Model Parameters:

1. λ the rate of recruitment of new HIV infected persons infected by X ,
2. λ' the rate of recruitment of new HIV infected persons infected by Y ,
3. k_1 the rate at which the unknown HIV infected persons are detected by the system, independently of other HIV-positive persons (through "random" screening),
4. k_2 the rate at which unknown HIV-infected persons are detected by the system through contact tracing,
5. k_3 the rate at which unknown HIV infected persons are detected by the system, through the doctor,
6. β the rate at which the undetected HIV-positive persons develop AIDS, reciprocal of the mean incubation
7. β' the rate at which the detected HIV-positive persons develop AIDS, the reciprocal of the mean time it takes to go from Y to Z ,
8. μ the mortality rate of the sexually active population,
9. μ' the mortality rate of the population with AIDS.

The model flow diagram is given in Figure 1.

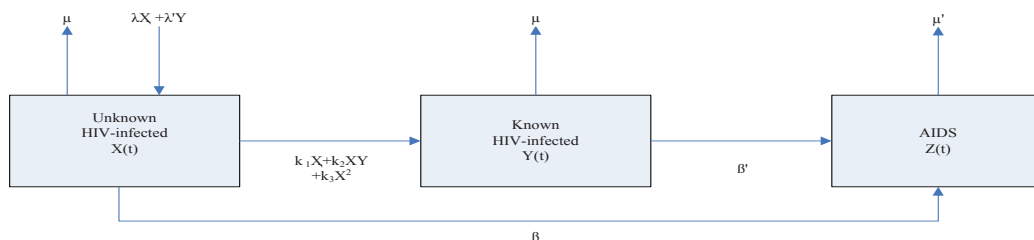


Figure 1: Model flow diagram.

The dynamics is described by the following system:

$$\begin{aligned}
\frac{dX}{dt} &= \sigma X - k_3 X^2 - k_2 XY + \lambda' Y, \\
\frac{dY}{dt} &= (k_1 + k_3 X) X - \gamma' Y + k_2 X Y, \\
\frac{dZ}{dt} &= \beta X + \beta' Y - \mu' Z.
\end{aligned} \tag{1}$$

with $\gamma = \beta + \mu$, $\sigma = \lambda - k_1 - \gamma$, $\gamma' = \beta' + \mu$ and we consider the system only in the region $\mathcal{D} = \{X \geq 0, Y \geq 0, Z \geq 0\}$. It is clear that \mathcal{D} is positively invariant under the flow induced by (1).

We give the following remarks regarding model (1):

1. In (1) there are three ways for individuals to go from "unknown HIV infected" (X) to "known HIV infected" (Y). One is through the nonlinear term $k_2 XY$ for contact tracing, where the individual is found through his contacts with persons that are known to live with HIV. The term $k_3 X^2$ models the detection through family doctors. The third way they can be detected is through the term $k_1 X$ which models all the other "random" ways of searching for seropositives. It is important to note that $1/k_1$ can be viewed as the mean time from infection to detection for the persons found through a random screening. Alternatively, we could express all manners in which an unknown infective can be detected to be in the general form of " $F(X, Y) X$ ", where $F(X, Y)$ is a recruitment function from the class X into the class Y . For our present study we will take the function $F(X, Y)$ as a polynomial of degree 1: $k_1 + k_2 Y + k_3 X$.
2. Previous study indicates that detection by contact tracing $k_2 XY$ takes a long time, with a mean time to find an infected contact of 54.3 months [4] (the mean time from detection to AIDS in Cuba is 86.8 months [4]). Of course variations are high, some persons have very few contacts and are easy to locate, others have a large number of contacts of which some are almost impossible to locate. Some persons have a lot of "casual" contacts and they do not remember enough information on these contacts to make it possible to find them, others have less contacts but with a better knowledge of their full names and sometimes even addresses that makes it possible for the Health System to find them. Some contacts, even if they are found, refuse to be tested for HIV. In general of more than 15000 contacts (or 80 % of all reported contacts) have been traced and tested. In general we try, as a first approximation, to find the value of k_2 , and its overall impact on the time it takes for a person living with HIV to be detected. The term $k_2 XY$ must be taken as an approximation of a more general term $k_2 F(X, Y)$ that could be further investigated in the future [10].
3. The term $k_3 X^2$ models the detection through family doctors. We take the term with X^2 because this detection indicates a kind of social interaction with persons that have an active sexual life that could put them at risk of infection with HIV. In such cases, the family doctors would advise these persons that they think are at risk to take a test to determine if they are HIV-infected. This source of detection has increased in importance in the detection system through the years and is not a random search in the population.
4. We assume that the known HIV-infected persons are infectious, but at a much lower rate than those that do not know they are infected due to education or change of behavior.

This has been shown, using Cuban HIV data of 1986-2000, that the infection rate of the known HIV-infected persons is about 5% of that of persons who did not yet know that they are infected [4]. In this case the infection rate of known HIV-positives λ' will be taken as a fraction of the infection rate of the undetected HIV-positive persons λ .

5. The progression to AIDS is modeled linearly, which could conceivably be modeled in a more general way. However, for the Cuban data the best fit to an incubation curve is still an exponential.
6. We assume that once a person develops AIDS it is no longer infectious.

We first consider the following two cases;

Case 1. If $\lambda' - \gamma' = 0$, the system has a disease-free equilibrium $P_0 = (0, 0, 0)$ if $\sigma + k_1 = \lambda - \gamma \neq 0$ and a set of endemic equilibria $P^* = (X^*, Y^*, Z^*)$ of the form $(\lambda' - k_2 X^*)Y^* + (\sigma + k_3 X^*)X^* = 0$ and $Z^* = \frac{\beta X^* + \beta' Y^*}{\mu'}$ if $\sigma + k_1 = \lambda - \gamma = 0$.

Case 2. If $\lambda' - \gamma' \neq 0$, the system has two equilibria, $P_0 = (0, 0, 0)$ is the disease-free equilibrium and $P^* = (X^*, Y^*, Z^*)$ is the endemic equilibrium, where

$$X^* = \frac{A}{B}, \quad Y^* = X^* \times \frac{C_1}{C_2}, \quad Z^* = \frac{\beta X^* + \beta' Y^*}{\mu'}. \quad (2)$$

with $A = \sigma \gamma' + \lambda' k_1$, $C_1 = \sigma + k_1 = \lambda - \gamma$, $C_2 = \gamma' - \lambda'$ and $B = k_2 C_1 + k_3 C_2$.

Set

$$\mathcal{R}_1 = \frac{\lambda'}{\gamma'}, \mathcal{R}_2 = \frac{\lambda}{\gamma} \text{ and } \mathcal{R}_0 = \lambda / (k_1 \gamma) + \lambda' k_1 / [\gamma' (k_1 + \gamma)] = \frac{k_1}{k_1 + \gamma} \mathcal{R}_1 + \frac{\gamma}{k_1 + \gamma} \mathcal{R}_2. \quad (3)$$

A , C_1 and C_2 can be rewritten as

$$A = \gamma' (k_1 + \gamma) (\mathcal{R}_0 - 1), \quad C_1 = \gamma (\mathcal{R}_2 - 1), \quad \text{and } C_2 = \gamma' (1 - \mathcal{R}_1).$$

The parameters \mathcal{R}_0 , \mathcal{R}_1 and \mathcal{R}_2 will play a significant role in the analysis of the behaviour of trajectories for (7).

Since Case 1 requires specific values of the parameters and hence is of little practical importance, we shall suppose in what follows that $\lambda' - \gamma' \neq 0$.

The endemic equilibrium is feasible (i.e. $P^* \in \mathcal{D}$) if and only if

$$A \times B = (\mathcal{R}_0 - 1) (\gamma k_2 (\mathcal{R}_2 - 1) + \gamma' k_3 (1 - \mathcal{R}_1)) > 0 \quad \text{and} \quad (4)$$

$$C_1 \times C_2 = \gamma \gamma' (\mathcal{R}_2 - 1) (1 - \mathcal{R}_1) > 0 \quad (5)$$

More precisely, the endemic equilibrium is feasible if and only if

$$\mathcal{R}_0 - 1, \mathcal{R}_2 - 1 \text{ and } 1 - \mathcal{R}_1 \quad (6)$$

have the same sign.

The Jacobian matrix of the linear approximation of the system in a neighborhood of an equilibrium point $P = (X, Y, Z)$ is given by

$$J(X, Y, Z) = \begin{pmatrix} \sigma - 2k_3 X - k_2 Y & \lambda' - k_2 X & 0 \\ k_1 + 2k_3 X + k_2 Y & -\gamma' + k_2 X & 0 \\ \beta & \beta' & -\mu' \end{pmatrix}.$$

There is one eigenvalue $-\mu'$ that is always strictly negative, which is associated with the variable Z , to study the stability of the equilibria of system (1), we only need to consider the system

$$\begin{aligned}\frac{dX}{dt} &= \sigma X - k_3 X^2 - k_2 XY + \lambda' Y, \\ \frac{dY}{dt} &= (k_1 + k_3 X)X - \gamma' Y + k_2 X Y.\end{aligned}\tag{7}$$

in the region $\mathcal{D}' = \{(X, Y) \mid X \geq 0, Y \geq 0\} \subset \mathcal{D}$. \mathcal{D}' , which is positively invariant under the flow induced by (7). We will denote J_1 the Jacobian matrix for the system (7) that is formed by the first two rows and columns of the matrix $J(X, Y, Z)$. Moreover, we will also denote $Q_0 = (0, 0)$ and $Q^* = (X^*, Y^*)$ to be the respective disease-free and endemic equilibria in \mathcal{D}' .

3 Local stability of Q_0 and Q^* .

3.1 Local Stability for the point Q_0 .

The Jacobian matrix at the point Q_0 is given by:

$$J_1(Q_0) = \begin{pmatrix} \sigma & \lambda' \\ k_1 & -\gamma' \end{pmatrix}$$

Q_0 , and therefore P_0 , is locally asymptotically stable (LAS for short) if and only if the trace of J_1 is strictly negative and its determinant strictly positive, i.e.

$$\begin{aligned}Q_0 \text{ LAS} &\iff \sigma - \gamma' < 0 \text{ and } -(\sigma\gamma' + k_1\lambda') > 0 \\ &\iff \sigma - \gamma' < 0 \text{ and } A < 0 \\ &\iff \mathcal{R}_0 < 1.\end{aligned}$$

When $\mathcal{R}_0 > 1$, Q_0 is unstable as a saddle equilibrium point.

3.2 Local Stability for the point Q^* .

Remember that Q^* is

$$X^* = \frac{\gamma'(k_1 + \gamma)}{B}(\mathcal{R}_0 - 1), \quad Y^* = X^* \frac{C_1}{C_2} = \frac{X^*}{\gamma'} \frac{\lambda - \gamma}{1 - \mathcal{R}_1} = \frac{X^*}{\gamma\gamma'} \frac{\mathcal{R}_2 - 1}{1 - \mathcal{R}_1}.$$

Q^* , and therefore P^* , is LAS if and only if it exists (i.e. (4) and (5) are satisfied or equivalently iff (6) is satisfied), the trace of $J_1(Q^*)$ is strictly negative and its determinant strictly positive, i.e. Q^* exists and

$$\tau_1 = \text{Tr}(J_1(Q^*)) = \sigma - \gamma' + k_2(X^* - Y^*) - 2k_3X^* < 0 \quad \text{and} \quad \Delta_1 = \det(J_1(Q^*)) > 0.\tag{8}$$

After some straight forward calculations we obtain that $\Delta_1 = A$ and condition $\Delta_1 > 0$ is equivalent to $\mathcal{R}_0 > 1$. Thus when Q_0 is LAS, if Q^* exists, it is unstable. Subsequently, when $\mathcal{R}_0 > 1$, we have also $\mathcal{R}_2 > 1$ and $\mathcal{R}_1 < 1$ to ensure $X^* > 0$, and $Y^* > 0$.

Let us suppose $\mathcal{R}_0 > 1$, $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 > 1$. Then $x = X^* > 0$ and $y = Y^* > 0$ and

$$\begin{aligned} xy\tau_1 &= (\sigma x - k_3x^2 - k_2xy)y - \gamma'xy - k_3x^2y + k_2x^2y \\ &= -\lambda'y^2 - k_3x^2y + [y(k_2x - \gamma')]x, \text{ since } \sigma x - k_3x^2 - k_2xy = -\lambda'y \text{ by (7.1)} \\ &= -\lambda'y^2 - k_3x^2y - (k_1x + k_3x^2)x, \text{ since } y(k_2x - \gamma') = -k_1x - k_3x^2 \text{ by (7.2)} \end{aligned} \quad (9)$$

which is negative and hence $\tau_1 < 0$. Finally, Q^* exists and is LAS iff $\mathcal{R}_0 > 1$ and $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 > 1$.

Remark: Q_0 being LAS implies that either Q^* does not exist in our domain, which is the case if either $B > 0$ (X^* does not exist) or $B < 0$ and $(\mathcal{R}_2 - 1)(1 - \mathcal{R}_1) < 0$ (Y^* does not exist); or Q^* exists, where $\mathcal{R}_2 < 1$ and $\mathcal{R}_1 > 1$, but Q^* is unstable.

4 Global stability of Q_0 and Q^* .

Lemma 1 *There are no periodic orbits in \mathcal{D}' .*

Proof:

Let $g : (X, Y) \mapsto \frac{1}{XY}$, then $\frac{\partial}{\partial X} \{g(X, Y)X'\} + \frac{\partial}{\partial Y} \{g(X, Y)Y'\} = -\left(\frac{\lambda'}{X^2} + \frac{k_3}{Y} + \frac{k_1 + k_3X}{Y^2}\right)$ keeps the same sign in \mathcal{D}' , and using the Dulac criteria we conclude that there are no periodic orbits in the set. ■

$\forall t \geq 0$ and $\forall k \geq 0$, we set $P_t = (X(t), Y(t))$ and $P_k = (X(t_k), Y(t_k))$ with $t_0 = 0$.

4.1 Global stability of Q_0 .

Theorem 1

If $\mathcal{R}_0 < 1$ and $\mathcal{R}_1 < 1$ then Q_0 is globally asymptotically stable (GAS for short) in \mathcal{D}' . Moreover, when $\mathcal{R}_0 > 1$, Q_0 is unstable.

Proof:

Q_0 is the unique equilibrium point in \mathcal{D}' . Let V be the function defined on \mathcal{D}' by

$$\forall (X, Y) \in \mathcal{D}', \quad V(X, Y) = \gamma'X + \lambda'Y.$$

V is a Lyapunov function for the point Q_0 on \mathcal{D}' and $\forall (X, Y) \in \mathcal{D}'$,

$$V'(X, Y) = \gamma'X [(k_1 + \gamma)(\mathcal{R}_0 - 1) + (k_3X + k_2Y)(\mathcal{R}_1 - 1)]. \quad (10)$$

$\mathcal{R}_1 < 1$ then $V'(X, Y) < 0$ for all $(X, Y) \in \mathcal{D}'$. Moreover, $V'(X, Y) = 0$ iff $X = 0$, or $\mathcal{R}_0 = 1$ and $\mathcal{R}_1 = 1$. Along the axis $\{X = 0\}$, $X' \geq 0$, we conclude that the largest invariant subset in $\{(X, Y) \in \mathcal{D}' \mid V'(X, Y) = 0\}$ is the singleton $\{Q_0\}$, and from LaSalle's invariant principle we conclude that Q_0 is GAS in \mathcal{D}' .

We have shown previously that if $\mathcal{R}_0 > 1$, Q_0 is a saddle equilibrium point. Therefore, Q_0 is unstable when $\mathcal{R}_0 > 1$. ■

Theorem 2

If $\mathcal{R}_0 < 1$, $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$, then the basin of attraction of Q_0 is a triangle formed by the axes and a line that goes through the point Q^ and has slope*

$$-\frac{\lambda_2 + \gamma' - k_2X^*}{\lambda' - k_2X^*}.$$

Proof:

Q^* is a saddle point with a stable and an unstable manifold both of dimension 1. Let λ_1 be the positive eigenvalue, λ_2 be the negative eigenvalue and E^s the eigenspace associated to λ_2 and W^u the manifold that is tangent to $Q^* + E^s$ at each point. E^s is the straight line with slope

$$-\frac{\lambda_2 + \gamma' - k_2 X^*}{\lambda' - k_2 X^*}.$$

We know that

1. $\lambda' - k_2 X^* = \frac{\lambda' B - k_2 A}{B} = \frac{\gamma'(\mathcal{R}_1 - 1)(k_2 \sigma - \lambda' k_3)}{B} > 0$ because $\mathcal{R}_1 - 1 > 0$ and both σ and B are negative.
2. $\gamma' - k_2 X^* = \frac{\gamma' B - k_2 A}{B} = \gamma'(1 - \mathcal{R}_1)(k_1 k_2 + \gamma' k_3) > 0$ because $1 - \mathcal{R}_1 < 0$ and $B < 0$. Then $\lambda_2 + \gamma' - k_2 X^* > 0$.

Hence the slope is negative. This means that there is a triangular region formed by the axes and E^s that forms the basin of Q_0 . A trajectory that starts in this region can not leave the region because the vector field at the axes points inwards and it cannot cross E^s . Therefore this region is invariant and all trajectories starting inside the region must have Q_0 as it is a ω -limit set. ■

Theorem 3

Suppose that $\mathcal{R}_0 > 1$, $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 > 1$. Then Q_0 is unstable, Q^* does not exist and trajectories are unbounded.

Proof:

We have seen before that when $\mathcal{R}_0 > 1$, Q_0 is unstable, and (6) implies that Q^* is in \mathcal{D}' . Let $N = X + Y$. Then $N' = X' + Y' = \gamma(\mathcal{R}_2 - 1)X + \gamma'(\mathcal{R}_1 - 1)Y$. Denote $a = \min(\gamma(\mathcal{R}_2 - 1), \gamma'(\mathcal{R}_1 - 1))$. Then $a > 0$ and $N' \geq a(X + Y) = aN$ so we have $N(t) \geq N(0)e^{at}$, therefore N is not bounded. ■

Let $X' = f(X, Y)$, $Y' = g(X, Y)$, $\varphi : x \mapsto x \frac{k_3 x - \sigma}{\lambda' - k_2 x}$ if $\lambda' - k_2 x \neq 0$ and $\psi : x \mapsto x \frac{k_3 x + k_1}{\gamma' - k_2 x}$ if $\gamma' - k_2 x \neq 0$. Let us note by \mathcal{C}_φ and \mathcal{C}_ψ the curves that represent the functions φ and ψ . Then

$$X' = f(X, Y) = \begin{cases} (\lambda' - k_2 X)(Y - \varphi(X)) & \text{if } \lambda' - k_2 X \neq 0 \\ X(\sigma - k_3 X) & \text{otherwise,} \end{cases} \quad (11)$$

and

$$Y' = g(X, Y) = \begin{cases} (\gamma' - k_2 X)(\psi(X) - Y) & \text{if } \gamma' - k_2 X \neq 0 \\ X(k_1 + k_3 X) & \text{otherwise.} \end{cases} \quad (12)$$

Let x such that $\lambda' - k_2 x \neq 0$ and $\gamma' - k_2 x \neq 0$, then we have

$$\psi(x) - \varphi(x) = x \frac{-Bx + A}{(\lambda' - k_2 x)(\gamma' - k_2 x)} \quad (13)$$

Theorem 4 Suppose that $\mathcal{R}_0 > 1$, $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$. Then Q_0 is unstable, Q^* does not exist and trajectories are unbounded.

Proof:

In this case, we have $\sigma < 0$, $\lambda' > \gamma'$ and $\lambda \leq \gamma$, $A = \gamma'(k_1 + \gamma)(\mathcal{R}_0 - 1) > 0$ and $B = \gamma k_2(\mathcal{R}_2 - 1) + \gamma' k_3(1 - \mathcal{R}_1) < 0$. Then we have $-Bx + A > 0$, $\forall x \geq 0$. Also, we have seen before that when $\mathcal{R}_0 > 1$, Q_0 is unstable, and (6) leads that Q^* is not in \mathcal{D}' .

Lemma 2

- If $0 < x < \frac{\gamma'}{k_2}$, then $0 < \varphi(x) < \psi(x)$.
- If $\frac{\gamma'}{k_2} < x < \frac{\lambda'}{k_2}$, then $\psi(x) < 0 < \varphi(x)$.
- If $x > \frac{\lambda'}{k_2}$, then $\varphi(x) < \psi(x) < 0$.

The proof follows directly from (13).

Remark: When φ and ψ are both nonnegative, $\mathcal{C}_\varphi \cap \mathcal{C}_\psi = \{Q_0\}$.

For $(x, y) \in \mathcal{D}'$, we set

$$D_1 = \{(x, y), x > 0, 0 < y < \varphi(x)\}, D_2 = \{(x, y), x > 0, \varphi(x) < y < \psi(x)\}, D_3 = \{(x, y), 0 \leq x < \frac{\gamma'}{k_2}, y > \psi(x)\}$$

and have the following lemma.

Lemma 3

1. If $P_t \in D_1$ then $X' < 0$ and $Y' > 0$. Moreover, by continuity, if $P_t \in \mathcal{C}_\varphi$, $X' = 0$ and $Y' > 0$.
2. If $P_t \in D_2$, then $X' > 0$ and $Y' > 0$. Moreover, by continuity, if $P_t \in \mathcal{C}_\psi$, $X' > 0$ and $Y' = 0$, if $P_t \in \mathcal{C}_\varphi$, $X' = 0$ and $Y' > 0$.
3. If $P_t \in D_3$, then $X' > 0$ and $Y' < 0$. Moreover, by continuity, if $P_t \in \mathcal{C}_\psi$, $X' > 0$ and $Y' = 0$.

For proof of Lemma 3:, see Lemma 2 and (13).

First, we remark that by Lemma 3, D_2 is positively invariant under the flow induced by (7), but the trajectories leave all bounded subregions since we have for $Y = M$, $Y' > 0$, $\forall M > 0$. By using Lemma 3, we have the following cases:

1. If $P_0 \in D_1$, then X decreases and Y increases and the trajectory must cross \mathcal{C}_φ at a time $t_1 > 0$ and enter region D_2 . But in this region, X also increases and the trajectory follows the curve \mathcal{C}_φ . Subsequently, $X(t) \xrightarrow[t \rightarrow +\infty]{} \frac{\lambda'}{k_2}$.
2. If $P_0 \in D_2$, we have the same conclusion as in the previous case.
3. If $P_0 \in D_3$, then X increases and Y decreases, hence the trajectory must cross \mathcal{C}_ψ at a time $t_1 > 0$ and enter region D_2 . Thus we have the same conclusion as previous cases. ■

4.2 Global stability of Q^* .

In this subsection we suppose that $\mathcal{R}_0 > 1$, $\mathcal{R}_1 < 1$, and $\mathcal{R}_2 > 1$. Then Q^* exists and is *LAS* and Q_0 is unstable.

Lemma 4

1. $X^* \in]0, \frac{\gamma'}{k_2}[$.

$$2. X^* \in \begin{cases}]0, \frac{\lambda'}{k_2}[& \text{if } \frac{\sigma}{k_3} < 0 < \frac{\lambda'}{k_2} \\]\frac{\sigma}{k_3}, \frac{\lambda'}{k_2}[& \text{if } 0 < \frac{\sigma}{k_3} < \frac{\lambda'}{k_2} \\]\frac{\lambda'}{k_2}, \frac{\sigma}{k_3}[& \text{if } \frac{\lambda'}{k_2} < \frac{\sigma}{k_3} < \frac{\gamma'}{k_2} \\]\frac{\lambda'}{k_2}, \frac{\gamma'}{k_2}[& \text{if } \frac{\gamma'}{k_2} < \frac{\sigma}{k_3} \end{cases}$$

Proof:

First observe that $\lambda > \gamma$, $\lambda' < \gamma'$, and $B = k_2\gamma(\mathcal{R}_2 - 1) + k_3\gamma'(1 - \mathcal{R}_1) > 0$. Hence we have

$$\begin{aligned} X^* - \frac{\gamma'}{k_2} &= \frac{\gamma'(\mathcal{R}_1 - 1)(k_1k_2 + \gamma'k_3)}{k_2B}, \\ X^* - \frac{\lambda'}{k_2} &= \frac{\gamma'(1 - \mathcal{R}_1)(k_2\sigma - \lambda'k_3)}{k_2B}, \\ X^* - \frac{\sigma}{k_3} &= \frac{(\lambda - \gamma)(\lambda'k_3 - \sigma k_2)}{k_3B}. \quad \blacksquare \end{aligned}$$

Recall that X' and Y' can be rewritten as in (11) and (12), respectively. Also (13) is equivalent to

$$\psi(x) - \varphi(x) = xB \frac{X^* - x}{(\lambda' - k_2x)(\gamma' - k_2x)}. \quad (14)$$

The sign of this difference is the sign of the product $(X^* - x)(\lambda' - k_2x)(\gamma' - k_2x)$. When φ and ψ are both nonnegative, $\mathcal{C}_\varphi \cap \mathcal{C}_\psi = \{Q_0, Q^*\}$. We now give the main theorems for the global stability of Q^* .

Theorem 5 *Suppose that $\mathcal{R}_0 > 1$, $\mathcal{R}_1 < 1$, and $\mathcal{R}_2 > 1$. If $\sigma \leq 0$, then Q^* is GAS in \mathcal{D}' .*

Proof:

For $(x, y) \in \mathcal{D}'$ set

$$\begin{aligned} D_{1,1} &= \{x > X^*, 0 < y < \psi(x)\} & D_{1,2} &= \{0 < x < X^*, 0 < y < \varphi(x)\} \\ D_1 &= D_{1,1} \cup D_{1,2} & D_2 &= \{0 < x < X^*, \varphi(x) < y < \psi(x)\} \\ D_{3,1} &= \{X^* < x < \frac{\lambda'}{k_2}, \psi(x) < y < \varphi(x)\} & D_{3,2} &= \{\frac{\lambda'}{k_2} < x < \frac{\gamma'}{k_2}, y > \psi(x)\} \\ D_3 &= D_{3,1} \cup D_{3,2} & D_{4,1} &= \{0 < x < X^*, y > \psi(x)\} \\ D_{4,2} &= \{X^* < x < \frac{\lambda'}{k_2}, y > \varphi(x)\} & D_4 &= D_{4,1} \cup D_{4,2} \end{aligned}$$

We now give a lemma which will be used in the proof of Theorem 5.

Lemma 5 *Suppose $\sigma \leq 0$.*

- (1) • If $0 < x < \frac{\lambda'}{k_2}$, then $\varphi(x) \geq 0$ and $\psi(x) \geq 0$.
• If $\frac{\lambda'}{k_2} < x < \frac{\gamma'}{k_2}$, then $\varphi(x) \leq 0$ and $\psi(x) \geq 0$.
• If $x > \frac{\gamma'}{k_2}$ then $\varphi(x) \leq 0$, and $\psi(x) \leq 0$.

(2) In $]0, \frac{\gamma'}{k_2}[$, we have

$$\psi(x) - \varphi(x) \begin{cases} > 0 & \text{if } 0 < x < X^* \quad \text{or } \frac{\lambda'}{k_2} < x < \frac{\gamma'}{k_2} \\ = 0 & \text{if } x = X^* \\ < 0 & \text{if } X^* < x < \frac{\lambda'}{k_2}. \end{cases}$$

- (3) • If $P_t \in D_1$, then $X' < 0$ and $Y' > 0$. Moreover, by continuity, if $P_t \in \mathcal{C}_\psi$ (D_1), $X' < 0$ and $Y' = 0$, if $P_t \in \mathcal{C}_\varphi$ (D_2), $X' = 0$ and $Y' > 0$.
• If $P_t \in D_2$, then $X' > 0$ and $Y' > 0$. Moreover, by continuity, if $P_t \in \mathcal{C}_\psi$, $X' > 0$ and $Y' = 0$, if $P_t \in \mathcal{C}_\varphi$, $X' = 0$ and $Y' > 0$.

- If $P_t \in D_3$, then $X' < 0$ and $Y' < 0$. Moreover, by continuity, if $P_t \in \mathcal{C}_\psi$, $X' < 0$ and $Y' = 0$ and if $P_t \in \mathcal{C}_\varphi$, $X' = 0$ and $Y' < 0$.
- If $P_t \in D_4$, then $X' > 0$ and $Y' < 0$. Moreover, by continuity, if $P_t \in \mathcal{C}_\psi$ ($D_{4,1}$), $X' > 0$ and $Y' = 0$, if $P_t \in \mathcal{C}_\varphi$ ($D_{4,2}$), $X' = 0$ and $Y' < 0$.

The proof of Lemma 5 follows from Lemma 4 and (14).

We first remark that by Lemma 5, D_2 is a bounded region, positively invariant under the flow induced by (7). D_3 is also positively invariant under the same flow and trajectory entering D_3 delimits a bounded subregion of D_3 , which becomes positively invariant. Indeed, on the line $Y = M$, $Y' < 0$, $\forall M > Y^*$. Moreover $D_2 \cap D_3 = \{Q^*\}$.

By using Lemma 5, we have the following situations:

1. If $P_0 \in D_1$, then X decreases and Y increases and at a time $t_1 > 0$, the trajectory must cross \mathcal{C}_ψ and enter region D_3 or cross \mathcal{C}_φ and enter the bounded positively invariant region D_2 containing only Q^* (noting that Q_0 is unstable). If the trajectory enters region D_3 , $D_3 \cap \{x > 0, Y = Y(t_1)\}$ determines a positively invariant subregion of D_3 and its contains only Q^* . By Lemma 1 there are no periodic orbits, then the Poincaré-Bendixson Theorem entails that P_t tends towards Q^* .
2. If $P_0 \in D_2$ or $P_0 \in D_3$ we have the same conclusion as in the previous case.
3. If $P_0 \in D_4$ then X increases and Y decreases and at a time $t_1 > 0$, the trajectory must cross \mathcal{C}_φ and enter region D_3 or cross \mathcal{C}_ψ and enter region D_2 . The first case allows us to conclude that P_t tends towards Q^* . ■

Next, for $\sigma > 0$, we consider three separate cases. The proof of the following theorem for the first case where $\frac{\sigma}{k_3} < \frac{\lambda'}{k_2}$ is similar to the proof of Theorem 5.

Theorem 6 *Suppose that $\mathcal{R}_0 > 1$, $\mathcal{R}_1 < 1$, and $\mathcal{R}_2 > 1$. If $\sigma > 0$ and $\frac{\sigma}{k_3} < \frac{\lambda'}{k_2}$, then Q^* is GAS in \mathcal{D}' .*

For the second case of $\frac{\gamma'}{k_2} < \frac{\sigma}{k_3}$, we have the following theorem:

Theorem 7 *Suppose that $\mathcal{R}_0 > 1$, $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 > 1$. If $\sigma > 0$ and $\frac{\gamma'}{k_2} < \frac{\sigma}{k_3}$, then Q^* is GAS in \mathcal{D}' .*

Proof:

For $(x, y) \in \mathcal{D}'$ set

$$\begin{aligned}
D_{1,1} &= \{X^* < x < \frac{\gamma'}{k_2}, \varphi(x) < y < \psi(x)\} & D_{1,2} &= \{\frac{\gamma'}{k_2} < x < \frac{\sigma}{k_3}, y > \varphi(x)\} \\
D_{1,3} &= \{x \geq \frac{\sigma}{k_3}, y > 0\} & D_1 &= D_{1,1} \cup D_{1,2} \cup D_{1,3} \\
D_{2,1} &= \{0 < x < X^*, y < \psi(x)\} & D_{2,2} &= \{X^* < x < \frac{\gamma'}{k_2}, y < \varphi(x)\} \\
D_2 &= D_{2,1} \cup D_{2,2} & D_{3,1} &= \{\frac{\lambda'}{k_2} < x < X^*, y > \varphi(x)\} \\
D_{3,2} &= \{X^* < x < \frac{\gamma'}{k_2}, y > \psi(x)\} & D_3 &= D_{3,1} \cup D_{3,2} \\
D_{4,1} &= \{x < \frac{\lambda'}{k_2}, y > \psi(x)\} & D_{4,2} &= \{\frac{\lambda'}{k_2} < x < X^*, \psi(x) < y < \varphi(x)\} \\
D_4 &= D_{4,1} \cup D_{4,2}
\end{aligned}$$

Lemma 6 *Suppose $\sigma > 0$ and $\frac{\gamma'}{k_3} < \frac{\sigma}{k_3}$.*

- If $0 < x < \frac{\lambda'}{k_2}$, then $\varphi(x) \leq 0$ and $\psi(x) \geq 0$.

- If $\frac{\lambda'}{k_2} < x < \frac{\gamma'}{k_2}$, then $\varphi(x) \geq 0$ and $\psi(x) \geq 0$.
- If $\frac{\gamma'}{k_2} < x < \frac{\sigma}{k_3}$, then $\varphi(x) \geq 0$ and $\psi(x) \leq 0$.
- If $x > \frac{\sigma}{k_3}$, then $\varphi(x) \leq 0$ and $\psi(x) \leq 0$.

(ii) For $x > 0$, we have

$$\psi(x) - \varphi(x) \begin{cases} > 0 & \text{if } 0 < x < \frac{\lambda'}{k_2} \quad \text{or } X^* < x < \frac{\gamma'}{k_2} \\ = 0 & \text{if } x = X^* \\ < 0 & \text{if } \frac{\lambda'}{k_2} < x < X^* \quad \text{or } x > \frac{\gamma'}{k_2}. \end{cases}$$

- (iii)
- If $P_t \in D_1$, then $X' < 0$ and $Y' > 0$. Moreover, by continuity, if $P_t \in \mathcal{C}_\psi$, $X' < 0$ and $Y' = 0$, if $P_t \in \mathcal{C}_\varphi$, $X' = 0$ and $Y' > 0$.
 - If $P_t \in D_2$, then $X' > 0$ and $Y' > 0$. Moreover, by continuity, if $P_t \in \mathcal{C}_\psi$, $X' > 0$ and $Y' = 0$, if $P_t \in \mathcal{C}_\varphi$, $X' = 0$ and $Y' > 0$.
 - If $P_t \in D_3$, then $X' < 0$ and $Y' < 0$. Moreover, by continuity, if $P_t \in \mathcal{C}_\psi$, $X' < 0$ and $Y' = 0$, if $P_t \in \mathcal{C}_\varphi$, $X' = 0$ and $Y' < 0$.
 - If $P_t \in D_4$, then $X' > 0$ and $Y' < 0$. Moreover, by continuity, if $P_t \in \mathcal{C}_\psi$, $X' > 0$ and $Y' = 0$ and if $P_t \in \mathcal{C}_\varphi$, $X' = 0$ and $Y' < 0$.

Proof: See Lemma 4 and (14). ■

By using Lemma 6, we have the following situations:

- If $P_0 \in D_4$ then X increases and Y decreases and at a time $t_1 > 0$, the trajectory must cross \mathcal{C}_ψ and enter D_2 .
- If $P_0 \in D_3$ then X decreases and Y decreases and at a time $t_1 > 0$, the trajectory must cross \mathcal{C}_φ and enter D_4 .
- If $P_0 \in D_2$ then X increases and Y increases and at a time $t_1 > 0$, the trajectory must cross \mathcal{C}_φ and enter D_1 .
- If $P_0 \in D_1$, then X decreases and Y increases and at a time $t_1 > 0$, the trajectory must cross \mathcal{C}_ψ and enter D_3 with $X^* < X_1 < X_0$ and $Y_0 < Y_1$. In D_3 , X and Y both decrease and at a certain time $t_2 > t_1$, the trajectory must cross \mathcal{C}_φ and enter D_4 with $X_2 < X^*$ and $Y_2 < Y_1$. In D_4 , X increases and Y decreases and at a certain time $t_3 > t_2$, the trajectory must cross \mathcal{C}_ψ and enter D_2 with $X_2 < X_3 < X^*$ and $Y_3 < Y_2$. In D_2 , X increases and Y increases and at a certain time $t_4 > t_3$, the trajectory must cross \mathcal{C}_φ and enter D_1 with $X^* < X_4 < X_1$ and $Y_3 < Y_4 < Y_2$. This establishes a circulation flow. The trajectory stays inside a rectangle of vertices $\{(X_1, Y_2), (X_1, Y_3), (X_2, Y_2), (X_2, Y_3)\}$ and as there are no closed orbits the ω -limit set is the point Q^* . ■

To complete the the global stability analysis of Q^* , we only need the following theorem for the remaining case where $\frac{\lambda'}{k_2} < \frac{\sigma}{k_3} \leq \frac{\gamma'}{k_2}$, the proof of which is similar to that of Theorem 7:

Theorem 8 Suppose that $\mathcal{R}_0 > 1$, $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 > 1$. If $\sigma > 0$ and $\frac{\lambda'}{k_2} < \frac{\sigma}{k_3} \leq \frac{\gamma'}{k_2}$, then Q^* is GAS in \mathcal{D}' .

Using Theorems 5-8 together, we conclude that as long as $\mathcal{R}_0 > 1$, $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 > 1$, Q^* is always GAS in \mathcal{D}' .

5 Conclusions

In this work, we have identified three threshold parameters of epidemiological importance, namely \mathcal{R}_0 , \mathcal{R}_1 , and \mathcal{R}_2 , for the dynamic behavior of the system in question. A summary of their respective roles in the asymptotic state of the system is given in Table 1. Previous modeling studies of HIV with secondary reproduction numbers includes [7, 8, 9, 12].

Table 1: Asymptotic states for the model. "GAS" denotes equilibrium is globally asymptotically stable, "LAS" denotes it is locally asymptotically stable and "NE" denotes equilibrium does not exist in the domain

\mathcal{R}_0	\mathcal{R}_1	\mathcal{R}_2	Q_0	Q^*	$(X, Y) \rightarrow$
< 1	< 1	< 1	GAS	NE	Q_0
< 1	< 1	> 1	GAS	NE	Q_0
< 1	> 1	< 1	LAS	unstable	Q_0 or unbounded
> 1	< 1	> 1	unstable	GAS	Q^*
> 1	> 1	< 1	unstable	NE	unbounded
> 1	> 1	> 1	unstable	NE	unbounded

The biological interpretations of these parameters are discussed as follows. $\mathcal{R}_0 = \lambda / (k_1 + \gamma) + \lambda' k_1 / [\gamma' (k_1 + \gamma)]$ gives the number of infections by an infective who is detected via random screening; $\mathcal{R}_1 = \lambda' / (\beta' + \mu)$ is the number of infections caused by an infective after he/she has been tested positive for HIV; and $\mathcal{R}_2 = \frac{\lambda}{\gamma}$ is the number of infections caused by an infective that is not detected during asymptomatic period, i.e., if an infective either develops AIDS-related illness or pass away before progression to AIDS.

We note that \mathcal{R}_0 can be considered as the basic reproduction number, if we consider the detection of HIV-positive individuals in Cuba as part of disease surveillance instead of an intervention measure, especially in light of the realistic model assumption that those detected to be HIV-positive can still infected others, albeit at a lower level, before the onset of AIDS-defined illnesses [4]. Moreover, \mathcal{R}_0 determines whether the DFE (Q_0) is locally asymptotically stable, as is the typical role of a basic reproduction number. \mathcal{R}_1 and \mathcal{R}_2 are secondary reproduction numbers, which help us to determine the asymptotic behavior of the system, often relating to the endemic equilibrium. In the present model, whether \mathcal{R}_1 is larger than unity determines the existence of an unstable endemic equilibrium Q^* when $\mathcal{R}_0 < 1$. When $\mathcal{R}_0 > 1$, $\mathcal{R}_1 < 1$ in combination with $\mathcal{R}_2 > 1$ ensure the existence of a globally asymptotically stable equilibrium Q^* .

Serving as the threshold parameters for the model system, these reproduction numbers have obvious and epidemiologically meaningful interpretation. For the proposed model of detection and surveillance of HIV epidemic in Cuba, our results indicate that random screening is most important as a mean of surveillance, since whether the number of infections due to an infective detected through random determines whether the DFE is (locally) asymptotically stable. In other words, if the averaged total number of infections by an infective detected through random screening exceeds one, then there will always be an epidemic. On the other hand, local asymptotic stability for DFE can be achieved (i.e., R_0 can be brought down to less than one) if: (i) random screening is sufficiently effective (k_1 large), and (ii) infection by detected HIV-positive individuals is minimal (λ' small).

Our results further highlight the importance of the education for the known infectious, in light of the second threshold parameter $\mathcal{R}_1 = \lambda' / \gamma'$. If the known infectious do not change

through education to practice less risky sexual habits and their infection rate is still high (i.e., λ' sufficiently large) so that the average number of infections by a known infective (\mathcal{R}_1) exceeds unity, the endemic equilibrium is always unstable and there is always a possibility for the total number of infectious (i.e., $X + Y$) to increase without bound. This is true even when $\mathcal{R}_0 < 1$, provided that the initial population sizes are outside the domain of attraction of the DFE. This scenario of adverse impact of public health measures, which had been shown previously to be theoretically possible in [1, 7, 13], is only possible if k_1 is sufficiently small compared to γ , knowing that \mathcal{R}_0 is a convex combination of \mathcal{R}_1 and \mathcal{R}_2 (see Equation (3)). In other words, an ill-designed detection system might adversely lead to the epidemic increasing without bounded if (i) random screening is not comprehensive enough (k_1 too small); (ii) lack of education program to change behavior (λ' too high); and (iii) the prevalence is too high when the system is first implemented (initial infective populations outside of the domain of attraction of the DFE). This result further highlights the importance of universal testing in high-prevalence regions [6, 11]. On the other hand, if through adequate education to change behavior of the known infectious (so that λ' is sufficiently low) the average number of infections by a known infective is less than one, then either the DFE Q_0 or the endemic equilibrium Q^* is globally asymptotically stable, leading to a more manageable epidemic for the public health purposes, even if the disease is not eradicated.

5.1 Application to the Cuban HIV/AIDS data.

The modeling results are clearly relevant to our understanding of the current state of the HIV epidemic in Cuba. We will use the model (1) to fit the data of the known HIV positives and AIDS cases in Cuba. We have divided the period 1986-2008 into two different time periods, namely 1986-1999 and 1999-2008, to take into account the introduction of the family doctors in the detection system. In each period we have parameters that can be estimated from the data. These are β , β' , μ , μ' and $X(0)$. $Y(0)$ and $Z(0)$ are known. In previous work ([15], [3], [4], [12]) estimates for λ and λ' have been obtained.

The family doctors program had actually started after 1990, but only as a pilot project where the family doctors typically did not prescribe HIV testing. It is only after 1999 that detection through the family doctors started to take on an important role in the yearly detection figures, arriving at more than 30% of new detections in a year. Another significant difference between the two periods chosen is λ' . In the first years (1986-1999) the sanatorial system played an important role in preventing HIV transmission from persons that had been detected. Hence we suppose that there is practically no transmission from the persons living with HIV (Y) and assume $\lambda' = 0$ for the first period.

We fitted the model to the data to obtain values for k_1 , k_2 and k_3 by minimizing an error function. As traditional optimization methods failed to work properly we used a genetic algorithm approach to find an initial point for starting the optimization method using a gradient method. To compute standard errors for the parameters, 200 fitting runs were made using different values of the known parameters, taken randomly from their confidence interval. Using PET a software written on MATLAB, we obtain the least-square estimates for the unknown model parameters (k_1 , k_2 and k_3), for each of the two periods of the Cuban HIV epidemic from 1986 to 2008, by fitting the Cuban HIV data of the persons known to live with HIV to the model as described previously. The model fit for $Y(t)$ is given in Figure 2. Here the resulting numbers for 1999 obtained from the first stage of estimation using data from 1986-1999 was used as initial values for the second stage of estimation using the 1999-2008 data. The estimated mean values of the parameters k_1 , k_2 , and k_3 for each of the two periods with 95% confidence intervals, obtained from the 100 best fits, are given in Tables 2 and 3.

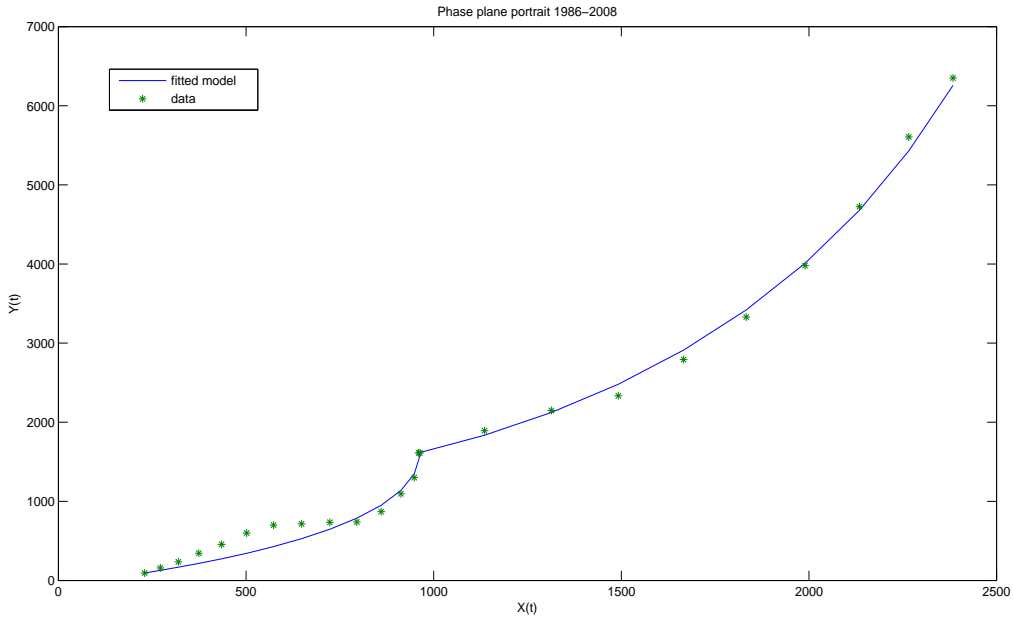


Figure 2: Phase plane portrait for the years 1986-2008. The dots $(X_{\text{Model}}(t), Y_{\text{Data}}(t))$ are the real data, the solid line $(X_{\text{Model}}(t), Y_{\text{Model}}(t))$ denotes the model-generated curve.

Table 2: Estimated mean values with the 95% confidence intervals for parameters k_1 and k_2 in the period 1986-1999 ($k_3 = 0$). UCI and LCI denote the respective upper and lower bounds for the 95% confidence intervals.

	k_1	k_2
Mean	0.1347	2.381×10^{-5}
LCI	0.1345	2.366×10^{-5}
UCI	0.1349	2396×10^{-5}

We can also compute the theoretical values of the number of the unknown persons living with HIV, $X(t)$, from the estimation results. The theoretical values of $X(t)$ from 1999 to 2008 are given in Figure 3. By comparing the estimation results for the two periods, we conclude that detection by random screening (k_1) improved significantly after 1999, perhaps reflecting the steeper increase in reported cases after 2000 (see Figure 2), while detection via contact tracing (k_2) was at similar level throughout the whole course of the epidemic. Detection by family doctors (k_3) was slightly higher than that of contact tracing after 1999 but of similar magnitude. Both the analytical result (of the dynamics) and the data-fitting parameter estimates indicate that random screening was the most effective route of detection, while contact tracing and family played mainly secondary roles, as had been previously proposed in [11]. The estimates of the model parameters also allow us to calculate the three reproduction numbers, \mathcal{R}_0 , \mathcal{R}_1 , and \mathcal{R}_2 , with the 95% confidence intervals for each of the two time periods which are given in Table 4.

As we can see, for both time periods the Cuba HIV epidemic is in the case of $\mathcal{R}_0 > 1$, $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 > 1$. Q_0 is unstable and Q^* is globally asymptotically stable with the tra-

Table 3: Estimated mean values with the 95% confidence intervals for parameters k_1 , k_2 and k_3 in the period 1999-2008. UCI and LCI denote the respective upper and lower bounds for the 95% confidence intervals.

	k_1	k_2	k_3
Mean	0.2195	2.728×10^{-5}	6.801×10^{-5}
LCI	0.2192	2.725×10^{-5}	6.783×10^{-5}
UCI	0.2198	2.732×10^{-5}	6.818×10^{-5}

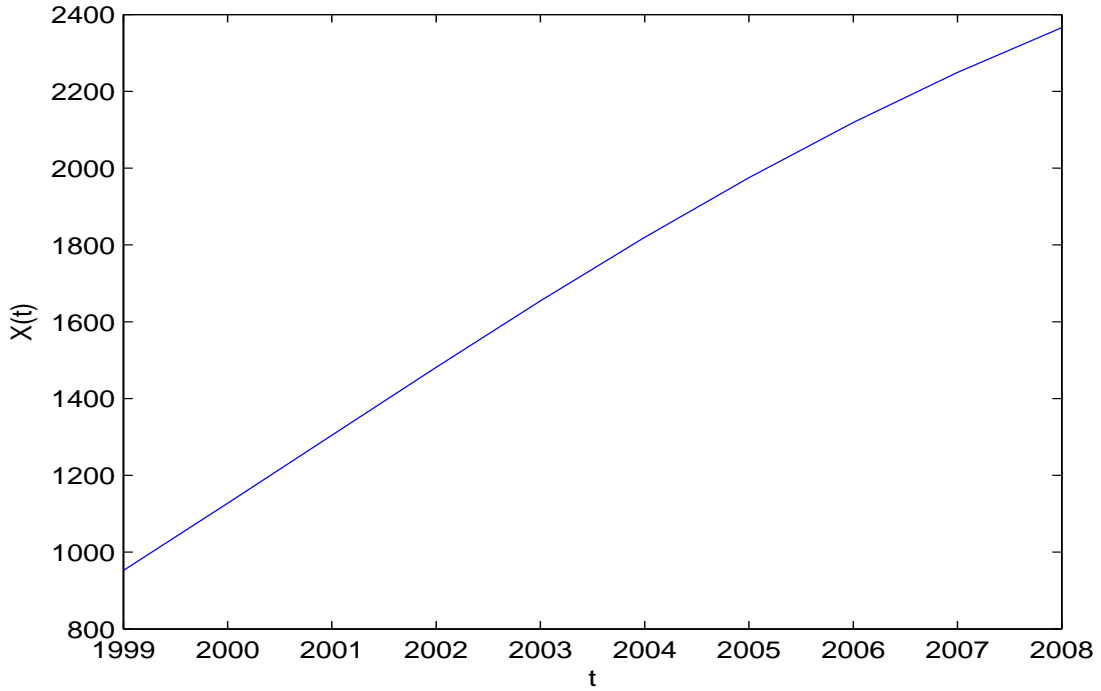


Figure 3: Model-generated curve for unknown HIV-infected in Cuba during 1986-2008.

jectories approaching Q^* asymptotically. Hence we can conclude that the HIV epidemic in Cuba is tending (in the long term) towards an endemic steady state which we can estimate from our parameters using the expression obtained from our modeling for $P^* = (X^*, Y^*, Z^*)$ given in Equation (2). That is, assuming no drastic changes in the prevention, transmission, detection, or treatment of HIV in Cuba in the long term future, there could be, eventually, around 2700 persons living with HIV that do not know they are infected. Further noting from Figure 3 that the theoretical number of unknown persons living with HIV from the model is around 2400, we speculate with optimism that, at the endemic steady state, the number of persons living with HIV that represent the main core for the transmission of the epidemic in Cuba will not increase drastically in the long term future.

The assumption that the parameter do not change in the long term is not a very real one, taking into account that every year new information is gained on the virus and there is ample research on treatment, vaccines and other aspects that affect the dynamics of the epidemic. For example existing therapy reduces the probability of transmission for HIV, in terms of

Table 4: Estimated mean values with the 95% confidence intervals for \mathcal{R}_0 , \mathcal{R}_1 , and \mathcal{R}_2 . UCI and LCI denote the respective upper and lower bounds for the 95% confidence intervals.

	1986-1999		1999-2008	
	LCI	UCI	LCI	UCI
\mathcal{R}_0	1.824	1.837	1.858	1.859
\mathcal{R}_1	0	0	0.762	0.765
\mathcal{R}_2	4.446	4.665	4.428	4.434

our model this means that coefficient λ' is reduced and this will make \mathcal{R}_1 smaller, changing the value of the asymptotic point. But therapy delays the onset of AIDS, this means that β' gets smaller, also changing \mathcal{R}_1 but making it bigger. So long term predictions (as in the case of asymptotic behavior) make sense only as an indicator of how is the epidemic going to behave. In this sense in table 1, we see that if $\mathcal{R}_1 > 1$ trajectories could be unbounded, and this would mean that the epidemic is out of control. It is very important to manage the value of \mathcal{R}_1 .

Rapatski et al. [16] pointed out the need to consider the parameters that appear in models for the HIV-AIDS epidemic to be varying with time. We are approaching this point of view in another ongoing work, but we realize that there are several problems with the approach of nonconstant coefficients, and this is due (from our point of view) to the fact that there is independent estimation for the number of undetected persons living with HIV. That is why in this paper we chose to use parameters that are constant or are step functions (with 2 steps for now) that also produce a change in the model itself, changing the recruitment function from X to Y , $F(X, Y)$, from a linear polynomial in Y for the period 86-99, to a linear polynomial in X and Y for the period 99-2008.

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