Mathematical modeling of the HIV/AIDS epidemic in Cuba

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AIDS was first reported on June 5, 1981 by the CDC.
Highest prevalence is in sub-Saharan Africa (5%).
Caribbean region has second highest prevalence.
As of 2010, 60 mil HIV infected, 30 mil AIDS deaths.
In 2011, there were 34 mil people living with HIV.
Newly infected: 3.2 mil in 2001, 2.5 mil in 2011.
AIDS deaths: Peak of 2.3 mil in 2005, 1.7 mil in 2011.
What is AIDS?

An HIV-infected individual has AIDS if
- He/She has fewer than 200 T-lymphocytes per microliter OR
- One or more of 26 various diseases including
  - Kaposi’s sarcoma, lymphoma, candidias, etc.

Symptoms: fever, weight loss, night sweats, diarrhea.
Progression to AIDS

HIV

Protein spike

Virus RNA

CD4 cell

DNA

Virus RNA enters CD4 cell

Nucleus

CD4 receptor

Virus DNA enters nucleus

Virus RNA turning into DNA

Virus DNA makes parts for new HIV

New copies of HIV

Virus DNA sewn into cell's DNA
HIV/AIDS in Cuba

- HIV prevalence is 0.2%.
- 99% of transmissions are through sexual relations.
- 77-80% of HIV infected are men.
- Average of 1.6 mil tests performed each year.
- Antiretroviral therapy (ARV) coverage is 100%.
- In 1983 Cuba initiated program to control HIV/AIDS.
Design a national HIV prevention program
Develop efforts for prevention of vertical transmission
Undertake epidemiological surveillance and control
Spearhead scientific research and development
Establish a national sanatorium network

“Health is a human right.”
## HIV/AIDS data for Cuba

<table>
<thead>
<tr>
<th>Year</th>
<th>HIV cases</th>
<th>AIDS cases</th>
<th>Death due to AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>99</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>1987</td>
<td>75</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>1988</td>
<td>93</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>1989</td>
<td>121</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>1990</td>
<td>140</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>1991</td>
<td>183</td>
<td>37</td>
<td>17</td>
</tr>
<tr>
<td>1992</td>
<td>175</td>
<td>71</td>
<td>32</td>
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<tr>
<td>1993</td>
<td>102</td>
<td>82</td>
<td>59</td>
</tr>
<tr>
<td>1994</td>
<td>122</td>
<td>102</td>
<td>62</td>
</tr>
<tr>
<td>1995</td>
<td>124</td>
<td>116</td>
<td>80</td>
</tr>
<tr>
<td>1996</td>
<td>234</td>
<td>99</td>
<td>92</td>
</tr>
<tr>
<td>1997</td>
<td>363</td>
<td>129</td>
<td>99</td>
</tr>
<tr>
<td>1998</td>
<td>362</td>
<td>150</td>
<td>98</td>
</tr>
<tr>
<td>1999</td>
<td>493</td>
<td>176</td>
<td>122</td>
</tr>
<tr>
<td>2000</td>
<td>545</td>
<td>251</td>
<td>142</td>
</tr>
<tr>
<td>2001</td>
<td>642</td>
<td>392</td>
<td>117</td>
</tr>
<tr>
<td>2002</td>
<td>644</td>
<td>407</td>
<td>90</td>
</tr>
</tbody>
</table>
Compartmental model:

1. \( S(t) \): the susceptible population
2. \( X(t) \): undiagnosed HIV infected people
3. \( Y(t) \): diagnosed HIV infected people
4. \( Z(t) \): people diagnosed with AIDS

Earlier mathematical models:

- de Arazoza and Lounes (2002)
- Rapatski et al. (2006)
Parameters and model

1. \( \lambda \): recruitment rate of the susceptible class.
2. \( \alpha \): transmission rate of HIV+ by sexual transmission with \( X \).
3. \( \hat{\beta} \): rate at which HIV-infected class develop AIDS.
4. \( k \): rate at which \( X \) class are diagnosed through contact tracing.
5. \( \hat{k} \): rate at which \( X \) are diagnosed through random testing.
6. \( \mu \): mortality rate of the adult class.
7. \( \hat{\mu} \): mortality rate of the population with AIDS.

Model equations:

\[
\begin{align*}
\dot{S} &= \lambda - \alpha X S - \mu S \\
\dot{X} &= \alpha X S - kXY - (\mu + \hat{\beta} + \hat{k}) X \\
\dot{Y} &= kXY + \hat{k}X - (\mu + \hat{\beta}) Y \\
\dot{Z} &= \hat{\beta} (X + Y) - \hat{\mu} Z
\end{align*}
\]
Basic reproduction number $R_0$

Basic reproduction number $R_0$ is the number of secondary infections caused by an infectious individual that enters a fully susceptible population. $R_0$ is determined by computing the spectral radius of the matrix formed by the product of the next generation matrix, $F$, and the inverse of the transition matrix, $V$, given by

$$F = \begin{pmatrix} \frac{\alpha \lambda}{\mu} & 0 & 0 \\ \frac{\hat{k}}{k} & 0 & 0 \\ \hat{\beta} & \hat{\beta} & 0 \end{pmatrix}, \quad V = \begin{pmatrix} (\mu + \hat{\beta} + \hat{k}) & 0 & 0 \\ 0 & (\mu + \hat{\beta}) & 0 \\ 0 & 0 & \hat{\mu} \end{pmatrix}.$$ 

A routine computation yields

$$R_0 = \frac{\lambda \alpha}{\mu(\mu + \hat{\beta} + \hat{k})}.$$
Disease-free equilibrium

The model has a disease-free equilibrium (DFE), \( E_0 = \left( \frac{\lambda}{\mu}, 0, 0, 0 \right) \).

Proposition

1. \( E_0 \) is locally asymptotically stable if \( R_0 < 1 \) and unstable if \( R_0 > 1 \).
2. \( E_0 \) is global asymptotically stable if \( R_0 \leq 1 \).

Proof.

\[
J(E_0) = \begin{pmatrix}
-\mu & -\alpha \lambda / \mu & 0 & 0 \\
0 & \alpha \lambda / \mu - (\mu + \hat{k} + \hat{\beta}) & 0 & 0 \\
0 & \hat{k} & -\mu - \hat{\beta} & 0 \\
0 & \hat{\beta} & -\hat{\mu} & 0
\end{pmatrix}
\]

Eigenvalues are \( h_1 = -\mu, h_2 = -\hat{\mu}, h_3 = -(\mu + \beta_2), \) and
\[
h_4 = \alpha \lambda / \mu - (\mu + \hat{k} + \beta_1) = (R_0 - 1)(\mu + \hat{k} + \beta_1).
\]

\[

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\]
Endemic equilibrium

The model has endemic equilibrium $E = (S^*, X^*, Y^*, Z^*)$ where

\[ X^* = \frac{(\mu + \hat{\beta})Y^*}{\hat{k} + kY^*}, \quad S^* = \frac{\lambda}{\alpha X^* + \mu}, \quad Z^* = \frac{(X^* + Y^*)\hat{\beta}}{\hat{\mu}}, \]

$Y^*$ is the positive root of

\[ aY^2 + bY + c = 0, \quad (0.1) \]

and

\[
\begin{align*}
    a &= k(\mu k + \alpha(\mu + \hat{\beta})) > 0 \\
    b &= \alpha(\mu + \hat{\beta})(\mu + \hat{\beta} + \hat{k}) + k\mu\hat{k} + \frac{\lambda\alpha k}{R_0} - \lambda\alpha k \\
    c &= \hat{k}(\mu(\mu + \hat{\beta} + \hat{k}) - \lambda\alpha) = \hat{k}\mu(\mu + \hat{\beta} + \hat{k})(1 - R_0).
\end{align*}
\]
Theorem

The system can have at most one positive equilibrium. More precisely,

1. If $R_0 > 1$, there exists a unique positive stable equilibrium \( E = (S^*, X^*, Y^*, Z^*) \).
2. If $R_0 < 1$, there is no positive equilibrium.

Proposition

1. \( E \) is locally asymptotically stable if $R_0 > 1$.
2. \( E \) is global asymptotically stable if $R_0 > 1$. 
Data fitting

<table>
<thead>
<tr>
<th></th>
<th>$\lambda$</th>
<th>$\alpha$</th>
<th>$\mu$</th>
<th>$k$</th>
<th>$\beta$</th>
<th>$\hat{k}$</th>
<th>$\hat{\mu}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val.</td>
<td>$10^5$</td>
<td>$1.55 \times 10^{-7}$</td>
<td>0.02</td>
<td>0.3850</td>
<td>0.14</td>
<td>$9 \times 10^{-5}$</td>
<td>3/4</td>
</tr>
<tr>
<td>Rapatski</td>
<td>NA</td>
<td>$9.327 \times 10^{-8}$</td>
<td>0.0053</td>
<td>0.3850</td>
<td>0.14</td>
<td>$3.26 \times 10^{-5}$</td>
<td>3/4</td>
</tr>
</tbody>
</table>

**Table**: Estimated parameter values.

with initial conditions

$$S(0) = 5,000,000, \quad X(0) = 100, \quad Y(0) = 94, \quad Z(0) = 3.$$
Figure: Plots of $Y(t)$ and $Z(t)$ for $R_0 = 1.45$ (left) and for $R_0 = 1.45, 0.73$ (right).
Optimal control

\[
\begin{cases}
\dot{S} &= \lambda - \alpha (1 - u_1(t)) XS - \mu S \\
\dot{X} &= \alpha (1 - u_1(t)) XS - u_2(t)kXY - u_3(t)\hat{k}X - (\mu + \hat{\beta})X \\
\dot{Y} &= u_2(t)kXY + u_3(t)\hat{k}X - (\mu + \hat{\beta})Y \\
\dot{Z} &= \hat{\beta} (X + Y) - \hat{\mu}Z
\end{cases}
\]

where \( 0 \leq u_i(t) \leq U_i, \ i = 1, 2, 3. \)

- \( u_1(t) \): educational programs, condom use
- \( u_2(t) \): contact tracing
- \( u_3(t) \): random testing

Objective functional

\[
J(u_1, u_2, u_3) = \int_0^T BX(t) + a_1u_1^2(t) + a_2u_2^2(t) + a_3u_3^2(t) \, dt
\]
Optimal control

Goal: Find optimal controls \((u_1^*, u_2^*, u_3^*)\) such that

\[
J(u_1^*, u_2^*, u_3^*) = \min \left\{ J(u_1, u_2, u_3) \mid (u_1, u_2, u_3) \in \Gamma \right\}
\]

where

\[
\Gamma = \{(u_1, u_2, u_3) \mid u_i(t) \text{ is Lebesgue measurable on } [0, T], 0 \leq u_i(t) \leq U_i \}.
\]

Existence is guaranteed since

1. Integrand of objective functional is convex on closed, convex control set \(\Gamma\).
2. Model is linear in the control variables.
3. Model is bounded by a linear system in the state variables.
Optimality system

State system

\[
\begin{align*}
\dot{S} &= \lambda - \alpha (1 - u_1(t))X S - \mu S \\
\dot{X} &= \alpha (1 - u_1(t))X S - u_2(t)kXY - u_3(t)\hat{k}X - (\mu + \hat{\beta})X \\
\dot{Y} &= u_2(t)kXY + u_3(t)\hat{k}X - (\mu + \hat{\beta})Y \\
\dot{Z} &= \hat{\beta}(X + Y) - \hat{\mu}Z
\end{align*}
\]

Adjoint system

\[
\begin{align*}
\dot{\lambda}_1 &= \lambda_1[\alpha (1 - u_1(t))X - \mu] - \lambda_2\alpha(1 - u_1(t))X \\
\dot{\lambda}_2 &= -B + \lambda_1\alpha (1 - u_1(t))S - \lambda_2[\alpha (1 - u_1(t))S - u_2(t)kY \\
&\quad - u_3(t)\hat{k} - (\mu + \beta)] - \lambda_3[u_2(t)kY + u_3(t)\hat{k}] - \lambda_4\beta \\
\dot{\lambda}_3 &= \lambda_2u_2(t)kX - \lambda_3[u_2(t)kX - (\mu + \beta)] - \lambda_4\beta \\
\dot{\lambda}_4 &= \lambda_4\hat{\mu}
\end{align*}
\]

subject to \( \lambda_1(T) = \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = 0. \)

Characterization of control

\[
\begin{align*}
u_1^* &= \max \left\{ 0, \min \left( 1, \frac{1}{2a_1} \left[ (\lambda_2 - \lambda_1)\alpha XS \right] \right) \right\} \\
u_2^* &= \max \left\{ 0, \min \left( 1, \frac{1}{2a_2} \left[ (\lambda_2 - \lambda_3)kXY \right] \right) \right\} \\
u_3^* &= \max \left\{ 0, \min \left( 1, \frac{1}{2a_3} \left[ (\lambda_2 - \lambda_3)\hat{k}X \right] \right) \right\}
\end{align*}
\]
References


Diekmann, O, Hesterbeek, JAP, Metz, JAJ, On the definition and the computation of the basic reproduction ratio $R_0$ in models for infectious diseases in heterogeneous populations, J. Math. Biol. 28 (1990) 365-381.


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Questions??