Mathematical modeling of the HIV/AIDS epidemic in Cuba

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HIV/AIDS epidemic

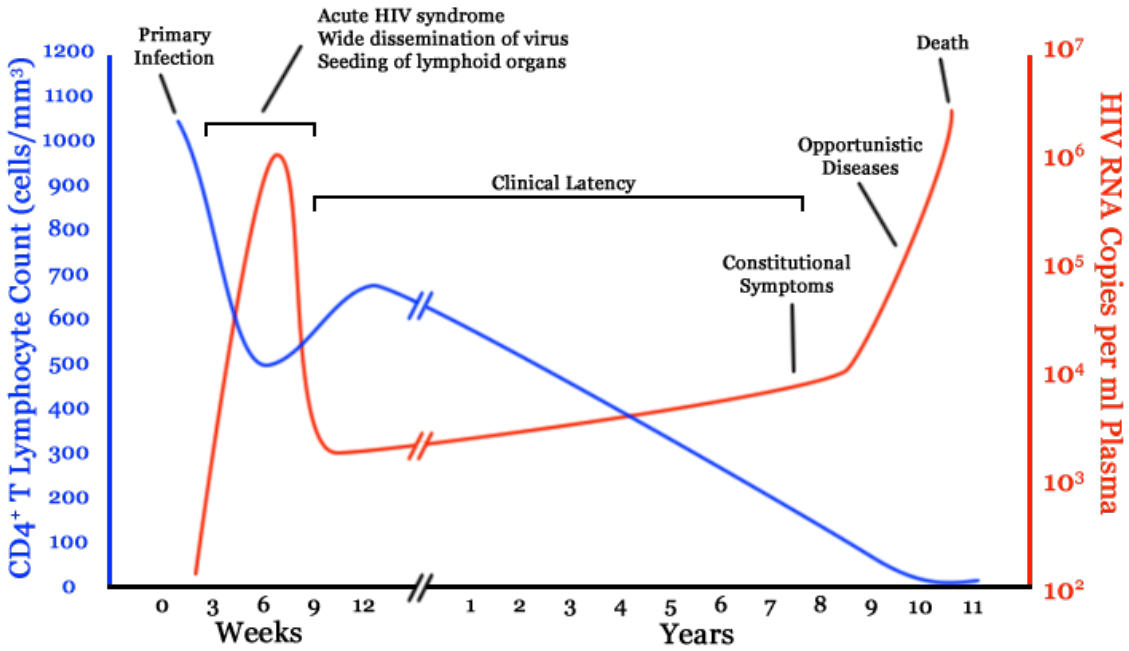
- AIDS was first reported on June 5, 1981 by the CDC.
- Highest prevalence is in sub-Saharan Africa (5%).
- Caribbean region has second highest prevalence.
- As of 2010, 60 mil HIV infected, 30 mil AIDS deaths.
- In 2011, there were 34 mil people living with HIV.
- Newly infected: 3.2 mil in 2001, 2.5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

What is AIDS?

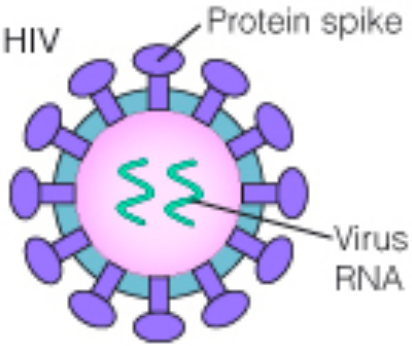
An HIV-infected individual has AIDS if

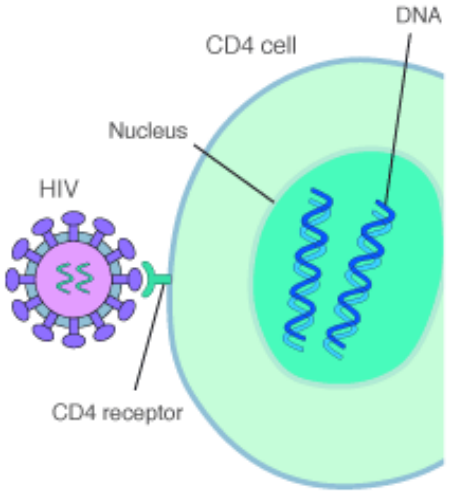
- He/She has fewer than 200 T-lymphocytes per microliter OR
- One or more of 26 various diseases including
  - Kaposi's sarcoma, lymphoma, candidias, etc.

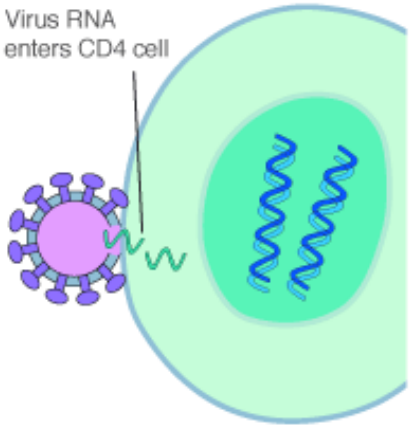
Symptoms: fever, weight loss, night sweats, diarrhea.

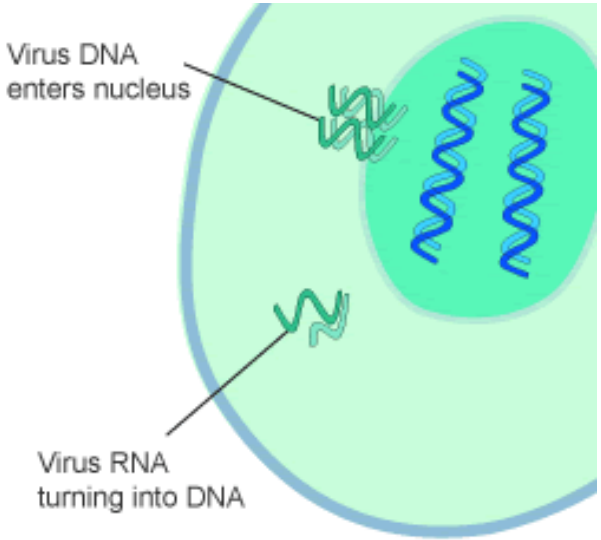


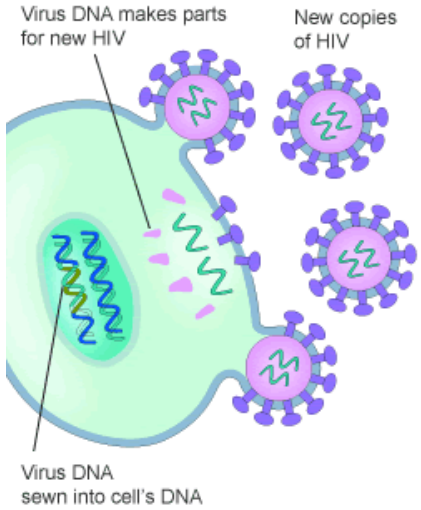
Progression to AIDS











HIV/AIDS in Cuba

- 1st HIV+ in late 1985; 1st AIDS death in 1986.
- 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.

National AIDS Commission

1. Design a national HIV prevention program
2. Develop efforts for prevention of vertical transmission
3. Undertake epidemiological surveillance and control
4. Spearhead scientific research and development
5. Establish a national sanatorium network

"Health is a human right."

HIV/AIDS data for Cuba

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

Compartments

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. λ: recruitment rate of the susceptible class.
2. α: transmission rate of HIV+ by sexual transmission with X.
3. $\widehat{\beta}$: rate at which HIV-infected class develop AIDS.
4. k: rate at which X class are diagnosed through contact tracing.
5. $\widehat{k}$: rate at which X are diagnosed through random testing.
6. μ: mortality rate of the adult class.
7. $\widehat{\mu}$: mortality rate of the population with AIDS.

Model equations:

$$\begin{cases} \dot{S} &= \lambda - \alpha X S - \mu S \\ \dot{X} &= \alpha X S - kXY - (\mu + \widehat{\beta} + \widehat{k}) X \\ \dot{Y} &= k X Y + \widehat{k} X - (\mu + \widehat{\beta}) Y \\ \dot{Z} &= \widehat{\beta} (X + Y) - \widehat{\mu} Z \end{cases}$$

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

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

A routine computation yields

$$R_0 = \frac{\lambda\alpha}{\mu(\mu+\widehat{\beta}+\widehat{k})}.$$

Disease-free equilibrium

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

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.

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

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

Endemic equilibrium

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

$$X^* = \frac{(\mu + \widehat{\beta})Y^*}{\widehat{k} + kY^*}, \; S^* = \frac{\lambda}{\alpha X^* + \mu}, \; Z^* = \frac{(X^* + Y^*)\widehat{\beta}}{\widehat{\mu}},$$

Y^* is the positive root of

$$aY^2 + bY + c = 0, \tag{0.1}$$

and

$$\begin{aligned} a &= k(\mu k + \alpha(\mu + \widehat{\beta})) > 0 \\ b &= \alpha(\mu + \widehat{\beta})(\mu + \widehat{\beta} + \widehat{k}) + k\mu\widehat{k} + \frac{\lambda\alpha k}{R_0} - \lambda\alpha k \\ c &= \widehat{k}(\mu(\mu + \widehat{\beta} + \widehat{k}) - \lambda\alpha) = \widehat{k}\mu(\mu + \widehat{\beta} + \widehat{k})(1 - R_0). \end{aligned}$$

Endemic equilibrium, cont'd

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

	λ	α	μ	k	β	$\widehat{k}$	$\widehat{\mu}$
Val.	10^5	1.55×10^{-7}	0.02	0.3850	0.14	9×10^{-5}	$3/4$
Rapatski	NA	9.327×10^{-8}	0.0053	0.3850	0.14	3.26×10^{-5}	$3/4$

Table: Estimated parameter values.

with initial conditions

$$S(0) = 5,000,000, \quad X(0) = 100, \quad Y(0) = 94, \quad Z(0) = 3.$$

Plots

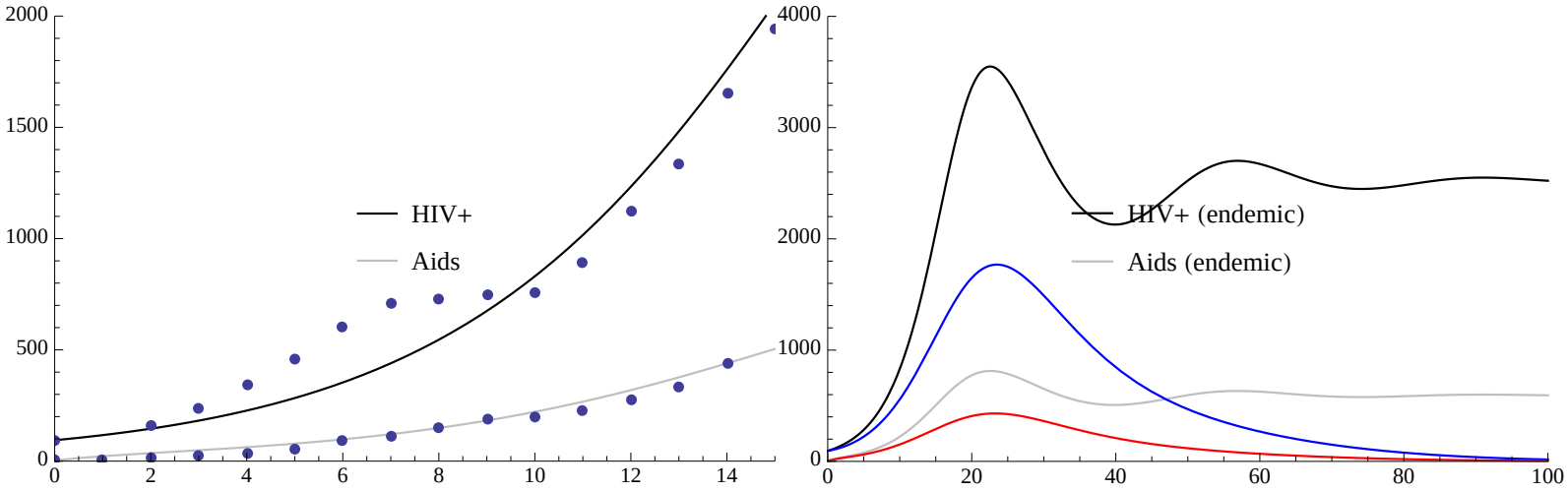


Figure: Plots of $Y(t)$ and $Z(t)$ for $R_0 = 1.45$ (left) and for $R_0 = 1.45, 0.73$ (right).

Optimal control

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

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

1. $u_1(t)$: educational programs, condom use
2. $u_2(t)$: contact tracing
3. $u_3(t)$: 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

$$J(u_1^*, u_2^*, u_3^*) = \min \{J(u_1, u_2, u_3) | (u_1, u_2, u_3) \in \Gamma\}$$

where

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

Existence is guaranteed since

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

Optimality system

State system

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

Adjoint system

$$\begin{aligned}
\dot{\lambda_1} &= \lambda_1[\alpha(1-u_1(t))X - \mu] - \lambda_2\alpha(1-u_1(t))X \\
\dot{\lambda_2} &= -B + \lambda_1\alpha(1-u_1(t))S - \lambda_2[\alpha(1-u_1(t))S - u_2(t)kY \\
&- u_3(t)\widehat{k} - (\mu+\beta)] - \lambda_3[u_2(t)kY + u_3(t)\widehat{k}] - \lambda_4\beta \\
\dot{\lambda_3} &= \lambda_2 u_2(t)kX - \lambda_3[u_2(t)kX - (\mu+\beta)] - \lambda_4\beta \\
\dot{\lambda_4} &= \lambda_4\widehat{\mu}
\end{aligned}$$

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

Characterization of control

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

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Questions??